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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

Doctoral Thesis

Supervisor: PharmDr. Daniela Fialová, Ph.D.

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List of Abbreviations

ACEI(s)	Angiotensin Converting Enzyme Inhibitor(s)
ADL	Activities of Daily Living
ADLH	Activities of Daily Living Hierarchy scale
AE(s)	Adverse Effect(s)
ALPRA	Alprazolam
ATC code	Anatomical Therapeutic and Chemical code
BBB	Blood–brain barrier
BROMA	Bromazepam
BROTI	Brotizolam
BZD(s)	Benzodiazepine(s)
CAP	Clinical Assessment Protocol
CI	Confidential Interval
CNS	Central Nervous System
CPS	Cognitive Performance Scale
CZ	Czech Republic
CYP	Cytochrome P450
DDD(s)	Defined Daily Dose(s)
DIA	Diazepam
DIS 13	Medicinal product delivery reporting system
EN	England
FI	Finland
FR	France
GABA	γ-aminobutyric acid
$GABA_A$	γ-aminobutyric acid type A receptor
GE	Germany
GIT	Gastrointestinal Tract
HAS	Haute Autorité de Santé
IADL	Instrumental Activities of Daily Living
IL	Israel
interRAI AC	InterRAI Acute Care instrument
interRAI LTCF	InterRAI Long-Term Care Facilities instrument
IQR	Interquartile Range
IT	Italy
LORA	Lorazepam
MAH	Marketing Authorisation Holder
MIDA	Midazolam
NH(s)	Nursing Home(s)
NICE	The National Institute for Health and Care Excellence
NL	The Netherlands
OR	Odds Ratio
OXA	Oxazepam
PIM(s)	Potentially Inappropriate Medication(s)
PR	Prolonged Release

RR	Rate Ratio
SD	Standard Deviation
SHELTER	Service and Health in the Elderly project
SUKL	State Institue for Drug Control (in Czech language: Státní Ústav pro Kontrolu Léčiv)
TEMA	Temazepam
UGT	Uridine 5-diphospho-glucuronosyltransferase
US	The United States of America
VZP	General Health Insurance Fund (in Czech language: Všeobecná Zdravotní pojišťovna)
WHO	World Health Organisation
ZOLPID	Zolpidem
ZOPIC	Zopiclone

Abstract

Objectives

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

Methods

A narrative review of literature focused on pharmacokinetics, pharmacodynamics, adverse effects and association of benzodiazepines with falls in older population was conducted. The evaluation of benzodiazepine use in long term care facilities was analysed in a retrospective cross-sectional study using data from the EC 7th Framework Program SHELTER project (Service and Health in the Elderly in Long Term Care). A prospective cohort study data of acutely hospitalized patients in Australia were used to evaluate association between benzodiazepines and falls. To describe utilization of benzodiazepines in the Czech Republic, data from the State Institute for Drug Control and from databases of General Health Insurance Fund were used. This dissertation thesis is a summary of published articles from above stated works and analyses.

Results

The study of patients in long term care facilities showed excessive benzodiazepine use and significant differences in type of benzodiazepines prescribed across European countries and Israel. Analyses of acutely hospitalized patients showed statistically significant association between use of diazepam and falls compared to other benzodiazepines, in particular to oxazepam. The evaluation of benzodiazepine prescription in the Czech Republic outlined decrease in benzodiazepines utilization between 2009-2013 years in older population and variation in prescription patterns across different age groups.

Conclusions

This doctoral thesis gives a comprehensive overview of information and knowledge on benzodiazepine use in older patients. It provides both detail theoretical information on pharmacological characteristics, clinical use and risks of benzodiazepines in geriatric population and important findings from cross-sectional, outcome and utilization studies describing patterns, outcomes and utilization trends in benzodiazepine use in older patients.

Key words: benzodiazepines, geriatric population, pharmacokinetics, pharmacodynamics, indications, contraindications, adverse drug effects, falls, Europe, Israel, Australia

Abstrakt

Záměr

Hlavními cíli této disertační práce bylo zhodnotit dostupné informace týkající se farmakologických vlastností benzodiazepinů a jejich změn vlivem stárnutí organismu; zhodnotit prevalenci použití benzodiazepinů u geriatrických pacientů v léčebnách pro dlouhodobě nemocné; analyzovat vztah mezi užitím benzodiazepinů a pády v populaci akutně hospitalizovaných geriatrických pacientů a zmapovat vývoj preskripce benzodiazepinů v prostředí České republiky.

Metodika

Byla provedena nesystematická literární rešerše, která se stala zdrojem pro přehledový článek zaměřený na farmakokinetiku, farmakodynamiku, nežádoucí účinky a vliv užití benzodiazepinů na výskyt pádů u geriatrické populace. Hodnocení užití benzodiazepinů v léčebnách pro dlouhodobě nemocné v evropských zemích bylo provedeno v rámci retrospektivní průřezové analýzy dat z evropského projektu SHELTER (Service and Health in the Elderly in Long Term Care). Za účelem posouzení vlivu benzodiazepinů na výskyt pádů byla provedena analýza dopadů v prospektivní kohortové studii hospitalizovaných seniorů v Austrálii. Ke zmapování trendů ve spotřebách benzodiazepinů v České republice byla použita data ze Státního ústavu pro kontrolu léčiv a z databáze Všeobecné zdravotní pojišťovny. Tato disertační práce sestává z publikací všech výše uvedených studií a analýz.

Výsledky

Výsledky analýz u seniorů v léčebnách pro dlouhodobě nemocné poukázaly na vysokou prevalenci užití těchto léčiv v ošetřovatelských zařízeních a statisticky významné rozdíly v typu předepisovaných benzodiazepinů v evropských zemích a Izraeli. Analýzy provedené na databázi akutně hospitalizovaných pacientů prokázaly statisticky významnou asociaci výskytu pádů u uživatelů diazepamu v porovnání s uživateli všech ostatních benzodiazepinů a zejména v porovnání s oxazepamem. Analýzy spotřeb benzodiazepinů v České republice poskytly údaje o snížení spotřeb těchto léčiv v letech 2009–2013 u starší populace, a zároveň informace o odlišnostech v různých věkových skupinách.

Závěry disertační práce

Tato disertační práce poskytuje obšírné vědecké poznatky z oblasti terapie benzodiazepinů u geriatrických pacientů. Zahrnuje nejen teoretické vědecké poznatky o farmakologických vlastnostech, klinickém použití a rizicích benzodiazepinů 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 benzodiazepinů u geriatrické populace.

Klíčová slova: benzodiazepiny, geriatrická populace, farmakokinetika, farmakodynamika, indikace, kontraindikace, nežádoucí účinky, pády, Evropa, Izrael, Austrálie

Introduction

Background

Benzodiazepines (BZDs) belong to the group of anxiolytic 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.[1] Since their first introduction in 1960s, there have been about 30 BZDs developed, launched, and used.[2] 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%[3-10], while in community-dwelling older adults the prevalence reaches up to 38%[11-13]. The pharmacological profile of BZDs in older adults may be influenced by changes in activity of Cytochrome P450 (CYP)[14], decrease in albumin plasma levels[15], and increased sensitivity of ageing central nervous system to BZDs[16-18]. A particular concern about BZD use is determined by a poor evidence of their effectiveness[19] and high potential to cause adverse effects (AEs), such as falls and fractures, cognitive impairment, functional decline, and delirium[20-27]. 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.[28] Older adults are more likely to develop physiological and psychological dependence on BZDs.[29] The addictive potential of BZDs placed them in Schedule IV of the United Nations Convention on Psychotropic Substances[30], 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.[31]

Although the main objective of this thesis is the use of BZDs, in some parts, where the data were available, the analyses of selective benzodiazepine receptor agonists commonly called as Z-drugs (zolpidem, zopiclone, zaleplone and eszopiclone) were conducted as well. Z-drugs were introduced in late 1980s and 1990s.[32] Compared to BZDs, substances from the Z-drugs 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.[33] 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.[34,35] Concerns related to potential of abuse and dependence of Z-drugs has risen in some studies as well.[36-38] Zolpidem was included on the Schedule IV of the United Nations Convention on Psychotropic Substances due to abuse and dependence potential.[30] The prevalence of Z-drug use in general population reaches up to 50%[39,20] and up to 25% in older patients[20,40-43].

Gaps in research evidence

Numerous studies reported a wide range of BZD prevalence in different settings of care across countries. However, these studies used various methods of data collection and evaluation, as so the direct comparisons are difficult. Use of the interRAI assessment instrument for Long-Term Care Facilities (interRAI LTCF) and the interRAI Acute Care instrument (interRAI AC) enabled description and cross-country comparisons of health and functional status of older patients, as well as comparisons of medication use, at the same time period across different care settings.

