

Good Practice for Outpatient Prescription of Zolpidem in Slovenia from 2008 to 2016

Scientific article

UDC 616.8-009.836+615

KEY WORDS: zolpidem, older people, medication prescription, gender, insomnia

ABSTRACT - The aim of this study was to analyse the outpatient prescription of widely used hypnotic zolpidem in Slovenia in the period from 2008 to 2016 by gender and age, to present the trends, and to analyse the prescription in Slovenian regions. 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. Compiled anonymised data were processed by means of descriptive statistics, contingency tables, correlation, Pearson χ^2 test, ANOVA and linear regression. Results showed that zolpidem was prescribed mostly to women; the highest number of prescriptions were prescribed to women in the age groups 51 - 60 and 71 - 80 years. Patients younger than 55 years received only 29.87% of prescriptions in comparison with patients older than 55 years, who received 70.13% of all prescriptions. Data revealed differences in prescription by age, gender and Slovenian regions. Prescription of zolpidem has been in constant decrease since 2012, which is an example of good practice indicating that the guidelines for the treatment of insomnia in Slovenia are respected.

Znanstveni članek

UDK 616.8-009.836+615

KLJUČNE BESEDE: zolpidem, starostniki, predpisovanje zdravil, spol, nespečnost

POVZETEK - Namen pričujoče raziskave je bil analizirati ambulantno predpisovanje v Sloveniji pogosto uporabljanega hipnotika zolpidema v obdobju od 2008 do 2016 po spolu in starosti, prikazati trende predpisovanja ter predpisovanje po regijah. Ne-benzodiazepinski hipnotiki so bili klasificirani po Anatomsko terapevtsko kemijski klasifikaciji (ATC) WHO; določeni so bili definirani dnevni odmerki (DDD) zdravil na 1000 prebivalcev na dan. Zbrani anonimizirani podatki so bili obdelani z deskriptivno statistiko, za analizo so bile narejene kontingenčne tabele, korelacija, Pearsonov test χ^2 , ANOVA in linearna regresija. Zolpidem je bil v glavnem predpisan ženskam; največ receptov so prejele ženske v starostnih skupinah od 52 do 60 ter od 71 do 80 let. Pacienti, mlajši od 55 let, so prejeli 29,87 % receptov v primerjavi s pacienti, starejšimi od 55 let, ki so prejeli 70,13 % vseh receptov. Ugotovili smo, da so starejši od 55 let in ženske prejeli značilno več receptov za zolpidem. Analiza je pokazala razlike v predpisovanju zolpidema, razen po starosti in spolu, tudi po slovenskih regijah. Predpisovanje zolpidema je v konstantnem upadu od leta 2012, kar je primer dobre prakse in odraz upoštevanja smernic za zdravljenje nespečnosti.

1 Introduction

Demographic ageing is considered to be one of the most serious challenges in the European Union, including Slovenia (Agren & Berensson, 2006). Sleep problems are common in older people, and the prevalence of insomnia increases with age. Older people often find it more difficult to fall asleep, have more fragmented sleep and wake up earlier (Kang et al., 2012; Bliwise, 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 older people 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. Nonpharmacological or pharmacological therapies may be used to achieve these goals (Wong & Nguyen, 2014). Pharmacological 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). Nonpharmacological treatment options include cognitive-behavioural therapy, which involves various behavioural 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 gamma-aminobutyric acid (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 as well as cognitive function after the night-time administration that may persist into next day (Kang et al., 2012; Bogan, 2008).

However, in older insomnia patients zolpidem could increase the risk of fractures, therefore it should be prescribed carefully and the older patients 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 aged 80 years or older without cognitive or mental complications (Kajiwara et al., 2015).

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

Monitoring of medication consumption helps to identify its medical, economic and social consequences. Knowledge and understanding of information on the prescription data is crucial for the adoption of measures (Jelenc, 2013; Kostnapfel Rihtar & Albreht, 2017).

