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Autoreferát disertační práce



**Evaluation of rationality and risks of  
pharmacotherapy in older patients in long-term  
care facilities**

*Use of benzodiazepines and their potential adverse  
effects in older patients*

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## List of Abbreviations

AE(s)	Adverse effect(s)
ATC	Anatomical Therapeutic and Chemical code
BZD(s)	Benzodiazepine(s)
CI	Confidential Interval
CZ	Czech Republic
CYP	Cytochrome P450
DDD(s)	Defined daily dose(s)
DIS 13	Medicinal product delivery reporting system
interRAI AC	InterRAI Acute Care instrument
interRAI LTCF	InterRAI assessment instrument for Long-Term Care Facilities
IRR	Incidence Rate Ratio
IQR	Interquartile Range
MAH	Marketing Authorisation Holder
NH(s)	Nursing Home(s)
OR	Odds Ratio
PR	Prolonged Release
SD	Standard Deviation
SHELTER	Service and Health in the Elderly project
SUKL	State Institute for Drug Control (Státní ústav pro kontrolu léčiv)
VZP	General Health Insurance Fund (Všeobecná Zdravotní pojišťovna)
UGT	Uridine 5-diphospho-glucuronosyltransferase
US	United States
WHO	World Health Organisation

## **Abstract**

Main objectives of this doctoral thesis were to review available information on pharmacological properties of benzodiazepines (BZDs) and age-related changes; to evaluate the prevalence of BZD use in older patients residing in long term care facilities; to investigate the association between use of BZDs and the occurrence of falls in acutely hospitalized older patients; and to describe utilization of BZDs in the Czech Republic (CZ).

The study of patients in long term care facilities showed excessive BZD use and significant differences in type of BZDs prescribed across countries. Analyses of acutely hospitalized patients showed statistically significant association between use of diazepam and falls compared to other BZDs and in particular compared to oxazepam. The evaluation of BZD prescription in the CZ outlined BZDs utilization and prescription patterns across different age groups.

This doctoral thesis provides theoretical information about pharmacological characteristics, clinical use and risks of BZDs in geriatric population, as well as it outlines results of cross-sectional, outcome and utilization studies performed on real geriatric patients using BZDs.



## Abstrakt

Hlavními cíli této disertační práce bylo uceleně popsat informace dostupné ve vědecké literatuře týkající se farmakologických vlastností benzodiazepinů (BZDs) a změn jejich terapeutické hodnoty vlivem stárnutí organismu; zhodnotit prevalenci použití BZDs u geriatrických pacientů v léčebnách pro dlouhodobě nemocné; analyzovat vztah mezi BZDs a pády v populaci akutně hospitalizovaných geriatrických pacientů a zmapovat vývoj spotřeb a preskripce jednotlivých BZDs v České republice (CZ).

Výsledky šetření u pacientů institucionalizovaných v léčebnách dlouhodobě nemocných ukázaly vysokou prevalenci užití BZDs a statisticky signifikantní rozdíly v typu předepisovaných BZDs v různých zemích. Analýzy databáze akutně hospitalizovaných pacientů prokázaly statisticky významnou asociaci výskytu pádů u uživatelů diazepamu v porovnání s uživateli všech ostatních BZDs a zejména v porovnání s oxazepamem. Analýzy spotřeb BZDs v CZ poskytly údaje o spotřebách a předepisování těchto léčiv v různých věkových skupinách.

Tato disertační práce zahrnuje nejen teoretické vědecké poznatky o farmakologických vlastnostech, klinickém použití a rizicích BZD v terapii geriatrické populace, ale zároveň poskytuje výsledky retrospektivní průřezové analýzy, prospektivní kohortové studie a analýz veřejných databází, které poskytují informace o preskripci, klinickém užití a vývoji spotřeb BZD u geriatrické populace.