Despite evidence of the use of BZDs and Z-drugs worldwide, there is a lack of studies explaining their excessive use focusing on other factors than age, gender, anxiety, insomnia or depression. This research thus provides an explanation of country specific prescription patterns of individual BZDs and Z-drugs, potential influence of historical, social and economic factors, clinical treatment conventions and patients' preferences.

Although few studies had evaluated the relationship between BZDs and falls, as far as we are aware, this research is the first to evaluate the associations between specific substances from the BZD drug class and prior history of falls. The comparison between particular substances from the drug class of BZDs showed differences in propensity to cause falls and these findings might be explained by pharmacological characteristics and changes of these drugs in the old age.

Finally, the prevalence of BZD use and their prescription patterns in the Czech Republic (CZ) was not described in any other recent study. This research provides insight into the history of BZD use and its changes over the years on the Czech pharmaceutical market including age stratification. Description of medical specialties prescribing BZDs is first published also in this thesis.

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Objectives, methods and outline of the thesis

Objectives of the thesis

Chapter 1

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 and current evidence regarding prevalence and risks of falls in older BZD users.

Chapter 2

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

Chapter 3

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

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

Research methods of the thesis

Chapter 1

This chapter is conceptualized as a narrative review of literature focused on current information on pharmacokinetics, pharmacodynamics, adverse effects and association of BZDs with falls in older population.

Chapter 2

The analyses of BZD and Z-drug use in long term care facilities were based on retrospective cross-sectional 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 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, 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 enabled to evaluate the prevalence of overall use of these drugs as well as to uncover patterns of prescription of particular substances from these drug classes in each country. Univariate and multivariate logistic regressions were conducted to evaluate factors significantly associated with the excessive use of BZDs and Z-drugs.

Chapter 3

Analyses of dataset from prospective cohort study of 1,412 acutely hospitalized patients aged 70 years and older in 11 hospitals in Australia between July 2005 and May 2010 were conducted. Data were collected using the interRAI AC instrument specifically developed for older patients´ assessment in 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 confounders.

Chapter 4

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 databases of the General Health Insurance Fund (Všeobecná zdravotní pojišťovna - VZP) were used. Descriptive statistical methods were applied to analyse the number of BZDs utilized in general population and with respect to particular age groups.

Outline of the thesis

Chapter 1

This chapter presents a non-systematic review of literature that provides comprehensive information on BZD use in older population, changes in pharmacokinetics and pharmacodynamics of these drugs and consequent potential adverse effects. The role of BZDs in multifactorial risks of falls is discussed in general overview as well as with regards to particular substances from this drug class.

Chapter 2

This chapter describes prevalence of BZD and Z-drug use in older nursing home residents in 7 European countries (including the CZ) and Israel using a comprehensive assessment tool (interRAI LTCF instrument) enabling cross country comparison. It also investigates risk factors of excessive BZD and Z-drug use.

Chapter 3

This chaper outlines the results of research focused on BZD use and its association with falls in acutely hospitalized older patients. It reveals the difference between particular substances from the BZD drug class showing their comparison in regards to the propensity to cause falls.

Chapter 4

This chapter gives an overview of BZD utilization in the CZ over specific timeframe (2009-2013 year) and variation in their use across different age groups. It also presents prescribing patterns across different medical specialties.

Chapter 1

Current evidence on pharmacological and clinical properties of benzodiazepines in older adults and their associations with falls

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Abstract

BZDs belong to the group of hypnosedative medications. They are commonly prescribed for anxiety disorders and sleep problems and are widely used in younger adults as well as in the older population. However, their pharmacological profile can be influenced by age-related changes in pharmacokinetics and pharmacodynamics resulting in an increased potential to cause adverse effects such as daily sleepiness, fatigue, falls, cognitive impairment, and confusion. Falls in older people are described as multifactorial adverse events, with use of particular medications being one of the potential risk factors. 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.

Introduction

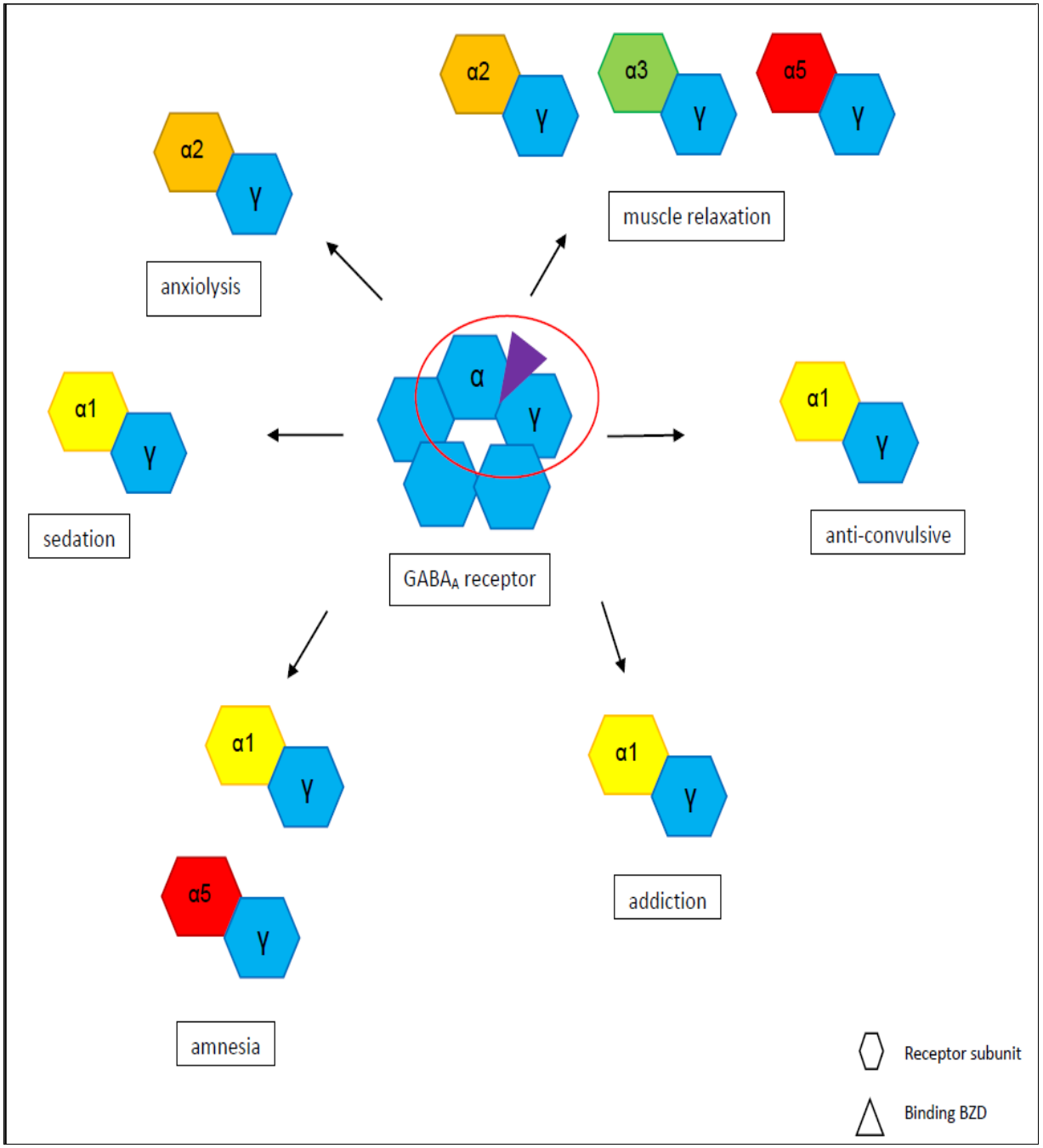
BZDs belong to the group of hypnosedative drugs. Their properties allow their indication for a number of conditions including anxiety disorders, insomnia, control of epileptic seizures, treatment of alcohol withdrawal syndrome, depression, and muscle spasms. Since the introduction of the first BZD chlordiazepoxide in 1960, there have been about 30 other compounds developed and used either as anxiolytics or hypnotics, eventually both.[1] According to the European Monitoring Centre for Drugs and Drug Addiction (http://www.emcdda.europa.eu/publications/drug-profiles/benzodiazepine)[2], statistics for the year 2009 showed that Europe had the highest average consumption of BZDs in defined daily doses (DDDs) per 1000 inhabitants per day, with a global consumption of around 21 billion DDDs. The main concern about BZD use is their association with adverse effects, addictive potential and abuse, as well as adverse events in older patients. In 1984, BZDs were included in Schedule IV of the United Nations Convention on Psychotropic Substances[3], established to control the import and export of psychoactive substances. Following their development and introduction to the market, most of the BZDs were added to Schedule IV thereafter. BZDs are also listed in Beers Criteria, the internationally acknowledged and used list of potentially inappropriate medications (PIMs) in older people[4]. Propensity of BZDs to cause falls placed them into the group of "fall-risk increasing drugs"[5]. Falls are well-recognized prominent external causes of unintentional injuries representing public health concern with serious consequences.