The aim of the present study was to analyse the prescription of zolpidem in Slovenia in the period from 2008 to 2016, with the emphasis on overall trends as well as differences in prescription: by gender, by age and by different Slovenian regions. The study was also aimed towards comparing the prescription of zolpidem to people older than 55 years with their younger counterpart, and according to gender.

2 Methodology

2.1 Data Source

The used source for this retrospective observational analysis originates from 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 2008 to 2016. All prescriptions reported from the pharmacies were analysed. Data were collected according to the Databases act in the area of health care (Official Gazette, 2000). The consent from the Republic Ethic Committee was not needed because the data used were anonymised.

2.2 ATC Classification

The presented medication 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 medications for the nervous system (group N) are divided into seven groups (N01 - N07). Psycholeptics represent the group N05, which is divided into 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 and statistical regions in Slovenia. Statistical software IBM SPSS Statistics version 21 for windows (SPSS Inc.) was used for data analysis. Compiled data were processed by means of descriptive statistics, contingency tables, correlation, Pearson's 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 2008 to 2016, 1,795,874 prescriptions for zolpidem were issued; it was mostly prescribed to women (1,171,625 prescriptions; 65.23%). Men received 624,249 prescriptions (34.77%). Regarding the number of DID for zolpidem, the highest value was observed in women in 2011 (15.70 DID), and the lowest in men in 2016 (7.25 DID). In women the number of DID for zolpidem slightly increased from 2008 to 2011 (15.32 to 15.70 DID), and then decreased to 12.81 DID in 2016. In men, however, the number of DID for zolpidem increased from 7.51 DID in 2008 to 8.49 DID in 2012 and then decreased to 7.25 in 2016. 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 2008 to 2016 by gender, DID and predictions for 2017 and 2018 are shown in Figure 1.

Figure 1: Prescription of zolpidem by gender and DID in Slovenia from 2008 to 2016, including predictions for 2017 and 2018

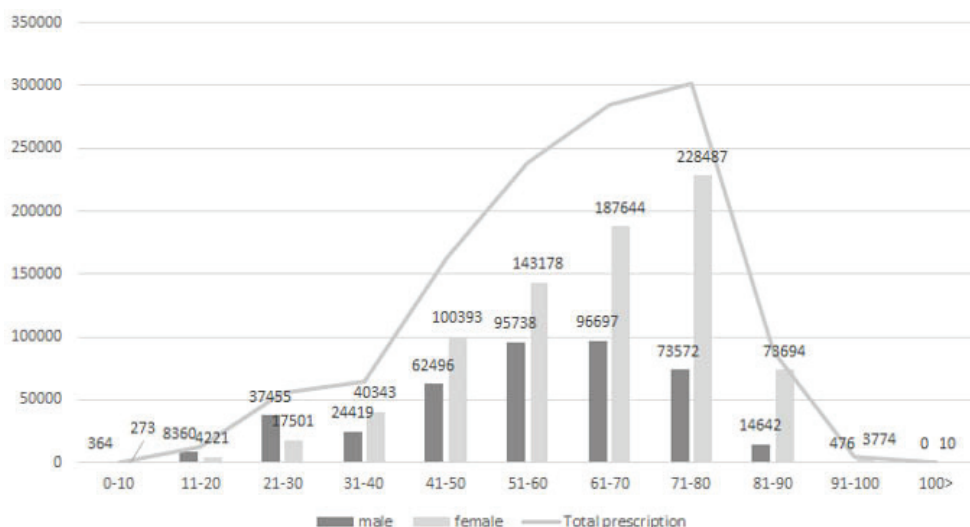


3.2 Prescription of Zolpidem by Gender and Age

In the observed period, the prescription of zolpidem was present in greater extent in women, however, it has been in constant decrease since 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 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 from 2008 to 2016



The costs of zolpidem prescriptions decreased from 1,903,865 EUR in 2008 to 1,407,319 EUR in 2016.

