

Outpatient Prescription of Zolpidem in Slovenia according to Gender and Age in the Period 2009-2014

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Abstract

Introduction: The aim of the study was to analyse the outpatient prescription of zolpidem in Slovenia in the period from 2009 to 2014 by gender and age, to present the trends and to analyse the prescription in Slovenian regions and by month of the year. Methodology: Non-benzodiazepine sedative hypnotics were classified according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System; Defined Daily Doses (DDD) per 1,000 inhabitants per day were used. The data on the outpatient prescription and utilization of zolpidem were collected from all pharmacies in Slovenia. Anonymized data were analysed; compiled data were processed by means of descriptive statistics, contingency tables, correlation, Pearson χ^2 test, ANOVA and linear regression. Results: In the period from 2009 to 2014 zolpidem was prescribed mostly to women (65.3%) in comparison with men (34.7%). Prescription has been in constant decrease from 2012; in men, a slight increase was observed in the same period. The highest number of zolpidem prescriptions was observed in women in the age groups from 51-60 years to age group 71-80 years. Patients younger than 55 years received 365.542 (29.87%) prescriptions in comparison with patients older than 55 years who received 858.195 prescriptions (70.13%). The significance in the Pearson χ^2 test was 0,000, meaning $p < 0.05$. Conclusion: In the period from 2009 to 2014 patients older than 55 years and women in Slovenia received significantly more prescriptions for zolpidem. Data revealed differences in prescription of zolpidem by age, gender, Slovenian regions and months of the year.

Keywords

zolpidem, gender, age, insomnia, medicines prescription, month

1. Introduction

Demographic ageing is considered to be one of the most serious challenges in European union, including Slovenia (Agren & Berensson, 2006). In the elderly sleep problems are common, the prevalence of insomnia increases with age. Older people often find it takes longer to get to sleep, have more fragmented sleep and wake up earlier (Kang et al., 2012; Blivise, 2005). In addition, a major physiological reason for poorer sleep quality with increasing age is chronic ill-health, disability and

impairment which cause pain and discomfort at night, resulting in sleep complaints and difficulties (Stewart et al., 2006). Ageing is also associated with increased daytime sleep via napping or dozing (Munch et al., 2005).

The most prevalent of all sleep disorders is insomnia, with 25% of the adult population reporting sleep difficulties and 6-10% fulfilling diagnostic criteria for a chronic insomnia disorder (Morin et al., 2014). Insomnia is the impaired ability to fall asleep, remain asleep or obtain restorative sleep (Schutte-Rodin et al., 2008). It is more prevalent in the elderly and may result in adverse outcomes such as daytime dysfunction and impaired quality of life (McCall, 2004). Insomnia may occur during the course of another medical condition or mental disorder (comorbid insomnia), or it may occur independently (primary insomnia) (MacFarlane et al., 2014).

There are significant gender differences in sleep disorders. Women have better sleep quality compared with men, with longer sleep times, shorter sleep-onset latency and higher sleep efficiency. Despite this, women have more sleep-related complaints than men. The amount of slow-wave sleep decreases with age in men and women. Normal physiologic periods, including menopause, are associated with alterations in sleep patterns. Studies of insomnia support a female predominance, with increased divergence of prevalence between men and women with older age (Krishnan & Collop, 2006).

The primary goals of insomnia management are to improve the quality and quantity of sleep and any related daytime dysfunction. Nonpharmacologic or pharmacologic therapies may be used to achieve these goals (Wong & Nguyen, 2014). Pharmacologic treatment options, indicated or off-label, include benzodiazepine receptor agonists, melatonin receptor agonists, sedating antidepressants, atypical antipsychotics, sedating antihistamines and unregulated substances (e.g., valerian, melatonin). Nonpharmacologic treatment options include cognitive-behavioral therapy, which involves various behavioral interventions (e.g., stimulus control therapy, relaxation training, sleep restriction therapy, sleep hygiene, paradoxical intention therapy). Patients also try self-help strategies including reading and relaxation, home remedies such as alcohol, and herbal therapies (MacFarlane et al., 2014).

One of the most commonly prescribed medications to treat insomnia is zolpidem, a non-benzodiazepine compound that acts by modulating the binding of GABA at the benzodiazepine-binding site on the GABAA receptor complex (MacFarlane et al., 2014). It is known for low tolerance, a quick induction time usually within 15 minutes, and a short half-life of two to three hours, which reduces the residual “hangover” effects, such as sleepiness and impaired psychomotor and cognitive function, after nighttime administration that may persist into next day (Kang et al., 2012; Bogan, 2008).