The aim of this chapter is to introduce the basic characteristics of BZDs leading to the differences between particular drugs and their risk/benefit profile when used in clinical practice. Common adverse effects of BZDs such as daily sleepiness, fatigue, coordination impairment, slowed thoughts, cognitive impairment, and confusion have been well described. However, this chapter will focus mainly on falls as a potential adverse effect of BZD use in older patients and the influence of different factors on this association.

Effects of BZDs on $GABA_A$ receptor sites

The pharmacological effect of BZDs is reached after specific binding of BZDs on the targeted site between the alpha and gamma subunit of γ-aminobutyric acid type A ($GABA_A$) receptor and subsequent chloride-ion influx, neuronal cell membrane hyperpolarization, and inhibition of neuronal firing. Several pharmacological and behavioural studies showed that there is a correlation between a specific alpha subunit isoform and one or more effects of BZDs (Figure 1).[6] $GABA_A$ receptors containing different specific isoforms of alpha subunits are located in different parts of the central nervous system (CNS). $GABA_A$ receptors containing the alpha1 subunit are highly concentrated in the cortex, thalamus, and cerebellum resulting in sedative effect, anterograde amnesia, and partly in anticonvulsive activity.[7] In contrast, $GABA_A$ receptors containing alpha2 subunits mediating the anxiolytic and myorelaxant effect of BZDs are mostly found in the limbic system, motor neurons, and dorsal horn of the spinal cord.[8] Interestingly, interaction with the $GABA_A$ receptor-containing specific alpha subunit isoform and even an affinity to it can differ between particular drugs from the BZD group.[8] Therefore, these differences in BZD affinity to specific $GABA_A$ receptor type in association with location of the receptor in the CNS, accompanied by their different pharmacokinetic properties, may account for diverse effects of various BZDs.

Figure 1. $GABA_A$ receptors subunit isoforms and their corresponding effects.



There have been found differences in BZD effects according to the isoform of the alpha subunit in the $GABA_A$ receptor they bind to. Binding to the receptors with alpha1 subunit results in sedation, an anticonvulsive effect, as well as addiction and partly amnesia.[7] Alpha2 subunit is responsible for an anxiolytic effect and muscle relaxations.[8] $GABA_A$ receptors containing alpha3 and alpha5 subunits mediate a myorelaxant effect, whereas alpha5 subunit contributes to memory impairment effect of BDZs.[6]

$GABA_A$, γ-Aminobutyric acid type A receptors; BZD, benzodiazepine; $GABA_A$, γ-Aminobutyric acid type A receptor; BZD, benzodiazepine.

BZDs and different pharmacokinetic properties

It is important to understand the pharmacokinetic properties of different BZDs as they contribute to the desired pharmacological effect as well as to the undesired AEs and adverse events (Table 1). Most BZDs are lipophilic weak bases with fairly rapid and complete absorption from the gastrointestinal tract (GIT) after oral administration. They reach the maximum plasmatic concentration usually within 1 h after oral administration. BZDs' lipophilicity correlates also with their rapid distribution in the CNS and their transport across the blood – brain barrier (BBB) via passive diffusion as well as with their accumulation in adipose tissues. Rapid onset of action (e.g., in diazepam, midazolam) is favourable in the treatment of insomnia; however, some patients may perceive the same effect as drowsiness, loss of control, muscle relaxation, and feeling of being "spaced out".[9] BZDs with slower onset of action (e.g., oxazepam, lorazepam) might be of benefit in anxiolytic indication and situations when the prompt hypnosedative effect is not desired.[9]

Table 1. Basic pharmacokinetic properties of BZDs.

Drug	Onset of action[a]	Initial biotransformation	Biological half-life of parent compound[a] $t_{1/2}$ (h)	Primary effect
Short acting BZDs				
Oxazepam	Intermediate to slow	Conjugation	6-20	Anxiolytic
Triazolam	Fast	Oxidation	2-5	Hypnotic
Midazolam	Fast	Oxidation	1,5-3	Hypnotic
Medium acting BZDs				
Alprazolam	Fast to intermediate	Oxidation	6-20	Anxiolytic
Lorazepam	Intermediate	Conjugation	10-40	Anxiolytic
Temazepam	Intermediate to slow	Oxidation, Conjugation	6-25	Hypnotic
Long acting BZDs[b]				
Diazepam	Fast	Oxidation	24 – 48[b,c]	Anxiolytic Hypnotic Anticonvulsive Muscle relaxant
Chlordiazpepoxide	Intermediate	Oxidation	6-27[b]	Anxiolytic
Medazepam	Intermediate	Oxidation	2-5[b]	Anxiolytic
Halazepam	Fast to intermediate	Oxidation	30-40[b]	Anxiolytic
Prazepam	Slow	Oxidation	1-3[b]	Anxiolytic

This table outlines basic pharmacokinetic properties of commonly used BZDs. Properties such as onset of action[50] and biological half-life[16,51] influence the choice of BZD in clinical practice. The biological half-life of BZDs given in the table might be prolonged in clinical situations when the activity of metabolizing enzymes is negatively influenced by factors such as hepatic impairment, drug interactions on enzymes (inhibition), age-related changes, and others. It is needed to account also for the half-life of active metabolites where applicable (e.g., diazepam, chlordiazepoxide, prazepam, medazepam), which may be influenced by changes in activity of CYP enzymes as well. For the purposes of insomnia treatment, the rapid onset of action in combination with medium duration of action is preferred.[16] However, in some patients this effect may be perceived as drowsiness, loss of control, muscle relaxation, and a feeling of being "spaced out". [9] Long-acting BZDs can result in daytime sleepiness and a hangover effect, while short-acting BZDs can cause daytime anxiety and memory impairment.[16] BZDs with long half-life may accumulate in adipose tissues and their action may be prolonged when used in older people. BZDs with a slower onset of action (e.g., oxazepam, lorazepam) might be of benefit in anxiolytic indication and situations when the prompt effect is not desired.[9]

BZDs, benzodiazepines; CYP, cytochrome P450.

[a] Classification and values may differ in the literature.