3.3 Prescription of Zolpidem in Slovenian Regions

Based on the analysis and use of zolpidem as defined daily dose in Slovenian regions in 2016, the highest consumption was observed in the region Osrednjeslovenska (1,629,980 DDD), followed by the regions Podravska (1,404,170 DDD) and Savinjska (963,430 DDD).

The highest consumption of zolpidem in DID was observed in regions Primorsko – Notranjska (14.8 DID), Pomurska (14.0 DID) and Podravska (12.0 DID), followed by Savinjska (10.4 DID) and Goriška region (10.3 DID).

3.4 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 Pearson's χ^2 test; the whole population was tested (Table 1).

Table 1: Pearson's χ^2 test between variables gender and prescription of zolpidem

	<i>Value</i>	<i>df</i>	<i>Asymp. Sig. (2-sided)</i>	<i>Exact Sig. (2-sided)</i>	<i>Exact Sig. (1-sided)</i>
<i>Pearson Chi-Square</i>	3256.633a	1	.000		
<i>Continuity Correction^b</i>	3256.512	1	.000		
<i>Likelihood Ratio</i>	3227.504	1	.000		
<i>Fisher's Exact Test</i>				.000	.000
<i>Linear-by-Linear Association</i>	3256.632	1	.000		
<i>N of Valid Cases</i>	7365699				

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

b. Computed only for a 2x2 table

The significance of the Pearson's 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) available, i.e. zaleplon, zopiclone and zolpidem (Stahl, 2000), only the latter is available in Slovenia. The sole indication for zolpidem is a 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 older people, 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 some medication or drug abuse, but also to stress or to cardiac 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 of women to men decreased in the period from 2008 - 2016. Data from the literature show that sleep disturbances increase with age in both genders and are 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 frequently than to those younger than 55 years.

Besides zolpidem's N05CF subgroup, hypnotics and sedatives are classified also in subgroups of N05CA (in 2008-2016 period there were no cases of prescribed medications from this subgroup in Slovenia) and N05CD with benzodiazepine hypnotics. Prescription of benzodiazepine hypnotics in the observed period decreased. Similarly, for anxiolytics (the most prescribed medicinal products among psycholeptics) the overall prescription of hypnotics in 2008 - 2016 period also decreased in Slovenia (from 54,043 prescriptions in 2008 to 35,237 prescriptions in 2016). Anxiolytics and hypnotics were both more frequently prescribed to women than men, but prescription and ratio of women to men of DID of medications both decreased in 2008 - 2016 period (Int Data, 2017).

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

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 disturbances 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, medications for treating 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 the use of non-benzodiazepine sedative-hypnotics in older people is associated with an increased risk of falls (Diem et al., 2014). A considerable number of accidental falls occur when patients wake up due to 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-benzodia-

zepine 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 older people, increases the risk of fractures by 1.7 times. Amnesia, somnambulism, nocturnal eating and driving are rare unusual complex behaviours/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 hospital data had not yet been available. The duration of prescription was not followed up.

5 Conclusion

On the basis of the results of this first study to assess the outpatient prescription of Z drugs and trends in the pharmacological treatment of insomnia with zolpidem in Slovenia, it is possible to conclude that the prescription of zolpidem has been in constant decrease since 2012, which is an example of good practice and indicates that the guidelines for the treatment of insomnia in Slovenia are 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.

Dr. Marjetka Jelenc, dr. Tatja Kostnapfel, dr. Branko Gabrovec, dr. Barbara Lovrečič, Aleš Korošec, dr. Mercedes Lovrečič

Primer dobre prakse ambulantnega predpisovanja zolpidema v Sloveniji v obdobju 2008-2016

Demografsko staranje predstavlja enega najresnejših izzivov, s katerim se srečuje Evropska unija, vključno s Slovenijo (Agren in Berensson, 2006). Pri starejših so težave s spanjem pogoste in prevalenca nespečnosti raste s starostjo. Starejši ljudje

pogosto potrebujejo več časa, da zaspijo, njihov spanec je fragmentiran in prebujajo se bolj zgodaj (Kang idr., 2012; Bliwise, 2005). Dodatno so psihična ovira za spanje kronične bolezni, invalidnost in okvare, ki povzročajo bolečino in neudobje ponoči (Stewart idr., 2006). Starostno nespečnost povezujejo tudi z dnevnimi dremeži (Munch idr., 2005).