## Introduction

BZDs belong to the group of anxiolytics and hypno-sedative drugs. Due to their various properties they are prescribed for a number of conditions including anxiety disorders, insomnia, alcohol withdrawal, depression, and muscle spasm.<sup>1</sup> Since their first introduction in 1960s, there have been about 30 BZDs developed, launched, and used.<sup>2</sup> The use of BZDs in older people in different settings is highly prevalent. In nursing home residents, the prevalence of BZD use ranges from 13% to 54%<sup>3-10</sup>, while in community-dwelling older adults the prevalence reaches up to 38%<sup>11-13</sup>. The pharmacological profile of BZDs in older adults may be influenced by changes in activity of Cytochrome P450 (CYP)<sup>14</sup>, decrease in albumin plasma levels<sup>15</sup>, and increased sensitivity of an ageing central nervous system to BZDs<sup>16-18</sup>. A particular concern about BZD use is determined by a poor evidence of their effectiveness<sup>19</sup> and high potential to cause adverse effects (AEs), such as falls and fractures, cognitive impairment, functional decline, and delirium<sup>20-27</sup>. BZDs are listed as potentially inappropriate medications in older adults in Beers Criteria due to their potential to increase risk of cognitive impairment, delirium, falls, and fractures.<sup>28</sup> Older adults are more likely to develop physiological and psychological dependence on BZDs.<sup>29</sup> The addictive potential of BZDs placed them in Schedule IV of the United Nations Convention on Psychotropic Substances<sup>30</sup>, established to control the import and export of psychoactive substances. BZDs-related AEs such as falls may result in higher economic burden. The costs of hospitalizations due to accidental fall injuries related to BZD use in the European Union were estimated between €1.5 and €2.2 billion each

year, with 90% of these costs contributing to fractures in older adults.<sup>31</sup>

Although the main objective of this thesis is to provide the comprehensive information about properties, risks and patterns of use of BZDs in older patients, in some parts, where the data were available, results of analyses of selective benzodiazepine receptor agonists commonly called as Z-drugs (zolpidem, zopiclone, zaleplone and eszopiclone), were provided as well. Z-drugs were introduced in late 1980s and 1990s.<sup>32</sup> Compared to BZDs, substances from the Z-drug group are indicated solely for treatment of insomnia. The development of Z-drugs intended to avoid some of the disadvantages of BZDs such as dependence, withdrawal syndrome, next day sedation and consequent AEs.<sup>33</sup> However, few studies showed that Z-drugs possess AEs comparable to BZDs such as cognition impairment, behaviour and psychomotor performance influence, daytime sleepiness and effect on driving ability.<sup>34,35</sup> Concerns related to potential of abuse and dependence of Z-drugs has risen in some studies as well.<sup>36-38</sup> Zolpidem was included on the Schedule IV of the United Nations Convention on Psychotropic Substances due to abuse and dependence potential.<sup>30</sup> The prevalence of Z-drug use in general population reaches up to 50%<sup>39,20</sup> and up to 25% in older patients<sup>20,41-43</sup>.

## **Objectives of the thesis**

### ***Chapter 1: Current evidence on pharmacological and clinical properties of benzodiazepines in older adults and their associations with falls.***

To review available information on BZD pharmacological properties and their changes during the aging of the organism, to describe risks of pharmacotherapy in geriatric patients using BZDs and current evidence regarding prevalence and risk of falls in older BZD users.

### ***Chapter 2: Prevalence of benzodiazepines and Z-drugs and predictive factors of their use in older nursing home residents in 7 European countries and Israel.***

To evaluate the prevalence of BZD use in older patients residing in long term care facilities in 7 European countries and Israel, to describe prescribing patterns and uniqueness of prescribing of BZDs within different health care systems while evaluating possible historical, social and economic influences.

### ***Chapter 3: Association between benzodiazepine use and falls.***

To investigate the association between use of individual BZDs and the occurrence of falls in acutely hospitalized older patients, when focusing on particular substances from BZD drug class and changes of their therapeutic properties in older patients.