However, in elderly insomnia patients zolpidem could increase the risk of fracture, therefore it should be prescribed carefully and the elderly should be provided with sufficient patient education (Kang et al., 2012; Lin et al., 2014). Low-dose zolpidem can be safely prescribed even to subjects 80 years of age or older without cognitive or mental complications (Kajiwara et al., 2015).

In 2012 a study regarding the behavioral habits and health of the inhabitants in Slovenia, including medicines intake showed that elderly people need more sedatives and hypnotics than middle aged inhabitants (Tomsic et al., 2014).

Monitoring of medicines consumption helps to identify medical, economic and social consequences of the medicines consumption. Knowledge and understanding of information on the prescription data is crucial for the adoption of measures (Jelenc, 2013; Kostnapfel & Korosec, 2014). The aim of the present study was to analyse the prescription of zolpidem in Slovenia in the period from 2009 to 2014 with emphasis on overall trends in prescription, differences in prescription: by gender, by age, by different Slovenian regions and by months. This study aimed to compare the prescription of zolpidem among people older than 55 years to their younger counterpart and regarding gender.

2. Methodology

2.1 Data Source

The used source for this retrospective observational analysis lies on the “Database of prescriptions for outpatients” of the Republic of Slovenia at the National Institute of Public Health (NIPH). The analysis encompassed data on the number of prescriptions for non-benzodiazepine sedative hypnotics, with an emphasis on zolpidem, in the period from 2009 to 2014. All prescriptions reported from the pharmacies were analysed. Data were collected according to the Databases act in the area of healthcare (Offic Gaz, 2015). The consent from the Republic Ethic Committee was not needed because the data used were anonymised.

2.2 ATC Classification

The presented medicines consumption illustration respects the WHO Anatomical-Therapeutic-Chemical (ATC) classification. The subgroup of psycholeptics (ATC code N05CF) from ATC classification was analysed. In fact, according to the ATC classification system the medicines for the nervous system (group N) are divided in seven groups (N01-N07). Psycholeptics represent the group N05, which is divided in several subgroups. Hypnotics and sedatives are classified in the group N05C, which is subdivided as well; zolpidem and other Z drugs belong to the subgroup of benzodiazepine related drugs (N05CF).

2.3 Statistical Analysis

ATC data were used to calculate Defined Daily Doses (DDD) per 1,000 inhabitants per day (hereinafter DID) (WHO, 2015). The analysis of zolpidem prescription was performed with regard to gender, age, statistical regions in Slovenia and months of the year. Statistical software IBM SPSS Statistics version 21 for windows (SPSS Inc., Chicago, IL, USA) was used for data analysis. Compiled data were processed by means of descriptive statistics, contingency tables, correlation, Pearson χ^2 test, ANOVA and linear regression. Statistical significance value of $p < 0.05$ was used to calculate the significance level. Linear regression was used to determine predictions. Data were presented in tabular form and using histograms. Age was classified in ten year age groups.

3. Results

3.1 Overall Trends in Prescription of Zolpidem

In the period from 2009 to 2014, 1,223.737 prescriptions for zolpidem were issued; it was mostly prescribed to women (799.518 prescriptions; 65.3%). Men received 424.219 prescriptions (34.7%). Regarding the number of DID for zolpidem the highest value was observed in women in 2011 (137.54 DID), the lowest in men in 2014 (70.56 DID). In women the number of DID for zolpidem increased from 133.86 DID in 2009 to 137.54 DID in 2011 and then decreased to 126.33 DID in 2014. In men the number of DID for zolpidem increased from 68.05 DID in 2009 to 73.59 DID in 2013 and then decreased to 70.56 in 2014. In 2009 zolpidem represented 16.71% of all prescribed hypnotics and sedatives (ATC group N05C), in 2014 the percentage did not change (16.07%).

The prescription of zolpidem from 2009 to 2014 by gender, DID and predictions for 2015 and 2016 are shown in Figure 1.