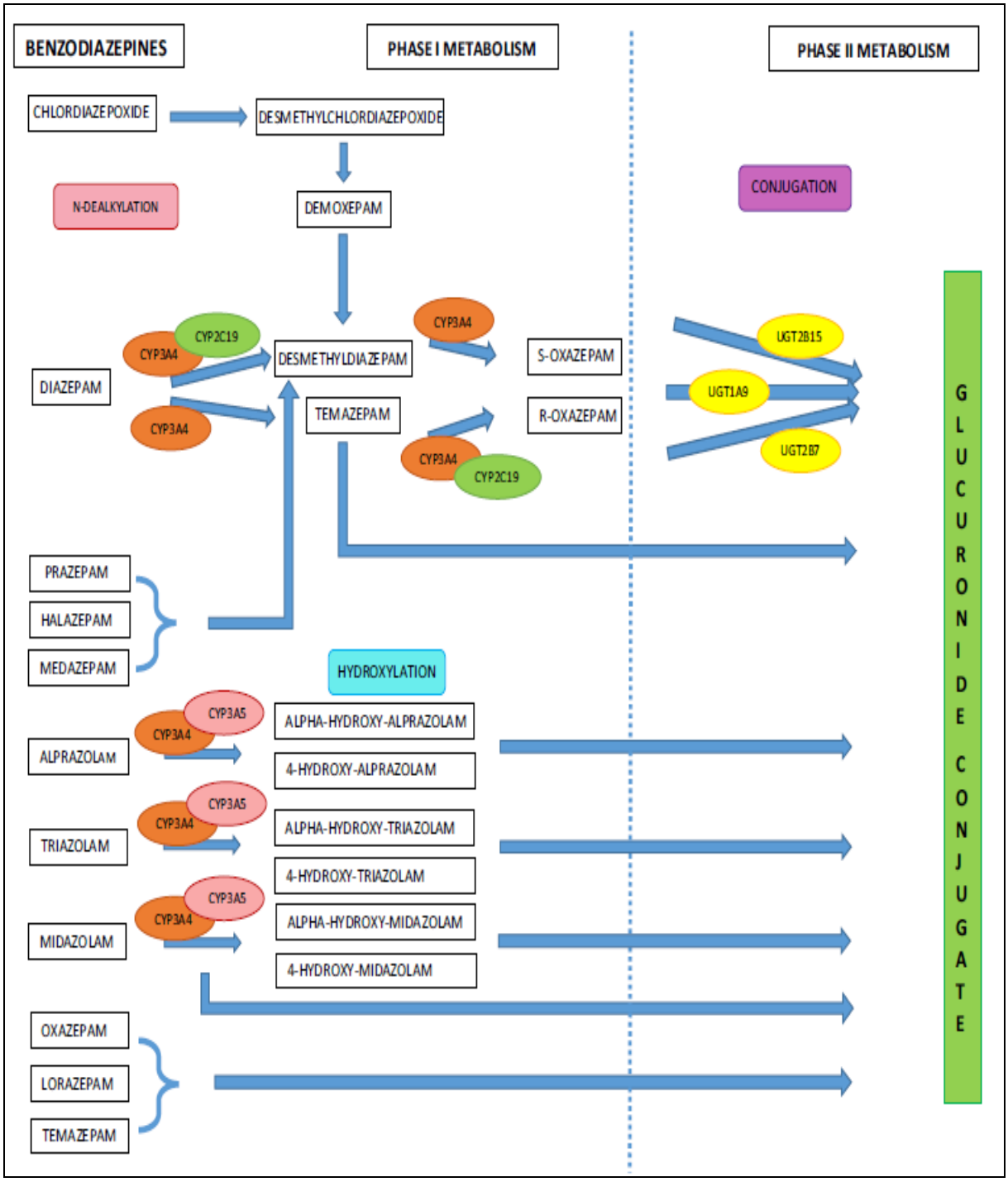
[b] Long half-life of long-acting BZDs is largely caused by their active metabolites. Half-life given in the table represents the half-life of parent compound.

[c] Drug has an active metabolite desmethyldiazepam with half-life of 40–80 h.

BZDs are extensively bound to plasma proteins (70–99%). The extent of binding to plasma proteins is important in regards to the concentration of so-called “free fraction” — the fraction of an active substance unbound to plasma proteins and responsible for the magnitude of pharmacodynamic effect. Various pathological changes may substantially impair the concentration of plasma albumin (the main plasma protein), for example, hepatic impairment, renal insufficiency, severe burns, etc. In old age, hepatic synthesis and plasma concentration of albumin may be lowered due to several physiological and pathological changes (by 4–20%) and may significantly increase the concentration of free BZDs fraction and transfer of BZDs across the BBB. In such situations there is a higher possibility of AEs of BZDs.

Principal pathways of BZD biotransformation (Figure 2) are hepatic microsomal oxidation, N-dealkylation, aliphatic hydroxylation, and glucuronide conjugation. Many enzymes of the CYP are involved in phase I of BZD metabolism; the most frequent are CYP3A4, CYP3A5, and CYP2C19.[10-15] Phase II of BZD metabolism is catalyzed mainly by uridine 5-diphospho-glucuronosyltransferase (UGT). According to the metabolic pathway involved in the biotransformation of some BZDs, co-administration of two drugs may result in potential or clinically significant drug–drug interaction. Due to decreased hepatic clearance (decreased activity of some metabolic pathways or increased production of some active metabolites), some drug–drug or drug–disease interactions may occur with higher significance.

Figure 2. Metabolic pathways of most common BZDs.



Principal pathways of BZD biotransformation include hepatic N-dealkylation, hydroxylation, and glucuronide conjugation. In phase I of BZD metabolism, there are numerous enzymes of the CYP involved: CYP3A4, CYP3A5, and CYP2C19 being the most frequent.[10-15] In phase I of metabolism, usually pharmacologically active metabolites of BZDs are created. These metabolites may have a long half-life (e.g., desmethyldiazepam up to 80 h). Many other drugs can be substrates, inhibitors, and/or inductors of CYP3A4, CYP3A5, and CYP2C19 isoenzymes. According to the metabolic pathway involved in the biotransformation of BZDs, coadministration of two or more drugs may result in potentially or clinically significant drug–drug interactions. Oxazepam, lorazepam, and temazepam are metabolized just in phase II, which is catalyzed mainly by UGT enzymes.[52, 53]
BZD, benzodiazepine; CYP, cytochrome P450; UGT, uridine 5-diphospho-glucuronosyltransferase.

Division of BZDs according to duration of their half-lives into short-acting, medium-acting, and long-acting BZDs is well known. BZDs having a long half-life are usually transformed also into active metabolites, which may accumulate during repeated administration.[16] When given in hypnotic indication, long-acting BZDs can cause a hangover effect and daytime sleepiness.[16] On the other hand, BZDs with rapid elimination such as triazolam can cause daytime anxiety and memory impairment.[16] Therefore, rapid onset in combination with a medium duration of action, are desired when BZDs are administered as hypnotics.[16] Similarly, different pharmacokinetic and pharmacodynamic properties of BZDs predict their therapeutic value in different clinical situations (risk/benefit ratio). The appropriate choice of particular substance in appropriate dosage regimen, drug combination, duration of the treatment, and administration to an appropriate patient may significantly increase the efficacy and decrease the risk of AEs of BZDs.

Aging, changes in BZD properties, and their consequences

There are a number of changes in pharmacokinetics and pharmacodynamics of drugs in the aging human body that have already been well reported.[17-19] Complex alterations in pharmacokinetic as well as pharmacodynamic properties of BZDs influence their beneficial therapeutic effect and propensity to cause AEs.

Age-related changes at the level of drug absorption involve reduction in splanchnic blood supply, reduction in peristaltic movements and atrophy of GIT mucosa.[20] There is also an association between aging and reduction in first-pass metabolism of drugs due to progressive reduction of liver volume and liver blood flow.[20] Therefore, bioavailability of drugs undergoing extensive first-pass metabolism, such as triazolam and midazolam, can be significantly increased. However, low-hepatic clearance drugs (e.g., diazepam) are said to be more affected by activity of intrinsic hepatic clearance determined by the activity of drug metabolizing enzymes within the hepatocyte.[21]

Distribution of lipophilic drugs, such as BZDs, may be affected by body fat increase and lean body mass decrease due to aging processes.[18,19] Consequently, increased distribution volume of lipophilic substances and their accumulation in adipose tissues lead to

prolongation of elimination half-life and duration of action of the drug, for example, elimination half-life of diazepam may increase up to 200 h in very old patients. Free fraction of drugs extensively bound to plasma proteins can be increased as a result of decreased levels of albumin in older people.[18,22]

Studies of drug-metabolizing enzyme content and activity in aging organism yielded conflicting results. Sotaniemi, Arranto, Pelkonen, and Pasanen (1997)[23] showed that CYP content in the liver biopsy declines at a rate of approximately 0.07 nmol/g per year after 40 years of age; while other studies found inconsistent results of reduction, paradoxical increase, or no significant change in hepatic clearance of drugs in older people[24]. Thus, we can expect changes in biotransformation of BZDs mainly metabolized via this enzymatic system (e.g., diazepam, chlordiazepoxide, alprazolam, midazolam, and triazolam). However, some researchers assume the decrease in liver size and blood flow to be the main reason for reduction of hepatic clearance of lipophilic drugs metabolized by CYP isoforms rather than the change in enzyme activity.[20,21,25,26] The conjugation metabolic pathway (phase II metabolic pathway) is usually less impaired or unimpaired in older adults[27] compared to CYP metabolic isoenzymes. Therefore, the use of oxazepam and lorazepam (the BZDs metabolized by UGT metabolism) might be a better choice in older patients, and these substances represent the antianxiety drugs of choice in older patients in case BZDs are indicated. Nevertheless, the literature shows that there might be also an impaired clearance of drugs undergoing conjugation in frail older people.[28] Physiological and functional changes in kidney affect the clearance of mainly water-soluble drugs.[20]

There is a wide spectrum of pharmacodynamic changes in aging organisms. Changes in the sensitivity of the autonomic nervous system, particularly diminishing sensitivity of baroreceptors, predispose older people to postural hypotension.[21] A number of medications, such as nitrates, centrally acting antihypertensives, and diuretics, can potentiate postural hypotension. Older patients are more likely to lose their balance after triazolam administration.[29] Impaired production of neurotransmitter peptides and changes in receptor affinities result in a higher sensitivity of CNS to BZDs.[26] It has been reported that a lower dose and lower plasma concentration of diazepam are required to produce a sedative effect in older patients.[22] This is most likely to be true also for other BZDs.