***Chapter 4: Prevalence of benzodiazepine use in the Czech Republic.***

To describe utilization of BZDs in the Czech Republic in general, in different age groups and to identify different medical specialists prescribing these drugs, as well as to evaluate differences in utilization of particular substances in different age groups.

## **Research methods used in the thesis**

### ***Chapter 1: Current evidence on pharmacological and clinical properties of benzodiazepines in older adults and their associations with falls.***

A non-systematic review of literature focused on current information on pharmacokinetics, pharmacodynamics, AEs and association of BZDs with falls in older population was conducted.

### ***Chapter 2: Prevalence of benzodiazepines and Z-drugs and predictive factors of their use in older nursing home residents in 7 European countries and Israel.***

The evaluation of BZDs and Z-drugs use in long term care facilities was based on retrospective cross-sectional analyse of data from the Service and Health in the Elderly (SHELTER) project. The data were collected during 2009 to 2011 in patients aged 65 and older residing in nursing homes (NHs) in 7 European countries (The Czech Republic, England, Finland, Germany, The Netherlands, Italy) and in Israel. The base line data from Sept 2009 - Dec 2009 were analysed in this study. The interRAI LTC instrument, representing a standardized and validated comprehensive tool, was used for data collection. For the purposes of this research the data regarding use of BZDs and Z-drugs in individual countries were analysed. Descriptive statistical methods were used to evaluate the prevalence of prevalence of these drugs as well as the patterns of prescription of particular substance from these drug classes in each country. Univariate and multivariate logistic regressions were conducted to

evaluate factors potentially influencing the excessive use of BZDs and Z-drugs.

### ***Chapter 3: Association between benzodiazepine use and falls.***

Analyses of dataset from prospective cohort study of acutely hospitalized patients aged 70 years and older admitted to general medical, orthopaedic and surgical wards in 11 hospitals in Australia were conducted. Patients within each cohort were recruited consecutively between July 2005 and May 2010. Data were collected using the InterRAI Acute Care instrument (interRAI AC) specifically developed for acute care settings. The association of falls and use of BZDs was evaluated using univariate statistical methods. To observe the differences between particular substances from the BZD drug class in regards to the association with falls, multivariate logistic regression analyses were conducted accounting for all relevant clinical cofounders.

### ***Chapter 4: Prevalence of benzodiazepine use in the Czech Republic.***

For the evaluation of BZD prevalence in the CZ data from the State Institute for Drug Control (Státní ústav pro kontrolu léčiv - SUKL) and from database of the General Health Insurance Fund (Všeobecná zdravotní pojišťovna - VZP) were used. Descriptive statistical methods were applied to analyse the number of BZDs used, expressed in Defined Daily Doses (DDDs), in general population and particular age groups, as well as to evaluate number of BZD users and specialization of prescribing clinicians.

## **Results of the thesis**

### ***Chapter 1: Current evidence on pharmacological and clinical properties of benzodiazepines in older adults and their associations with falls.***

This narrative literature review gives comprehensive information on pharmacokinetics, pharmacodynamics, indications, contraindications and adverse drug effects of BZDs in light of age-related changes. The review showed that BZDs' propensity to cause falls might be associated mainly with age-related changes in their biological half-life closely related to variations in metabolizing enzymes activity in aging organism and age-related changes in distribution (increase of adipose tissues, decrease level of albumin). Therefore, BZDs with long half-life are generally less preferred compared to those with medium or short biological half-life. However, results of studies are mixed and the research shows that long-acting as well as short-acting BZDs are associated with risk of falls in older people in different settings. BZDs contribute to the multifactorial character of falls occurring in older adults.