Med najpogostejše motnje spanja spada nespečnost. Kar 25 % odrasle populacije navaja težave s spanjem, 6–10 % le-teh zadostuje diagnostičnim kriterijem za kronično nespečnost (Morin idr., 2014). Nespečnost pomeni nezmožnost zaspati, spati ali doseči spanje, v katerem se spočijemo (Schutte-Rodin idr., 2008). Prevalenca nespečnosti je večja pri starejših, pri katerih se pojavljajo tudi negativni učinki, kot so zmanjšana dnevna funkcija in zmanjšana kakovost življenja (McCall, 2004). Nespečnost se lahko pojavi tudi zaradi drugega medicinskega stanja ali duševne motnje (komorbidna nespečnost), lahko pa se pojavi samostojno (primarna nespečnost) (MacFarlane idr., 2014).

Med spoloma obstajajo glede motenj spanja pomembne razlike. Ženske imajo v primerjavi z moškimi večjo kakovost spanja, z daljšim spancem, krajšo latentnostjo in večjo učinkovitostjo spanja. Kljub temu se ženske pogosteje pritožujejo nad spanjem (Krishnan in Collop, 2006).

Primarni cilj upravljanja nespečnosti je v izboljšanju kakovosti in količine spanja ter povezanih dnevnih funkcij. Nefarmakološke in farmakološke terapije se lahko uporabijo za doseganje teh ciljev (Wong in Nguyen, 2014). Eno izmed najpogostejše predpisanih zdravil za zdravljenje nespečnosti je zolpidem (MacFarlane idr., 2014). Njegove značilnosti so nizka toleranca, hitra indukcija spanja (ponavadi v 15 minutah) in kratka razpolovna doba (2 do 3 ure), kar zmanjšuje učinke težke glave ter okvare psihomotorne in kognitivne funkcije (Kang idr., 2012; Bogan, 2008).

Kljub temu lahko pri starejših, ki trpijo za nespečnostjo, zolpidem prispeva k povečanim tveganjem za zlome; zato sta potrebni previdnost pri predpisovanju zolpidema ter podučitev bolnikov o njegovi uporabi in učinkih (Kang idr., 2012; Lin idr., 2014). Zolpidem se lahko v manjših odmerkih varno predpisuje tudi starejšim od 80 let brez kognitivnih in duševnih zapletov (Kajiwara idr., 2015).

V raziskavi o vedenju in navadah prebivalcev Slovenije, ki je bila opravljena v letu 2012 je bilo na področju jemanja zdravil ugotovljeno, da starejši ljudje zaužijejo več sedativov in hipnotikov kot mlajši (Tomšič idr., 2014). Spremljanje porabe zdravil pomaga identificirati medicinske, ekonomske in socialne posledice jemanja zdravil. Poznavanje in razumevanje informacij o predpisovanju zdravil je ključno za sprejemanje ukrepov (Jelenc, 2013; Kostnapfel Rihtar in Albreht, 2017).

Namen pričujoče raziskave je bil analizirati predpisovanje zolpidema v Sloveniji v časovnem obdobju od 2008 do 2016 s poudarkom na trendu predpisovanja ter razlikah v predpisovanju po spolu, starosti in regijah. V pričujoči raziskavi smo primerjali tudi predpisovanje zolpidema po starosti (starejši od 55 let in mlajši) ter analizirali predpisovanje po spolu.