Due to age-related pharmacological changes of BZDs (increase in plasmatic levels of BZDs and increase in pharmacodynamic sensitivity to BZDs), the pharmacological activity of these medications in older patients may be almost double after administration of the same dose as in younger adults. For this reason, the dose of BZDs in older patients should be at least half the usual (standard) dose applied in younger adults. This rule is emphasized in many expert panel criteria of PIMs and also in the latest update of Beers Criteria published by the American Geriatrics Society in 2012[4].

Scope of falls: definition, epidemiology, causes, and consequences of falls

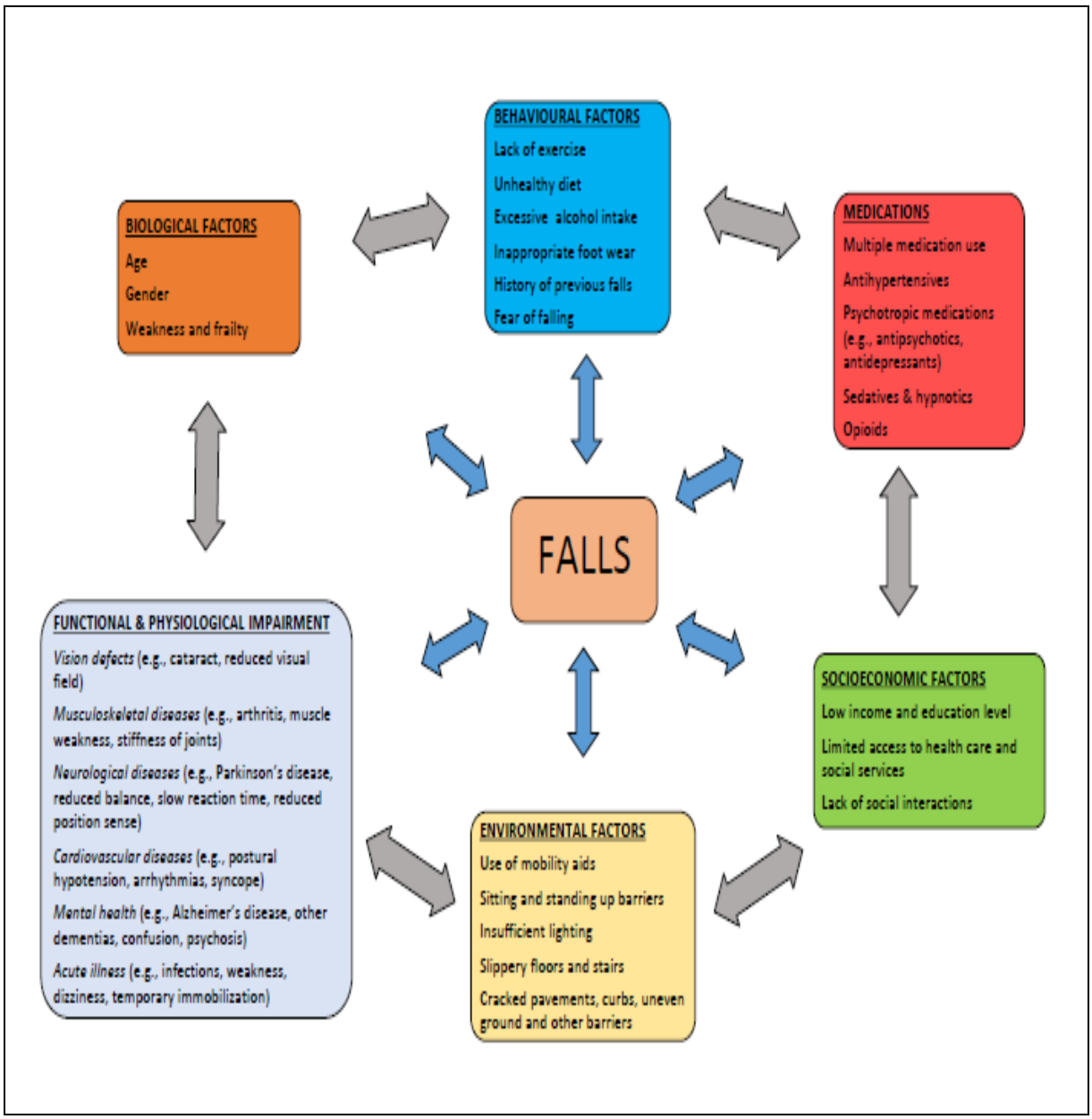
According to the World Health Organization (WHO) (2007)[30], fall is defined as *"inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest in furniture, wall or other objects."* Although the definition and meaning of fall might seem obvious, the interpretation of falls by patients, health professionals, and researchers might often differ. Older people usually refer to a fall as a loss of balance, whereas health professionals tend to describe it as an event leading to injuries and illness.[31] For epidemiological and intervention studies purposes, it is necessary to use a standardized and well-recognized definition and ascertain the questions construction in the assessment form and their consecutive evaluation.[32]

The incidence of falls varies among settings and populations. Between 20% and 33% of older people in community settings fall each year, with the relative rates increasing approximately 5% per year with cohort aging.[32] Multiple falls (two or more) are experienced by 25–50% of older people and up to 75% in the oldest old.[33] Falls occur predominantly in frail older people with multiple comorbidities and represent one of the major factors of patients moving to care homes.[34] Older people in care settings are particularly vulnerable with high prevalence of clinical impairment and functional disability, leading to an increased incidence of falls and fall-related injuries.[35] Residents of residential care facilities experience nearly five times more falls compared to community dwelling people of the same age.[32] Accidental falls

in patients hospitalized in acute care settings represented 30–40% of reported safety incidents.[34]

There are a number of risk factors of falls in older people originating from their own accumulated effects of age and comorbidities, interaction with surrounding environment[35], and risk-taking behaviour. A fall occurring in an older person is a complex interaction of risk factors. The more risk factors an old person is exposed to, the greater is the risk of falling and being injured. A complex of risk factors influencing the occurrence of falls in older people is shown in Figure 3.

Figure 3. Risk factors of falls.



Falls in older people have a multifactorial nature and represent a complex interaction of risk factors. Risk factors can be divided into particular subgroups: biological factors, factors of physiological and functional impairment, behavioral factors, medication use risk factors, socioeconomic factors, and environmental factors. The interaction of these risk factors is multidimensional, and their composite effect influences the occurrence of falls. The more risk factors an old person is exposed to, the greater is the risk of falling and being injured.

Age is associated with changes in physical, functional, cognitive, and affective capacities. There is an exponential increase of falls, fall-related injuries, and fall-related deaths with age, with women being more likely to fall and sustain a serious fracture.[32] Despite fewer occurrences of falls among men, falls in this gender are associated with more deaths and fatal injuries.[32] Chronic diseases of the cardiovascular, musculoskeletal, and neurological systems worsen the functional status of older people and deepen their dependency. In order to maintain independence, regular moderate physical activity, appropriate exercise, and a healthy diet and nutrition intake should be present in older people. Exercise can improve mobility, balance, and reaction time as well as bone mineral density in postmenopausal women.[30] A balanced diet with an appropriate amount of protein, calcium, vitamin D and other essential vitamins, and water may decrease the risk of injuries due to falls.[30] It has been shown that excessive intake of alcohol (14 or more drinks per week) is associated with an increased risk of falls in older people.[36]

A history of previous falls may predict a future fall and is associated with a threefold increase of risk of another fall in the future.[37,38] Previous falls resulting in reduced mobility, loss of strength and balance, and a fear of falling, being hurt, or hospitalized have also been identified as potential risk factors for future falls.[37]

Medication intake is another important group of risk factors associated with falls and fall-related injuries. Polypharmacy (defined as the use of five or more medications) and particular drug classes have been reported as potential risk factors leading to falls in older people.[38,39] Physiological and functional changes of aging organisms may result in unpredictable effects of some medications such as antihypertensives, psychotropic medications (e.g., antipsychotics, antidepressants), hypnotics and sedatives, and analgesics (e.g., opioids). Table 2 shows medications associated with falls in older people and their proposed mechanism of fall-related AEs. Woolcott et al. (2009)[40] showed that the use of sedatives and hypnotics, antidepressants, and BZDs in older patients demonstrated a significant association with falls.