### ***Chapter 2: Prevalence of benzodiazepines and Z-drugs and predictive factors of their use in older nursing home residents in 7 European countries and Israel.***

Of 4,156 nursing home residents (73.2% women, mean age  $\pm$  standard deviation [SD]  $83.4 \pm 9.4$ ) 1,113 (27.7%) used BZDs/Z-drugs. The mean  $\pm$  SD of the number of regular medications used was  $7.0 \pm 3.6$ . The highest prevalence of BZD/Z-drug use was found in Israel (44.1%), France (44.0%) and The Netherlands (26.5%). The most frequently prescribed



drugs were: zopiclone (17.8% of BZD/Z-drug users), lorazepam (17.7%) and oxazepam (16.9%). There were significant differences in the prevalence of BZDs/Z-drugs across countries: lorazepam, oxazepam and diazepam were used in the majority of countries, brotizolam (99.4% of users of this medication), temazepam (72.6%) and zolpidem (50.0%) showed predominant use in Israel, The Netherlands and France; respectively. Excessive prescription of BZDs/Z-drugs was significantly associated with the country of residence (adjusted Odds Ratio [OR] for Israel OR=6.7; 95% Confidence Interval [CI] 4.8-9.2,  $p<0.001$ ; for France OR=5.3; 95% CI 3.5-7.9,  $p<0.001$ ; for The Netherlands OR=2.4; 95% CI 1.7-3.4,  $p<0.001$ ) and specific disorders: insomnia (OR= 3.3; 95% CI 2.5-4.3,  $p<0.001$ ), anxiety (OR 1.9; 95% CI 1.4-2.6,  $p<0.001$ ), depression (OR 1.1; 95% CI 1.02-1.09,  $p=0.001$ ), and pain (OR 1.1; 95% CI 1.004-1.234,  $p=0.04$ ).

### ***Chapter 3: Association between benzodiazepine use and falls.***

Of 1,412 patients (55.1% women, mean age  $\pm$  SD was  $81.0 \pm 6.8$  years) 146 (10.3 %) were taking BZDs at admission and 155 (11.3%) at discharge. The mean number  $\pm$  SD of regular medications at admission was  $8.3 \pm 3.9$ , ranging from 0 to 24 medications. The mean number  $\pm$  SD of comorbidities was  $6.1 \pm 2.3$ . Incidence rates of in-hospital fallers for users and non-users of BZDs were not statistically different (incidence rate ratio [IRR] 1.03, 95% CI 0.58–1.82). There was also no significant association between BZD use at admission and history of falls in the previous 90 days compared with non-users. However, patients on diazepam were significantly more likely to have a history of falls compared with all other BZD users (70.8% vs. 36.1%;  $p=0.002$ ), particularly when

compared to oxazepam users (70.8% vs. 25.0%;  $p < 0.001$ ). Adjusting for confounders, use of diazepam at admission was positively associated with a history of falls compared with all other BZD users (OR=3.0; 95% CI 1.1–8.5;  $p = 0.036$ ), in particular when compared with oxazepam (OR=6.8; 95% CI 2.1–22.0;  $p = 0.001$ ).

#### ***Chapter 4: Prevalence of benzodiazepine use in the Czech Republic.***

Between 2009 and 2013, there were on average 60.8 million of DDDs of BZDs distributed and 23.0 million of DDDs reimbursed. The utilization of BZDs decreased approximately by 13.4%-19.7% (according to data source) during the period 2009-2013. The number of utilized DDDs remained stable in the youngest group (0-19 years) and decreased in younger adults (20-54 years). In older adults (55-85 years) the number of DDDs rapidly increased between 2010 and 2011 with a swift decrease in subsequent year 2012, while in the oldest old group (90-94 years) the number of DDDs constantly increased. The number of BZD users from VZP database represented approximately 5.5% of the Czech population and this proportion did not change substantially during 2009 to 2013. The highest average proportion of BZD users was in the age group of 85+ years (17.6% of the persons). The most frequently used BZD was alprazolam (average proportion of 62.2% of BZD users in 2009-2013 years), followed by diazepam (22.1%) and oxazepam (11.0%). After the age stratification, alprazolam remained the most frequently used BZD in all age groups (53.8%, 69.1%, and 62.6% of BZD users in 0-44, 45-64, and 65+ age group; respectively). Diazepam was more often used by younger population (35.4%, 17.0%, and 18.2% of BZD users in 0-44, 45-64, and 65+ age group;