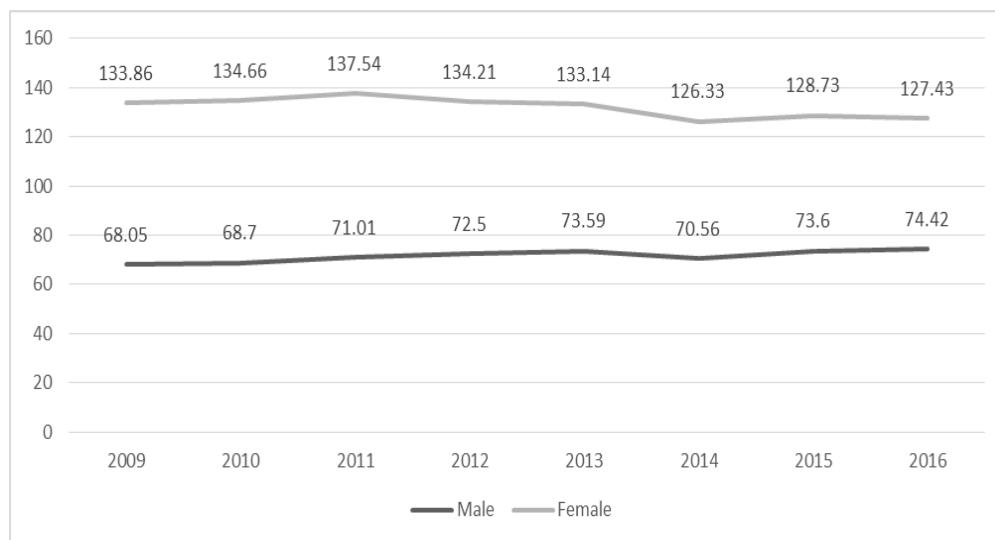


Figure 1. Prescription of Zolpidem by Gender and DID in Slovenia from 2009 to 2014, Including Predictions for 2015 and 2016

3.2 Prescription of Zolpidem by Gender and Age

In the observed period the prescription of zolpidem was present in greater extent in women, however it has been in constant decrease from 2012; in men, a slight increase was observed in the same period. Despite greater extension of prescription in women than in men in the observed period, the ratio decreased from 1:1.95 in 2009 to 1:1.71 in 2014. The highest number of zolpidem prescriptions was observed in women in the age groups from 51-60 years to 71-80 years.

Prescription of zolpidem by gender and age groups is shown in Figure 2.

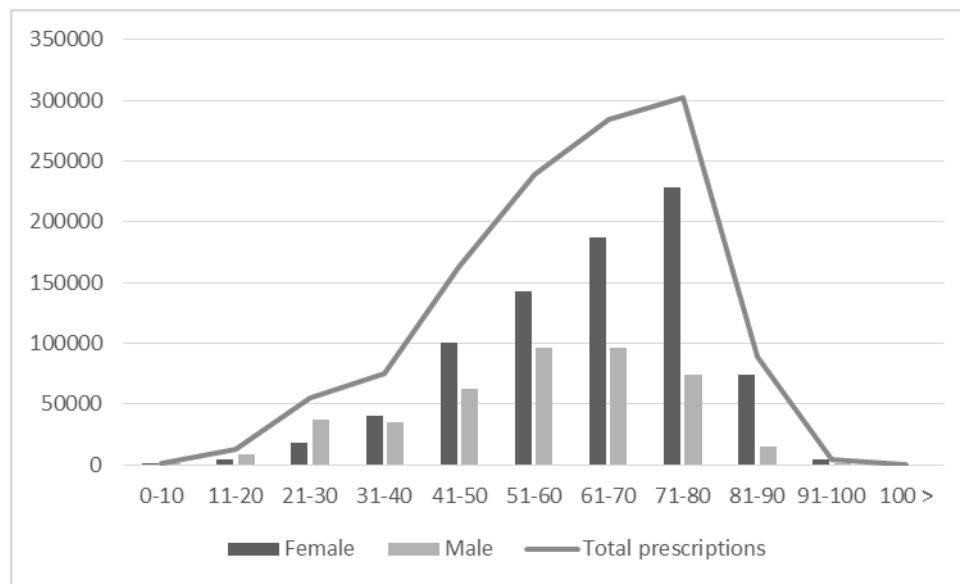


Figure 2. Number of Prescriptions of Zolpidem by Gender and Age Groups

3.3 Prescription of Zolpidem in Slovenian Regions

Based on the analysis of the prescriptions and use of zolpidem in Slovenian regions the highest consumption was observed in the region Osrednjeslovenska, followed by the regions Podravska and Savinjska. The lowest consumption of zolpidem was observed in regions Koroska, Zasavska, Spodnjeposavska and Notranjsko-Kraska. Prescriptions in three urban regions (Osrednjeslovenska, Podravska and Savinjska) represent 54.35% of all zolpidem prescriptions.