Environmental factors involving stairs, slippery floors, insufficient lighting, cracked pavements, etc. may considerably contribute to safety decrease in the everyday lives of

older people.[30] There have been a few studies showing that social determinants such as low income, education, housing, and social involvement may affect the health status and level of disability. These determinants may result in chronic health conditions and lack of access to appropriate health or social services that are, in turn, risk factors for falls.[37] Experiencing a fall may have various consequences on one's quality of life. Falls in older people are strongly associated with hip fractures, other fall-related injuries (e.g., brain haemorrhage), fall-related hospitalizations, and death.[30,32,37] Although not every fall-related injury is fatal, it may still impair an individual's existing comorbidities and, coupled with pneumonia or infection, indirectly result in death.[37] Falls and consequent injuries can often result in a patient's immobility and lead to reduced activity, loss of muscle mass and muscle tone, and also impair movement coordination. Immobilization of a patient may further generate inability to leave home, travel, or even perform everyday activities. Consequently, falls may affect a patient's mental health status and lead to depression, fear of falling, and a loss of confidence, creating a vicious cycle of risk factors of falls.

Table 2. Medications commonly associated with falls.

Medication class	**Fall-related (adverse) effects**
CNS acting drugs	
Benzodiazepines diazepam bromazepam flurazepam midazolam alprazolam oxazepam temazepam lorazepam	Sedation Dizziness Fatigue Postural hypotension Coordination impairment Slowed thoughts Cognitive impairment Confusion Delirium
Antipsychotics haloperidol clozapine olanzapine quetiapine chlorpromazine risperidone	Sedation Postural hypotension Dizziness Slowed movements Shuffling gait Blurred vision Confusion Anticholinergic effect
Antidepressants amitriptyline imipramine clomipramine trimipramine	Sedation Orthostatic hypotension Confusion Blurry vision Anticholinergic effect
Opioids codeine fentanyl hydrocodone oxycodone meperidine pentazocine morphin	Sedation Daily sleepiness Dizziness Confusion
Cardiovascular drugs	
Centrally acting antihypertensives methyldopa clonidine reserpine	Postural hypotension Bradycardia
Diuretics hydrochlorothiazide chlorthalidone furosemide	Postural hypotension Dehydration Lethargy

Table 2. Medications commonly associated with falls. – *Continued.*

Medication class	Fall-related (adverse) effects
Antiarrhytmics and vasodilating drugs digoxin procainamide propafenone diltiazem nifedipine verapamil nitroglycerine isosorbide dinitrate	Hypotension Postural hypotension Arrhythmias Syncope
Medications with anticholinergic effect	
1st generation antihistamines brompheniramine chlorpheniramine hydroxyzine **Skeletal muscle relaxants** carisoprodol orphenadrine tizanidine **Antimuscarinics for urinary incontinence** oxybutynin solifenacin tolterodine **Antispasmodics** atropine products hyoscyamine products scopolamine belladonna alkaloids	Blurred vision Drowsiness Dizziness Sedation Confusion Delirium

This table presents a list of medications commonly associated with falls and the proposed mechanisms contributing to falls in older patients. This table was created based on an expert panel consensus of PIMs in old age published by the American Geriatrics Society in 2012[4]. Reasons of inappropriateness of particular medications may be strongly associated with AEs such as falls. The list of medications is not exhaustive, and this table provides only examples of main medications within each drug class. The information cannot be fully comprehensive considering differences between pharmaceutical markets and medications' approvals across countries

PIMs, potentially inappropriate medications.

BZDs as risk factors of falls in older patients

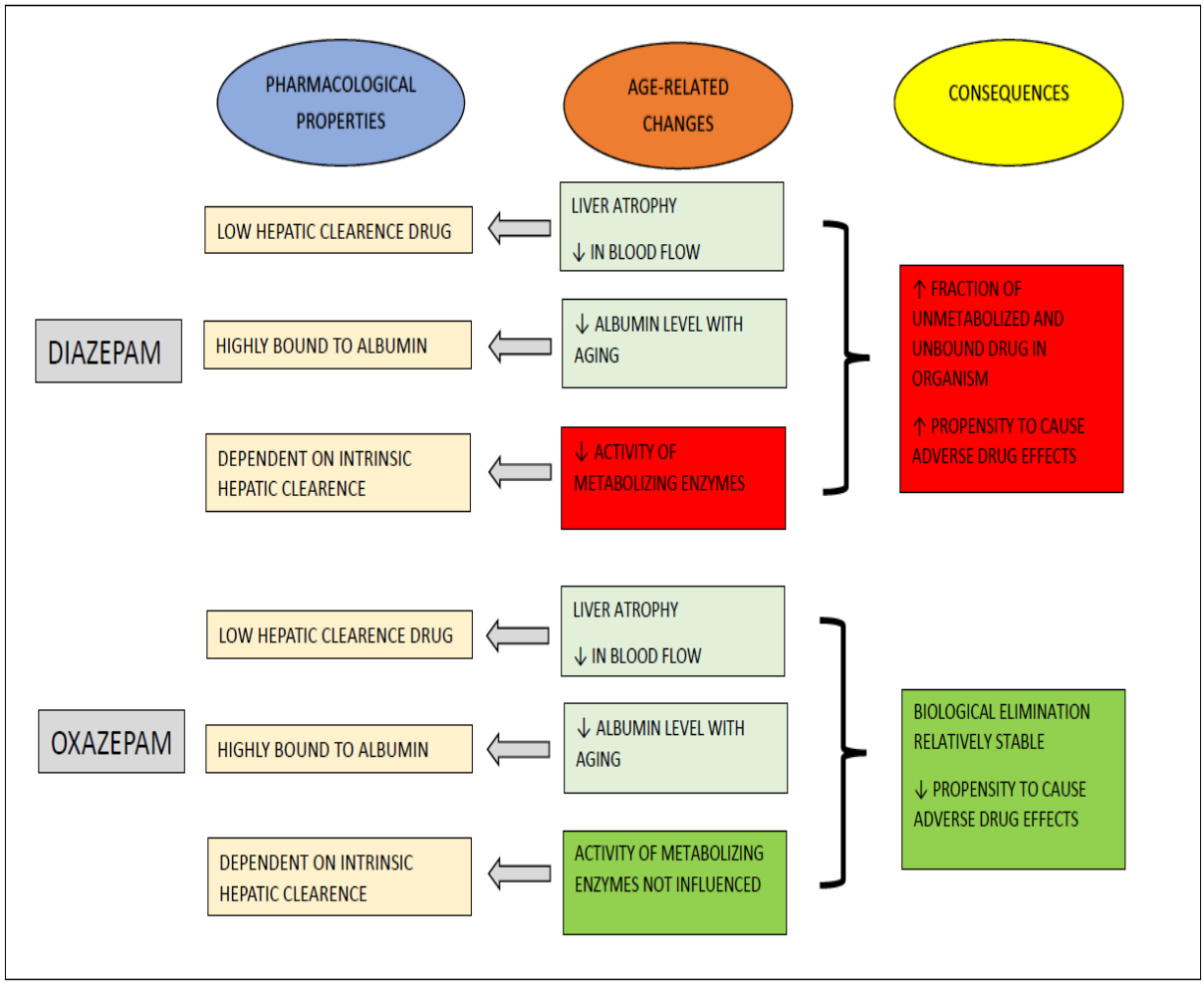
Several studies have evaluated the relationship between BZDs and falls and yielded conflicting results. The incidence rates of in-hospital falls range from 2.9 to 13 falls per 1000 bed-days.[25] However, there has been found a poor association with the use of BZDs. The lack of statistical differences between incidence rates of in-hospital fallers among users of BZDs compared with nonusers[41] may be confounded by the short time period of BZD use during patients' hospitalization as well as by different incidence rates of falls themselves in particular hospital wards. However, when examining in-hospital hip fractures, there has been reported nearly a twofold increase of risk of fractures in BZD users compared with nonusers[42] and an increased risk of falls with short half-life and very short half-life BZDs in particular[43]. Therefore, the relationship between in-hospital falls and the use of BZDs remains unconfirmed. It is also questionable how the new use of BZDs during hospitalization and/or their secession may influence the risk of falling, as these data are rarely collected.