respectively) and oxazepam by the older population (6.9%, 9.6%, and 15.2% of BZD users in 0-44, 45-64, and 65+ age group; respectively). BZDs were most often prescribed by general practitioners (45.8%) followed by psychiatrists (38.9%) and neurologists (3.7%).

## Discussion

### ***Chapter 1: Current evidence on pharmacological and clinical properties of benzodiazepines in older adults and their associations with falls.***

The non-systematic review presented in Chapter 1 describes how the pharmacological profile of BZDs can be influenced by age-related changes in pharmacokinetics and pharmacodynamics leading to increased potential of BZDs to cause AEs particularly in older adults (e.g., daily sleepiness, fatigue, falls, cognitive impairment, and confusion). Despite extensive evaluation of BZDs' contribution to falls in older patients, the research yielded mixed results, and differences between particular drugs or dosage regimens remain questionable. Risk/benefit ratios of particular active substances in the group of BZDs, their cautious indication for specific problems and rational selection, particularly in older adults with various multiple comorbidities, should be carefully evaluated in daily clinical practice.

### ***Chapter 2: Prevalence of benzodiazepines and Z-drugs and predictive factors of their use in older nursing home residents in 7 European countries and Israel.***

The study showed important differences in use of BZDs and Z-drugs among 7 European countries and Israel. Overall prevalence of BZD/Z-drug use was found to be 27.7% in this study which correlates with findings of other studies<sup>1-9</sup>. This research showed that not only the prevalence of BZD and Z-drug use differs across countries, but more importantly, the prescribing of individual active substances from this drug class follows different prescribing patterns and habits. Our

findings suggest that country of residence plays an important role beneath well-known clinical factors such as age, gender and appropriateness of indication<sup>5,44,45</sup>.

The highest prevalence of BZD/Z-drug use in this study was documented in Israel (44.1%) followed by France (44.0%) and The Netherlands (26.5%). The second lowest prevalence of BZD/Z-drug use was found in England (17.4%), while the lowest was in Germany (14.5%).

The most frequently used BZD in Israel was brotizolam, representing 59.8% of all BZDs/Z-drugs prescribed in Israel and 99.4% of overall brotizolam use in the overall study sample. After adjusting for confounders, the country of residence remained a strong predictor of BZD/Z-drug use. In case of Israel the adjusted OR was the highest OR= 6.7 (95 % CI 4.8-9.2). Few studies previously reported the use or prescribing patterns of BZDs/Z-drugs in NHs and other setting of care in Israel; showing the prevalence to be up to about 69% in different settings<sup>45-47</sup>. Studies of Israeli population also showed important differences between the Jewish and the Arab population denoting that these might be associated with the stigmatizing character of mental illnesses and stronger reliability on informal support in these groups.<sup>48</sup>

Germany was the country with the lowest prevalence of BZD/Z-drug use. These findings are consistent with another study of NH residents in Germany which reported the prevalence of 10.4%-12.6% of BZD use in anxiolytic indication, 3.3%-3.7% of BZD use in hypnotic indication and 4.5%-5.3% of Z-drug use.<sup>49</sup> Since 1980s the German Federal Institute for Drugs and Medical Devices restricted the BZD use to a maximum standard period of 2-4 weeks.<sup>50</sup> The overall prevalence of BZD use in Germany decreased from 8.9% to 7.4% between 2006 and 2010, in the population aged 60-74 years, and from 13.3% to 10.4% in those aged >75 years.<sup>51</sup>

In contrast, the prevalence of Z-drug use was relatively stable, with change from 3.2% to 3.0% between 2006 and 2010, in patients aged 60-74 years, and from 2.1% to 2.0% in patients aged >75 years.<sup>51</sup>

The findings of our study indicate that factors such as therapeutic recommendations and guidelines, treatment indication and restrictions, new treatment options, availability of particular substances on the market, prescribing policies as well as patient/clinician preferences and/or historical convention in treatment approaches, might specifically interfere with the prescribing patterns.