3.4 Prescription of Zolpidem by Months

Data also revealed big differences in the prescription of zolpidem by months of the year. The highest numbers of prescriptions were issued in January (104.190), March (104.130) and September (103.840). In summer time (June 95.250, July 94.130, August 92.780 prescriptions) and in February (92.340 prescriptions) the number of prescriptions for zolpidem was lower.

3.5 Statistical Analysis

Determination of the statistical significance of the prescription of zolpidem in patients aged 55 years or more was one of the aims of the present study. Data revealed that zolpidem was used in greater extent in patients aged 55 years or older. Patients younger than 55 years received 365.542 (29.87%) prescriptions in comparison with patients aged 55 years or more who received 858.195 prescriptions (70.13%).

The statistical significance of prescription of zolpidem by gender was analysed using Pearsons χ^2 test; the whole population was tested (Table 1).

Table 1. Pearson χ^2 Test between Variables Age and Prescription of Zolpidem

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3256,633 ^a	1	,000		
Continuity Correction ^b	3256,512	1	,000		
Likelihood Ratio	3227,504	1	,000		
Fisher's Exact Test				,000	,000
Linear-by-Linear Association	3256,632	1	,000		
N of Valid Cases	7365699				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 397454.76.

b. Computed only for a 2 x 2 table.

The significance of the Pearson χ^2 test was 0.000, meaning $p < 0.05$. In the whole population the relationship between these two variables was statistically significant. The results confirmed that the consumption of zolpidem was statistically significantly higher in women than in men.

4. Discussion

The newer sedative hypnotics that are not benzodiazepines are rapidly becoming the first line treatment for insomnia. Among three non-benzodiazepine sedative hypnotics agents (Z drugs) that are available, zaleplon, zopiclone and zolpidem (Stahl, 2000), only latest is available in Slovenia. The sole indication for zolpidem is short-term treatment of insomnia (Kaplan & Sandock, 1996). Zolpidem shares the ideal profile of a sedative-hypnotic agent (Stahl, 2000). As hypnotic it decreases time to sleep and increases total sleep time and efficiency but does not affect sleep architecture, has a rapid onset of action and a short duration (6-8 hours) of action (Bazire, 2003). Zolpidem has a longer than usual half-life in the elderly and in case of prolonged use a potential of abuse as tolerance and dependence may occur (Kaplan & Sandock, 1996).

Insomnia can be secondary to a psychiatric or general medical condition, to a medication or to drugs of abuse, but also to a stress or to circadian rhythm disturbances. However, the complaint of insomnia in the general population and the demand of outpatient treatment is widespread (Stahl, 2000). Nearly one third of adults report difficulty falling asleep, difficulty maintaining sleep, or non-restorative sleep (Di Bonaventura et al., 2015; Morin et al., 2006). In cases where sleep disorder is secondary to a medical or psychiatric disorder treating the primary condition often relieves the insomnia, and hypnotics can be avoided. In cases where the underlying disorder is not treatable or there is a need to relieve insomnia before underlying disorder can be relieved or insomnia cannot be adequately treated it may be necessary to treat insomnia symptomatically with sedative-hypnotic agent (Stahl, 2000).

Women report more sleep problems than men (Driver, 2012; Jehan et al., 2015). Similarly, in this study the outpatient prescription of zolpidem was significantly more frequent in women, 65.3% of all

prescription of zolpidem were prescribed to women, while the proportion women to men decreased in 2009-2014 period. Data from literature show that sleep disturbances increase with age in both genders and it is more common in older population when compared to their younger counterparts (Guidozzi, 2015). Present data show that in Slovenia zolpidem was prescribed in 70% of cases to people older than 55 years, significantly more frequent than to those younger than 55 years.

Besides zolpidem's N05CF subgroup, hypnotics and sedatives are classified also in subgroups of N05CA (in 2009-2014 period there were no cases of prescribed medicines from this subgroup in Slovenia) and N05CD with benzodiazepine hypnotics. Prescription of benzodiazepine hypnotics in the observed period decreased. Similarly as for anxiolytics (most prescribed medicinal products among psycholeptics) in Slovenia also overall prescription in hypnotics in 2009-2014 period decreased (from 54.043 prescriptions in 2009 to 35.237 prescriptions in 2014). Anxiolytics and hypnotics both were more frequently prescribed to women than men, but prescription and ratio women to men of DID of medicines both decreased in 2009-2014 period.