A meta-analysis of nine medication classes involving older individuals reported nearly a 40% increase in the risk of falls in older patients using BZDs in general.[40] There have been a few studies focusing on the association between falls and BZDs according to their half-lives. However, the research evidence is again mixed. Users of long half-life BZDs have been shown to have a greater risk of falls and hip fractures when compared with nonusers.[44, 45] On the other hand, the relationship between short half-life and very short half-life BZDs and falls has also been found in some studies[43], showing an increase of risk with increasing elimination half-life[46]. In the study focusing on differences between particular BZDs, patients using long half-life diazepam were over three times more likely to have a fall compared with BZD nonusers and almost seven times more likely to have a fall when compared with oxazepam users.[41] Interestingly, some authors postulate that dose intensity and frequency are strongly correlated to falls and hip fracture occurrences rather than to the biological half-life of BZDs.[45,46]

A possible explanation for the above mentioned findings may relate to the age-specific changes in the pharmacokinetic and pharmacodynamic properties of individual BZDs

(Figure 4). For example, diazepam is a subject to low hepatic clearance. Therefore, its elimination half-life and pharmacodynamic action are dependent on the unbound fraction of the drug in the blood and on intrinsic hepatic clearance determined by the activity of CYP.[21] As the activity of enzymes of phase I of biotransformation is decreased by aging, diazepam remains as an active parent compound in the blood for a longer time. Metabolism of diazepam's active metabolites (temazepam, desmethyldiazepam, and oxazepam) might be decreased as well and they can accumulate in the adipose tissues. As plasma protein level declines by aging, there is a higher concentration of unbound fraction of diazepam (and its metabolites) available to cross the BBB and act on $GABA_A$ receptors. All together with higher sensitivity of receptors to sedative and hypnotic effects and changes in pharmacological properties with aging, diazepam may have a higher propensity to cause adverse drug effects. On the other hand, despite oxazepam being a low hepatic clearance drug with extensive plasma protein binding, similar to diazepam, it is metabolized solely by glucuronidation — phase II of biotransformation. There are no active metabolites of oxazepam, and after conjugation it is eliminated by urine. It is of importance to mention that current findings suggest some changes in glucuronidation enzymes associated with frailty in oldest old patients.[47] However, in terms of pharmacological profile, we can consider oxazepam being the preferable choice in older patients when used in appropriate indication and dose.

Figure 4. Potential pharmacokinetic properties leading to the difference between diazepam and oxazepam in older people.



Diazepam and oxazepam are subject to low hepatic clearance. Therefore, their elimination half-life and pharmacodynamic action are dependent on the unbound fraction of the drug in the blood and on intrinsic hepatic clearance determined by the activity of CYP.[21] In the case of diazepam, which is metabolized by enzymes of phase I of biotransformation, the metabolism decreases with aging and diazepam remains as an active parent compound (and its metabolites) in the blood for a longer time. As plasma protein levels decline with aging, there is a higher concentration of unbound fraction of diazepam available to cross the BBB and act on the $GABA_A$ receptors. These properties may influence diazepam's propensity to cause AEs. On the other hand, oxazepam is metabolized solely by glucuronidation with no active metabolites. Its pharmacological profile is said to be uninfluenced by age-related metabolism changes. Consequently, we can consider oxazepam to be the more preferable choice in older patients when used in appropriate indication and dose.
$GABA_A$, γ-Aminobutyric acid type A receptor; CYP, cytochrome P450; BBB, blood–brain barrier.

Applications to other addictions and substance misuse

In this chapter, falls as an AE of BZD use were described from the perspective of age-related changes in organism, pharmacological properties of particular BZDs, and in the context of other risk factors of falls. Aging, as a continuous process, influences together with other factors, changes in human body physiology and functions resulting in the accumulation of chronic diseases, impairment of functional and clinical status, and worsening of one's dependency. These changes are usually accompanied by multiple medication use, including the use of PIMs. Psychotropic medications and CNS-acting drug classes such as opioids, sedatives, hypnotics, and antidepressants listed in the Beers Criteria[4] have been evaluated also as drugs associated with addiction and dependence. Moreover, it is not unusual to see these medications being taken simultaneously.

Regarding the abuse pattern in the adult population, BZDs are usually not the sole preferred drug of abuse, with about 80% of BZDs being a component of polydrug abuse, particularly in combination with opioids[48]. Current evidence suggests a relatively rare abuse of illegal drugs in the older population compared with younger adults and adolescents; however, the misuse and abuse of prescription medication with abuse potential should be perceived as an increasing problem in this population[49]. Older people represent a vulnerable group exposed to polypharmacy due to chronic comorbidities. Opioids and BZDs are being prescribed for pain, anxiety, and insomnia that are highly prevalent health problems in this population. Psychoactive medications with misuse and abuse potential are prescribed to approximately 25% of older people[49]. In addition to the age-related changes in pharmacokinetics and pharmacodynamics of many drugs, long-term use of medications can potentiate the risk of misuse and abuse.

It terms of falls in older people it is important to realize the multifactorial nature of this AE. As stated in previous sections, one of the essential risk factors of falls is the use of particular medications. The combination of two or more medications with falls potential can therefore increase the risk of this adverse event in older patients.

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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

Full text of Chapter 2 was submitted as a manuscript for publication:

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

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Abstract

Background

Use of BZDs and Z-drugs is common in older patients due to frequent anxiety and sleep disorders. The sedative potential of these drugs can be significantly altered by age-related pharmacological changes and result in adverse drug events.

Objective

To describe the prevalence of BZD/Z-drug use in nursing home residents and investigate country-specific prescribing patterns and independent risk factors associated with excessive BZD/Z-drug use.

Methods

This was a retrospective cross-sectional study analysing data of the SHELTER project. Data were collected prospectively during September 2009 - December 2011 using interRAI LTCF. Baseline study data (Sept-Dec 2009) were in this analysis. Data were collected in 57 nursing home facilities in 7 European countries (The Czech Republic, England, Finland, France, Germany, Italy, and The Netherlands) and Israel. Study participants included nursing home residents (approximately 500 residents per country) aged 65 years and older. Prevalence of BZDs/Z-drugs, prescribing patterns in participating countries and independent risk factors associated with their use were evaluated as main outcomes.

Results

Of 4,156 nursing home residents (73% women, mean age 83.4 ± 9.4); 1,113 (27.7%) used BZDs/Z-drugs. The highest prevalence of BZDs/Z-drugs was in Israel (44.1%), France (44.0%) and The Netherlands (26.5%). The most frequently prescribed 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 6.7; 95% Confidence Interval [CI] 4.8-9.2; OR for France 5.3; 95% CI 3.5-7.9; OR for The Netherlands 2.4; 95% CI 1.7-3.4) and specific disorders: insomnia (OR= 3.3; 95% CI 2.5-4.3), anxiety (OR 1.9; 95% CI 1.4-2.6), depression (OR 1.1; 95% CI 1.02-1.09), and pain (OR 1.1; 95% CI 1.004-1.234).

Conclusions

This study provides evidence about differences in BZD/Z-drug prevalence and prescribing patterns. Association with the country of residents denotes that social, cultural, economic and behavioural factors may play role in the uniqueness of use of these medications across countries.

Introduction

The nursing home (NH) environment should be considered a specific setting because of high prevalence of polymorbidity, polypharmacy, disability, geriatric syndromes and potentially inappropriate prescribing.[1-7] The variation in older population characteristics, criteria for admission to NH and prescribing policies across countries may contribute to significant differences in the quality of medications prescribed.

Many chronic conditions and geriatric syndromes common among NH residents (e.g., depression, dementia, anxiety, insomnia and behavioural and psychological symptoms of dementia)[8] are associated with adverse outcomes, reduced quality of life[9] and increasing care costs[10]. Despite of the evidence on limited effectiveness and potential harm[10-12], BZDs and Z-drugs are frequently used for management of geriatric syndromes. BZDs are prescribed for anxiety disorders, insomnia, as muscle relaxants, and as adjuvant therapy for depression or schizophrenia.[13,14] The indication for Z-drugs (selective benzodiazepine receptor agonists: zolpidem, zopiclone, zaleplone and eszopiclone) is the treatment of insomnia.[15] The proportion of prescription of BZDs in NHs in different studies ranged from 13% to 54%[8,16-22], while the prevalence of Z-drug use was reported between 15.4%-24.4%[23-26].