### ***Chapter 3: Association between benzodiazepine use and falls.***

The study of acutely hospitalized older adults in Chapter 3 showed that association with falls differs significantly between particular substances of BZDs in this drug class. Studies focusing on BZD use as a risk factor of in-hospital falls have yielded conflicting results. Our study found no statistically significant difference between incidence rates of in-hospital fallers among users of BZDs versus non-users. These findings might be due to the overall low incidence rate of in-hospital fallers (6.9 per 1,000 person-days) and the short periods of hospitalization (median [IQR] length of stay in hospital was 6 [4–11]). That is in accordance with one negative study which postulated that the results may have been confounded by the short time period of BZD use during hospitalization and use of short elimination half-life BZDs.<sup>52</sup>

In contrast, a population-based case-control study examining in-hospital hip fractures reported an adjusted OR of 2.1 (95% CI 1.1–3.8;  $p=0.035$ ) in BZD users compared with nonusers.<sup>53</sup>

Contrary to previous studies<sup>25,54-58</sup>, our present study found no statistically significant differences in history of falls between users and non-users of BZDs overall. The most recent meta-analysis of nine medication classes involving older individuals reported a Bayesian pooled OR of 1.4 (95% CI 1.2–1.7)<sup>25</sup>.

Although there were statistically significant differences in history of falls between users and non-users of BZDs overall in our study, in subgroups analyses, there was a significant association between occurrence of falls and diazepam users. It is of importance to mention that, the research evidence of differences between particular BZDs and falls according to their biological half-life is mixed<sup>54, 59-63</sup>. Our study showed clear evidence of patients using long-acting diazepam being over three times more likely to have a fall in the previous 90 days compared with BZD nonusers and all other BZD users, and almost seven times more likely when compared with oxazepam users. A possible explanation for the findings of our study relates to age-related changes in the pharmacokinetic and pharmacodynamic properties of individual drugs. Diazepam is the drug having low hepatic clearance which is dependent on the unbound fraction of the drug in the blood and on intrinsic hepatic clearance determined by the activity of drug metabolizing enzymes within the hepatocyte.<sup>64</sup> One study of drug-metabolizing enzymes found that CYP content declines already after 40 years of age.<sup>14</sup> In contrast, oxazepam is extensively metabolized by uridine 5-diphospho-glucuronosyltransferase (UGT) enzymes.<sup>65</sup> Drug metabolism by UGT enzymes appears to be preserved in fit older people, although it might be affected by frailty.<sup>64</sup> Other possible factors contributing to differences in falls risk between individual active substances from the BZD group may include age-related changes in receptors, neurotransmitters, and

second-messenger systems in the brain<sup>18</sup>, which are not yet accurately described for specific BZDs.

This study documented differences in the association between individual BZDs and a history of falls according to their biological half-life. Diazepam use was shown to be an independent risk factor of history of falls when compared with BZD non-users, all other BZD users and, in particular, with oxazepam users. These findings confirm that there might be significant differences in risk/benefit ratios of particular drugs in a group of BZDs. Consequently, the indications for, and selection of, a particular BZD for older patients should be carefully evaluated.