Metodološko gre za retrospektivno analizo, za katero so bili uporabljeni podatki iz baze Nacionalnega inštituta za javno zdravje »Evidenca porabe zdravil, izdanih na recept«. Analiza je zajemala podatke o številu predpisanih receptov za nebenzodiazepinske hipnotike, s poudarkom na zolpidemu v letih od 2008 do 2016. Soglasje Etične komisije ni bilo potrebno, saj so bili podatki anonimizirani. Podatki so bili izračunani glede na definirane dnevne odmerke na 1000 prebivalcev. Za analizo je bil uporabljen statistični program »IBM SPSS Statistics version 21 for windows« (SPSS Inc., Chicago, IL, USA). Uporabili smo deskriptivno statistiko, kontingenčne tabele, korelacijo, Pearsonov test χ^2 , ANOVO in linearno regresijo. Statistična pomembnost je bila določena pri $p < 0,05$.

Rezultati v analiziranem obdobju kažejo na večje predpisovanje zolpidema ženskam, a to predpisovanje od leta 2012 upada, medtem ko smo v istem obdobju pri moških opazili manjše povečanje predpisovanja. Najpogosteje je bil zolpidem predpisan ženskam v starostnih skupinah 51-60 in 71-80 let.

Ugotovili smo statistično večje predpisovanje zolpidema starejšim od 55 let. Pacienti, mlajši od 55 let, so prejeli 29,87 % receptov, pacienti, starejši od 55 let, pa kar 70,13 % vseh receptov. Statistično pomembno več zolpidema prejemajo ženske v primerjavi z moškimi. Dobljeni rezultati so skladni z rezultati raziskave o vedenjskih navadah in zdravju prebivalcev Slovenije, ki je bila opravljena v letu 2012; ljudje v starostni skupini 55-64 let jemljejo več sedativov in hipnotikov kot mlajši od 55 let. V isti raziskavi je bilo ugotovljeno, da ženske v Sloveniji jemljejo pomembno več zdravil iz skupin sedativov in hipnotikov kot moški (Tomšič idr., 2014).

Novi sedativni hipnotiki, ki niso benzodiazepini, postajajo prva izbira zdravljenja nespečnosti. Med tremi nebenzodiazepinskimi zdravili (zaleplon, zopiclone in zolpidem) (Stahl, 2000) je v Sloveniji na voljo le slednji. Edina indikacija za uporabo zolpidema je kratkoročno zdravljenje nespečnosti (Kaplan in Sandock, 1996). Zolpidem ima kot sedativni hipnotik idealni profil (Stahl, 2000). Kot hipnotik zmanjša čas, ki je potreben za spanec, ne vpliva na arhitekturo spanja, hitro učinkuje in ima kratek učinek (6-8 ur) (Bazire, 2003). Nespečnost pa je lahko tudi sekundarna, posledica psihiatričnega ali splošno medicinskega stanja, zdravil ali zlorabe zdravil, stresa ali motenj srčnega ritma. Pritoževanje nad težavami, povezanimi z nespečnostjo, je v splošni populaciji pogosto (Stahl, 2000). Skoraj tretjina odraslih poroča, da težko zaspi in težko ohrani spanec, sploh krepčilen spanec (Di Bonaventura idr., 2015, Morin idr., 2006).

V primerih, kjer je motnja spanja sekundarna glede na splošnomedicinsko ali psihiatrično stanje, zdravljenje primarnega stanja pogosto omili nespečnost, pri čemer hipnotikov ni potrebno uporabiti. V primerih, kjer osnovno zdravstveno stanje ne omogoča zdravljenja in je izražena potreba po zdravljenju nespečnosti pred zdravljenjem osnovne bolezni, pa je treba zdraviti težave zaradi nespečnosti simptomatsko, s sedativnimi hipnotiki (Stahl, 2000).

Ženske pogosteje poročajo o motnjah spanja kot moški (Driver, 2012; Jehan idr., 2015). V pričujoči raziskavi smo potrdili, da je ženskam predpisano statistično pomembno več zolpidema kot moškim (65,3 %), čeprav se je v letih 2008-2016 poraba zolpidema za ženske v primerjavi z moškimi zniževala.

Guidozzi (2015) navaja, da podatki iz literature kažejo, da se motnje spanja z leti povečujejo pri obeh spolih. Naši podatki kažejo, da je zolpidem predpisan v kar 70 % starejšim od 55 let.