The highest number of zolpidem prescriptions was observed in women in the age groups from 51-60 years to 71-80 years, while in both genders the frequencies in prescription of zolpidem increased with age. The results of the present analysis are consistent with results of the study regarding behavioral habits and health of the inhabitants in Slovenia which was conducted in 2012; elderly people, aged 55-64 years and older take more sedatives and hypnotics than people aged 53 or less. In the same study it was also observed that Slovenian women take significantly more medicines from the group of sedatives and hypnotics than men. However, numbers of prescriptions were not analysed (Tomsic et al., 2014).

Study showed large variations in prescription of zolpidem regarding the Slovenian regions as the highest consumption was observed in the regions Osrednjeslovenska, Podravska and Savinjska, where three major towns in the country are concentrated. In regions Koroska, Zasavska, Spodnjeposavska and Notranjsko-Kraska the lowest consumption of zolpidem was observed. The differences in prescription could be associated with the different availability and inequality in medical treatment (major towns vs rural regions).

Data also revealed big differences in the prescription of zolpidem by months of the year; in January, March and September the highest numbers of prescriptions were issued. On contrary, in summer time and in February the lowest number of prescriptions was issued. Seasonality seems to influence sleep fluctuation throughout seasons. Differences in prescription of zolpidem by months could be related to different photoperiod, which is the variability of hours of light throughout seasons what means summer with longest photoperiod seasons and winter with shortest photoperiod (Brambilla et al., 2015). Some authors revealed that this phenomenon could be influenced by seasonality in sleep timing, dark period and brighter photoperiods (Friborg et al., 2014). There is very little data available in the literature regarding prescription of zolpidem by seasons/months.

Hypnotic drugs are frequently used to treat insomnia with symptoms such as difficulty falling asleep or

staying asleep, awaking too early in the morning, and disturbance in sleep quality. However, these drugs have been associated with several adverse reactions, including alteration of sleep architecture, nightmares, agitation, confusion, lethargy, withdrawal, and a risk of dependence and abuse (Obayashi et al., 2013). Zolpidem has a significant dependence and abuse potential and its misuse was described (Victorri-Vigneau et al., 2014; Kapil et al., 2014). In Slovenia medicines for the diseases of the nervous system are among the most frequently used substances for the commitment of suicide and zolpidem is one of them (Leban & Brvar, 2015). It was also confirmed that use of non-benzodiazepine sedative-hypnotics in the elderly is associated with an increased risk of falls (Diem et al., 2014). A considerable number of accidental falls occur when a patient wakes because of a micturition urge during night. Thus, for patients with insomnia, it is important to select a hypnotic with a short half-life to avoid excessive suppression of psychomotor activity after sleeping (Olubodun et al., 2003). The newest generation of sleep-aid drugs, the non-benzodiazepine hypnotics such as zolpidem, was developed to overcome some of these disadvantages. In fact, short-acting non-benzodiazepines are known to be relatively safe hypnotics and are widely used to treat difficulty in falling asleep (Obayashi et al., 2013). Zolpidem has short elimination half-life and carries the low risk of falling. The maximum plasma concentration of zolpidem is reached 1.5 h after dosing (Olubodun et al., 2003). However, it was reported that zolpidem, which was expected to be less connected with effects such as fractures in the elderly increases the risk of fractures by 1.7 times. Amnesia, somnambulism, nocturnal eating and driving are rare unusual complex behaviors/side effects described in patients treated with zolpidem (Hoque & Chesson, 2009).

For patients over 65 years an initial dose of 5 mg of zolpidem is advised and prolonged use of zolpidem is not recommended (Kaplan & Sandock, 1996). Therefore, when prescribing zolpidem as sleeping pills to older insomnia patients, it is necessary to be aware of this risk, and the patients should be warned and educated (Kang et al., 2012).

4.1 Limitations

Only outpatients prescription were included in the study because it is not possible to include hospital data. The duration of prescription was not followed up, the prescribed dosage was assessed by standard unit (DID) and it was not assessed if insomnia was primary or secondary to health condition.

5. Conclusion

On the basis of the results of this first study to assess outpatient prescription of Z drugs and trends in the pharmacological treatment of insomnia with zolpidem in Slovenia it is possible to conclude that the guidelines for the treatment of insomnia in Slovenia are strictly respected.

Prescription of non-benzodiazepine hypnotics in Slovenia decreases, the decrease is even greater in the group of benzodiazepine hypnotics. People older than 55 years received significantly more prescriptions of zolpidem in comparison with younger people in the observed period; the prescription of zolpidem was present in much greater extent in women.

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