#### ***Chapter 4: Prevalence of benzodiazepine use in the Czech Republic.***

The study of BZD utilization in the CZ showed that BZD users represent approximately 5.5% of general Czech population. During years 2009 and 2013 the use of BZDs in DDDs decreased by 13.4% while the number of BZD users remained relatively stable with a change of +2.3% (given the results of the VZP database). In comparison, results of studies focusing on the use of BZDs in general population ranged from 2% to 8.9%<sup>66-70</sup>; however, the prevalence of BZD use in general population varied in published studies between 2.2% and 17.6% due to variation in definition of BZD use and observation period<sup>71</sup>.

In our study the analyses showed significant differences in utilization of BZDs between age groups, with older groups (age 55-84 years) consuming substantially higher amount of BZDs compared to younger adults (20-54 years). Interestingly, the number of patients in all age groups corresponded with trends in the number of DDDs, with exception of the children



population (0-4 years) showing relatively small number of DDDs and high number of patients. This finding might be due to use of lower doses or short-term use of BZDs for acute indications in the youngest groups (e.g., prevention and treatment of febrile seizures in infants, therapy of status epilepticus in infants), while the use in the older population might be more likely associated with long-term continuous use, preferences and prescribing conventions of clinicians. The use of BZDs in our study was the highest among the older population, particularly in the oldest groups of 85+ years old (17.6% of persons insured by the VZP). These findings correspond with many other studies worldwide showing sustained use of BZDs in general 85+ population of up to 25%<sup>70,71</sup>, while in the proportion of BZD uses in older population, residing in long-term care setting can reach up to 54%<sup>3-10</sup>.

The most frequently prescribed substances in our study were alprazolam (average proportion of 62.2% of BZD users in 2009-2013 years), diazepam (22.1%) and oxazepam (11.0%). In comparison, in the study of the United States (US) population the most frequently used BZDs were alprazolam and lorazepam<sup>71</sup>, the evaluation of the French population showed bromazepam being the most commonly used BZD, followed by Z-drugs zolpidem and zopiclone<sup>68</sup>. In the study of the Canadian population the most frequently prescribed BZDs were lorazepam, clonazepam, diazepam and alprazolam.<sup>72</sup> These differences can be caused by variance in availability of BZDs on the pharmaceutical market, differences in national recommendations and guidelines, drug policies as well as reimbursement and price issues.

When stratified by age, there were differences in BZD substances used in particular age groups in our study. Alprazolam was the most frequently used BZD in all age

groups; diazepam was more often used by younger population and oxazepam by the older population. These findings correspond with findings of low utilization of BZDs in DDDs but high numbers of patients in paediatric population (0-4 years). We assume that BZDs are used in this population mainly for acute indications where diazepam is the drug of choice.

The evaluation of BZD prescription in this study outlined that BZDs were prescribed most frequently by general practitioners (45.8%), followed by psychiatrists (38.9%) and neurologists (3.7%). This finding is consistent with other studies, showing general practitioners followed by psychiatrists being the most frequent BZD prescribers.<sup>70,73</sup>

These results indicate that mainly general practitioners should be important target audience to be addressed with recommendation on appropriate use of BZDs in general as well as older population.

While focusing on the age stratification, use of particular substances from the BZD drug class overall and in different age groups, this study shows substantial disparities across populations in quantity and prescribing patterns. The information about proportion of different clinical specialists prescribing BZDs together with the age stratification of BZD users give an insight into the clinical practice.

## **Overall conclusion**

This doctoral thesis provides comprehensive overview of information and current knowledge on pharmacological profile, clinical use and AEs of BZDs particularly in older population, as well as results from studies performed in real geriatric patients using BZDs. It also provides, to a smaller extend, information on use of Z-drugs as medications that share one of the indications as well as some of the most important AEs with BZDs.

By providing the unique insight into the differences in prevalence of BZDs/Z-drugs use across 7 European countries and Israel together with the comprehensive description of use of these drugs in some of the countries, this thesis tried to explain potential disparities between individual countries, showing that prescribing patterns are most probably influenced by number of different factors. However; more studies are needed to define and confirm or disprove the role of components such as social, cultural, economic and behavioural factors that play role in the uniqueness of prescribing patterns of these medications in different countries worldwide.