Ugotovili smo, da je prišlo v obdobju 2008-2016 do upada predpisovanja benzodiazepinov in anksiolitikov ter tudi hipnotikov (od 54.043 receptov v 2008 na 35.237 receptov v letu 2016). Anksiolitiki in hipnotiki so bili pogosteje predpisani ženskam, a je njihovo število v primerjavi z moškimi v opazovanem obdobju upadalo.

Zdravila iz skupine hipnotikov se uporabljajo za zdravljenje nespečnosti pri bolnikih s simptomi, kot so: težava zaspati ali ohraniti spanec, prezgodnje prebujanje in motnje v kvaliteti spanca. Ta zdravila pa so povezana z nekaterimi negativnimi učinki, ki vključujejo spremembo spalne arhitekture, nočne more, agitacije, zmedo, letargijo, odtegnitveni sindrom, ter nevarnost odvisnosti in zlorabe (Obayashi idr., 2013). Tudi zolpidem lahko privede do odvisnosti, prav tako ga lahko zlorablamo, njegova napačna uporaba je že opisana (Victorri-Vigneau idr., 2014, Kapil idr., 2014). V Sloveniji so kot sredstvo za samomore najpogosteje uporabljana zdravila z delovanjem na živčevje in zolpidem je eno izmed njih (Leban in Brvar, 2015). Ugotovljeno je bilo tudi, da so nebenzodiazepinski sedativni hipnotiki pri starejših povezani s povečanim tveganjem za padce (Diem idr., 2014). Do znatnega števila padcev pride, ko se pacienti ponoči zbudijo zaradi potrebe po uriniranju; za starejše paciente z nespečnostjo je zato treba izbirati hipnotik s kratko razpolovno dobo, da se izognemo pretirani supresiji psihomotorike (Olubodun idr., 2003). Nove generacije zdravil za zdravljenje nespečnosti, nebenzodiazepinski hipnotiki, kot npr. zolpidem, so bile razvite za premagovanje teh slabosti. Namreč, za nebenzodiazepinska zdravila s kratko razpolovno dobo je znano, da so relativno varni hipnotiki in široko uporabljani za zdravljenje težav s spanjem (Obayashi idr., 2013). Zolpidem ima kratko razpolovno dobo in ima zato manjši rizik za padce. Največja koncentracija zolpidema v krvi je dosežena uro in pol po zaužitju (Olubodun idr., 2003).

Glede na rezultate pričujoče raziskave o ambulantnem predpisovanju zolpidema in trendov v farmakološkem zdravljenju nespečnosti z zolpidemom v Sloveniji lahko zaključimo, da je upad predpisovanja zolpidema primer dobre prakse in kaže na dosledno upoštevanje smernic za zdravljenje nespečnosti.

LITERATURE

1. Agren, G. and Berensson, K. (2006). Healthy ageing. A challenge for Europe. The Swedish National Institute of Public Health, pp. 8–11.
2. Bazire, S. (2003). Psychotropic drug directory 2003/2004. The professionals' pocket handbook & aide memoire. London: The Both Press.
3. Bliwise, D. L. (2005). Normal aging. In: Kryger, M. H., Roth, T. and Dement, W. C. (eds.). Principles and practice of sleep medicine. 4th ed. Philadelphia, PA: Elsevier Saunders, pp. 24–38.
4. Bogan, R. K. (2008). Treatment options for insomnia: pharmacodynamics of zolpidem extended-release to benefit next-day performance. *Postgrad Med*, 120, No. 3, pp. 161–171.
5. Databases act in the area of healthcare (2000). Official Gazette no. 65/00. Retrieved on 08/11/2015 from the internet: <http://www.pisrs.si/Pis.web/pregledPredpisa?id=ZAKO1419>.

6. Di Bonaventura, M., Richard, L., Kumar, M., Forsythe, A., Flores, N. M. and Moline, M. (2015). The association between insomnia and insomnia treatment side effects on health status, work productivity, and healthcare resource use. Retrieved on 12/07/2015 from the internet: <http://www.plosone.org/article/abstract.action?uri=info:doi/10.1371/journal.pone.0137117&representation=PDF>.
7. Diem, S. J., Ewing, S. K., Stone, K. L., Ancoli-Israel, S., Redline, S. and Ensrud, K. E. (2014). Use of non-benzodiazepine sedative hypnotics and risk of falls in older men. *J Gerontol Geriatr Res*, 3, No. 3, pp. 158–171.
8. Driver, H. S. (2012). Gender differences in sleep. In: Morin, C. M. and Espie, C. A. (eds.). *Oxford Handbook of Sleep and Sleep Disorders*. 1st ed. Oxford: Oxford University Press. pp. 266–288.
9. Guidozzi, F. (2015). Gender differences in sleep in older men and women. *Climacteric*, 18, No. 5, pp. 715–721.
10. Hoque, R. and Chesson, A. (2009). Zolpidem-induced sleepwalking, sleep related eating disorder, and sleep-driving: fluorine-18-fluorodeoxyglucose positron emission tomography analysis, and a literature review of other unexpected clinical effects of zolpidem. *J Clin Sleep Med*, 5, No. 5, pp. 471–476.
11. Internal data. National Institute of Public Health. Ljubljana, 2017.
12. Jehan, S., Masters-Isarilov, A., Salifu, I., Zizi, F., Jean-Louis, G., Pandi-Perumal, S. R., Gupta, R., Brzezinski, A. and McFarlane, S. I. (2015). Sleep Disorders in Postmenopausal Women. Retrieved on 12/02/2015 from the internet: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4621258/pdf/nihms724718.pdf>.
13. Jelenc, M. (2013). Characteristics of prescriptions of medicines for patients with the highest number of prescriptions in Slovenia in 2011. Diploma thesis. Ljubljana, Medical Faculty.
14. Kajiwara, A., Yamamura, M., Murase, M., Koda, H., Hirota, S., Ishizuka, T., Morita, K., Oniki, K., Saruwatari, J. and Nakagawa, K. (2015). *Aging Ment Health*, 14, pp. 1–5.
15. Kang, D. Y., Park, S., Rhee, C. W., Kim, Y. , Choi, N. K., Lee, J. and Park, B. J. (2012). Zolpidem use and risk of fracture in elderly insomnia patients. *J Prev Med Pub Health*, 45, pp. 219–226.
16. Kapil, V., Green, J. L., Le Lait, C., Wood, D. M. and Dargan, P. I. (2014). Misuse of benzodiazepines and Z-drugs in the UK. *Br J Psychiatry*, 205, No. 5, pp. 407–408.
17. Kaplan, H. I. and Sandock, B. J. (1996). *Pocket handbook of psychiatric drug treatment*. 2nd ed. Baltimore: Williams & Wilkins.
18. Kostnapfel Rihtar, T. and Albreht, T. (Eds.) (2017). The consumption of medicines in Slovenia in 2016. National Institute of Public Health. Retrieved on 05/09/2017 from the internet: <http://www.nijz.si/sl/publikacije/poraba-zdravil-v-sloveniji-v-letu-2016>.
19. Krishnan, V. and Collop, N. A. (2006). Gender differences in sleep disorders. *Curr Opin Pulm Med*, 12, No. 6, pp. 383–389.
20. Leban, V. and Brvar, M. (2015). Drug poisoning. *Farm Vestn*, 66, pp. 306–312.
21. Lin, F. Y., Chen, P. C., Liao, C. H., Hsieh, Y. W. and Sung, F. C. (2014). Retrospective population cohort study on hip fracture risk associated with zolpidem medication. *Sleep*, 37, No. 4, pp. 673–679.
22. MacFarlane, J., Morin, C. M. and Montplaisir J. (2014). Hypnotics in insomnia: the experience of zolpidem. *Clinical Therapeutics*, 36, No. 11, pp. 1676–1701.
23. McCall, W. V. (2004). Sleep in the elderly: burden, diagnosis, and treatment. *Prim Care Companion J Clin Psychiatry*, 6, pp. 9–20.
24. Morin, C. M., Beaulieu-Bonneau, S., Ivers, H., Vallieres, A., Guay, B., Savard, J. and Merette, C. (2014). Speed and trajectory of changes of insomnia symptoms during acute treatment with cognitive-behavioral therapy, singly and combined with medication. *Sleep medicine*, 15, pp. 701–707.
25. Morin, C. M., LeBlanc, M., Daley, M., Gregoire J. P. and Mérette, C. (2006). Epidemiology of insomnia: Prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep Med*, 7, pp. 123–130.
26. Munch, M., Cajochen, C. and Wirz-Justice, A. (2005). Sleep and circadian rhythms in ageing. *Zeitschrift für Gerontologie und Geriatrie*, 38, pp. 121–123.