The study of association between use of BZDs and falls in acutely hospitalized patients confirms that there might be significant differences in risk/benefit ratios of particular drugs in a group of BZDs, particularly in older patients. In regards to these findings the indications for, and selection of, a particular BZD should be an essential part of the therapeutic approach in older adults.

The final part of this thesis describing the prevalence of BZDs use in CZ presents substantial differences across age groups in quantity and patterns of BZD prescription. The information on proportion of different clinical specialists prescribing BZDs together with the age stratification of BZD users give an insight into the clinical practice in CZ and provides an opportunity for comparisons with other countries.

In light of the potential inappropriate use of BZDs in geriatric population, propensity to cause AEs and addiction, this doctoral thesis is consistent with overall research knowledge about this drug class. Moreover, it also uncovered new information about the prevalence of BZDs across different countries, association between falls and particular substances as well as novel facts about the current situation in BZD use in Czech clinical practice and utilization of these drugs on the Czech pharmaceutical market.

## Publications of the author

### *Publications in extenso related to the doctoral theses*

#### With impact factor

**Ballokova A**, Peel NM, Fialova D, Scott IA, Gray LC, Hubbard RE.

*Use of Benzodiazepines and Association with Falls in Older People Admitted to Hospital: A Prospective Cohort Study.* Drugs Aging 2014; 31(4):299-310; doi:10.1007/s40266-014-0159-3.

IF = 2.610

**Ballóková Lukačšínová A**, Fialova D, Peel NM, Hubbard RE, Onder G, Topinková E, Gindin J, Shochat T, Gray LC, Bernabei R.

*Prescribing patterns of benzodiazepines and Z-drugs in older nursing home residents across European countries: results from the SHELTER study.*

Submitted to JAMA Psychiatry (May, 2016)

IF = 12.008

**Ballóková Lukačšínová A**, Vocelka M, Fuksa L, Fialová D. *Prescription and consumption of benzodiazepines in the Czech Republic between years 2009 and 2015.*

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IF = 2.939

Without impact factor

**Ballóková Lukačišinová A**, Fialová D.

*Benzodiazepines, age-related pharmacological changes, and risk of falls in older adults. Neuropathology of Drug Addictions and Substance Misuse. Volume 3: General Processes and Mechanisms, Prescription Medications, Caffeine and Areca, Polydrug Misuse, Emerging Addictions and Non-Drug Addictions.* 2016,

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<http://www.sciencedirect.com/science/article/pii/B9780128006344000330>

***Publications in extenso unrelated to the doctoral theses***

With impact factor

Poudel A, **Ballokova A**, Hubbard RE, Gray LC, Mitchell AC, Nissen LM, Scott IA.

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Without impact factor

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potenciálně nevhodných ve stáří. Vhodnost volby léčiv a  
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analysis of impact on early market entry, regular  
reimbursement system entry and public pharmaceutical  
expenditure.*

Journal of Pharmaceutical Policy and Practice 2015; 8  
(Suppl 1): O3.

### ***Poster/oral presentations***

**Ballokova A**, Peel NM, Fialova D, Scott IA, Gray LC, Hubbard RE.

*Use of benzodiazepines and history of falls in older people admitted to acute care settings in Australia.*

Princess Alexandra Hospital Health Symposium, Brisbane, Australia. 21 August, 2013.

**Ballokova A**, Peel NM, Fialova D, Scott IA, Gray LC, Hubbard RE.

*Use of benzodiazepines and history of falls in older people admitted to acute care settings in Australia.*

European Society of Clinical Pharmacy Annual Symposia 2013, Prague, Czech Republic. 16 October, 2013.

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*Use of benzodiazepines and Z-drugs in older nursing home residents in Europe and their association with adverse outcomes: results from the EU SHELTER project.*

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