27. Obayashi, K., Araki, T., Nakamura, K., Kurabayashi, M., Nojima, Y., Hara, K., Nakamura, T. and Yamamoto, K. (2013). Risk of falling and hypnotic drugs: Retrospective study of inpatients. *Drugs*, 13, pp. 159–164.
28. Olubodun, J. O., Ochs, H. R., von Moltke, L. L., Roubenoff, R., Hesse, L. M., Harmatz, J. S., Shader, R. I. and Greenblatt, D. J. (2003). Pharmacokinetic properties of zolpidem in elderly and young adults: possible modulation by testosterone in men. *Br J Clin Pharmacol*, 56, pp. 297–304.
29. Schutte-Rodin, S., Broch, L., Buysse, D., Dorsey, C. and Sateia, M. (2008). Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*, 4, pp. 487–504.
30. Stahl, S. M. (2000). *Essential psychopharmacology: neuroscientific basis and practical applications*. 2nd edition. USA: Cambridge University Press.
31. Stewart, R., Besset, A. and Bebbington, R. et al. (2006). Insomnia comorbidity and impact and hypnotic use by age group in a national survey population aged 16 to 74. *Sleep*, pp. 1391–1397.
32. Tomšič, S., Kofol Bric, T., Korošec, A. and Maučec Zakotnik, J. (2014). Challenges in improving behaviour and health. CINDI Project. Ljubljana, NIPH.
33. Victorri-Vigneau, C., Gerardin, M., Rousselet, M., Guerlais, M., Grall-Bronnec, M. and Jolliet P. (2014). An update on zolpidem abuse and dependence. *J Addict Dis*, 33, No.1, pp. 15–23.
34. Wong, E. and Nguyen, T. V. (2014). Zolpidem use in the elderly and recent safety data. *J Nurse Practitioners*, 10, No. 2, pp. 140–141.
35. World Health Organization Collaborating Centre for Drug Statistics Methodology. DDD Definition and General Considerations. Retrieved on 08/08/2015 from the internet: http://www.whocc.no/ddd/definition_and_general_considera/.

Marjetka Jelenc, PhD, MD, National Institute of Public Health, Ljubljana, Slovenia.

E-mail: marjetka.jelenc@nijz.si

Tatja Kostnapfel, PhD, M. Pharm, National Institute of Public Health, Ljubljana, Slovenia.

E-mail: tatja.kostnapfel@nijz.si

Branko Gabrovec, PhD, MSc, National Institute of Public Health, Ljubljana, Slovenia.

E-mail: branko.gabrovec@nijz.si

Barbara Lovrečič, PhD, MD, National Institute of Public Health, Ljubljana, Slovenia.

E-mail: barbara.lovrecic@nijz.si

Aleš Korošec, BSc, National Institute of Public Health, Ljubljana, Slovenia.

E-mail: ales.korosec@nijz.si

Mercedes Lovrečič, PhD, MD, National Institute of Public Health, Ljubljana, Slovenia.

E-mail: mercedes.lovrecic@nijz.si