There is a particular concern about the use of BZDs and Z-drugs in older patients and mainly in frail older patients, as the evidence on their effectiveness is relatively small[27], while their potential for adverse drug events such as falls, fractures, cognitive impairment, functional decline, and delirium has been well described.[23,28-34] Consequently, recommendations and policies to reduce prescription and consumption of BZDs and Z-drugs have been developed in many European countries.[15]

Previous studies reported a wide range of prevalence of BZD/Z-drug use in different settings of care across countries. Since these studies used various methods of data collection and evaluation, direct comparisons are difficult. The objective of this study was to identify the prevalence, risk factors and patterns of BZD and Z-drug use in older NH residents across

7 European countries and Israel, using the interRAI LTCF. This instrument enabled description and cross-country comparisons of health and functional status in older NH residents in several countries at the same time period. Special focus was given to explanation of country-specific prescription patterns of individual BZDs/Z-drugs and to description of factors associated with excessive use of these medications.

Methods

Study design

Data were collected as a part of the SHELTER project involving NH residents aged 65 years and older residing in 57 NH facilities in 7 European countries (The Czech Republic, England, Finland, France, Germany, Italy, and The Netherlands) and Israel. The SHELTER project was conducted in September 2009 - December 2011. For our analyses the data from the baseline assessment period (Sept - Dec 2009) were used. This project has been primarily designed to assess validity and reliability of the interRAI LTCF. One of the main aims of the project was to implement the interRAI LTCF instrument in a larger population and to create a unique database enabling comparisons of characteristics and outcomes of NH residents across different countries and health systems.[35] A complete and detailed description of the project methodology has been published elsewhere.[35]

Data collection

The interRAI LTCF assessment tool is a setting-specific instrument developed by the interRAI corporation a scientific not-for-profit organisation, and has been completely standardized, revised and validated during the past decades.[36] It comprises over 350 data elements including socio-demographic information, clinical status items, physical and cognitive status, medical diagnoses, symptoms, signs as well as patient medication information. There are a number of scales embedded within the instrument combining several single items that have been previously tested, standardized and validated to measure various clinical characteristics. Functional status was described by the Activities of Daily Living scale (ADL)[37] and ADL Hierarchy scale (ADLH)[37]. Cognitive status was evaluated using the Cognitive Performance Scale 2 (CPS2).[38] Depression presence and severity was captured by the

Depression Rating Scale[39]. The Pain scale[40] was used to summarize presence and intensity of pain. Communication abilities were measured by the Communication scale.[41] The level of consciousness was evaluated using Clinical Assessment Protocol (CAP)[42] for delirium. For detail description of scales used in analyses see the footnotes to Table 3 and Table 4.

The original version of the interRAI LTCF assessment tool was translated from English into languages of participating countries. About 500 residents from different NH facilities and geographical regions in each country participated in the SHELTER project. Study subjects were assessed by trained assessors. No exclusion criteria were adopted. Drug information included all medications patients had been taking in the 3 days prior to the assessment. Medication information was derived from multiple sources, including physician order sheets and medication administration record. The drug name (non-proprietary, proprietary), Anatomical Therapeutic and Chemical (ATC) code based on the WHO Collaborating Centre for Drug Statistics Methodology[43], formulation, dosage, frequency and route of administration were recorded. A complete and detailed description of data collection has been published elsewhere.[4, 35]

Outcome measures

In order to capture all possible existing BZDs and Z-drugs, the dataset was searched for all ATC codes available for these medication groups (Table 1). To capture the regular use of BZDs/Z-drugs, all medications described in the dataset as "used as needed" were excluded from the analyses. Analyses were conducted with all BZDs and Z-drugs regardless of their formulation, dosage, frequency or route of administration. According to use of BZDs/Z-drugs, patients were divided into four groups: non-users of BZDs/Z-drugs, users of BZDs/Z-drugs (all user of BZDs/Z-drugs), users of single BZD/Z-drug (patients using just a single drug from BZD/Z-drug group) and users of multiple BZDs/Z-drugs (patients using more than one BZD/Z-drug).

Table 1. List of ATC codes and drug names included into the analyses within the dataset.

ATC code	**Drug name**
Benzodiazepine anxiolytics	
N05BA01	Diazepam
N05BA02	Chlordiazepoxid
N05BA03	Medazepam
N05BA04	Oxazepam
N05BA05	Potassium Clorazepate
N05BA06	Lorazepam
N05BA07	Adinazolam
N05BA08	Bromazepam
N05BA09	Clobazam
N05BA10	Ketazolam
N05BA11	Prazepam
N05BA12	Alprazolam
N05BA13	Halazepam
N05BA14	Pinazepam
N05BA15	Camazepam
N05BA16	Nordazepam
N05BA17	Fludiazepam
N05BA18	Ethyl Loflazepate
N05BA19	Etizolam
N05BA21	Clotiazepam
N05BA22	Cloxazolam
N05BA23	Tofisopam
N05BA56	Lorazepam, combinations
Benzodiazepine hypnotics	
N05CD01	Flurazepam
N05CD02	Nitrazepam
N05CD03	Flunitrazepam
N05CD04	Estazolam
N05CD05	Triazolam
N05CD06	Lormetazepam
N05CD07	Temazepam
N05CD08	Midazolam
N05CD09	Brotizolam
N05CD10	Quazepam
N05CD11	Loprazolam
N05CD12	Doxefazepam
N05CD13	Cinolazepam
Z-drugs	
N05CF01	Zopiclone
N05CF02	Zolpidem
N05CF03	Zaleplon
N05CF04	Eszopiclone

Statistical analyses

Frequency distributions were used to describe the characteristics of the sample population and the prevalence of BZD/Z-drug users. To identify the relationship between BZD/Z-drug use and characteristics of the sample population, univariate analyses were conducted. For continuous variables the parametric (t-Test) or non-parametric (Mann-Whitney U Test) comparisons of means were used, depending on the distribution of the data. For categorical data Pearson's Chi-Square Test was performed. The relationship between factors potentially influencing the prescription of BZDs/Z-drugs was observed using univariate logistic regression. To estimate the relationship between the country of residence and use of BZDs/Z-drugs multivariate logistic regression was performed adjusted for factors: age, gender, functional and cognitive status, anxiety, insomnia, depression, delirium, pain, and communication problems. The level of significance was set at $p<0.05$ and all proportions were calculated as percentages of patients with available data. Analyses were performed using SPSS_ IBM Version 20 (SPSS, Inc., Chicago, IL, USA).

Ethics

Ethical approval was obtained from all subjects participating in the study in all countries, according to the local regulations. Participating subjects were invited to the study and were free to decline participation. Consent was obtained with assurance of data confidentiality.

Results

Of a total sample of 4,156 patients, 133 were excluded due to missing medication records. The sample population was of a mean age (± standard deviation [SD]) of 83.5 ± 9.4 years and a majority (73.2%, n=2,945) were women. The mean ± SD number of regular medications was 7.0 ± 3.6.

27.7% (n=1,113) of patients used BZDs/Z-drugs at the time of assessment. There were total of 1,255 BZDs/Z-drugs used in the sample. The difference between the number of BZD/Z-drug users and the number of BZDs/Z-drugs used accounts for 111 users of multiple BZDs/Z-drugs (users of more than 1 BZD and/or Z-drug) representing 10% of all BZD/Z-drug

users. The five most frequent BZDs/Z-drugs were zopiclone, lorazepam, oxazepam, brotizolam, and zolpidem (17.8%, 17.7%, 16.9%, 13.8%, and 11.7%; respectively). For details on frequencies of the use of particular BZDs/Z-drugs and their duplicates see Table 2.

Table 2. Prevalence of particular BZD/Z-drug users in the sample.

Drug	Frequency	Duplicity of prescribing[a]	Total number of prescribed BZDs/Z-drugs in the sample[b]	Percentage of BZD/Z-drug users (%)
Zopiclone	198	0	198	17.8
Lorazepam	190	7	204	17.7
Oxazepam	182	5	195[e]	16.9
Brotizolam	154	0	154	13.8
Zolpidem	130	0	130	11.7
Alprazolam	115	5	125	10.8
Temazepam	106	0	106	9.5
Bromazepam	39	1	41	3.6
Diazepam	34	3	40	3.3
Midazolam	23	0	23	2.1
Triazolam	9	0	9	0.8
Lormetazepam	9	0	9	0.8
Nitrazepam	7	0	7	0.6
Clobazam	4	0	4	0.4
Flunitrazepam	3	0	3	0.3
Potassium Clorazepate	2	0	2	0.2
Flurazepam	2	0	2	0.2
Tofisopam	2	0	2	0.2
Prazepam	1	0	1	0.1
TOTAL	1,210[c]	21	1,255	110.7[d]

[a] Duplicity – this column represents multiple BZD/Z-drug users who received two same drugs from the BZD or Z-drug groups

[b] Total number of BZDs/Z-drugs prescribed in the sample is calculated as frequency + (number of duplicities x2).

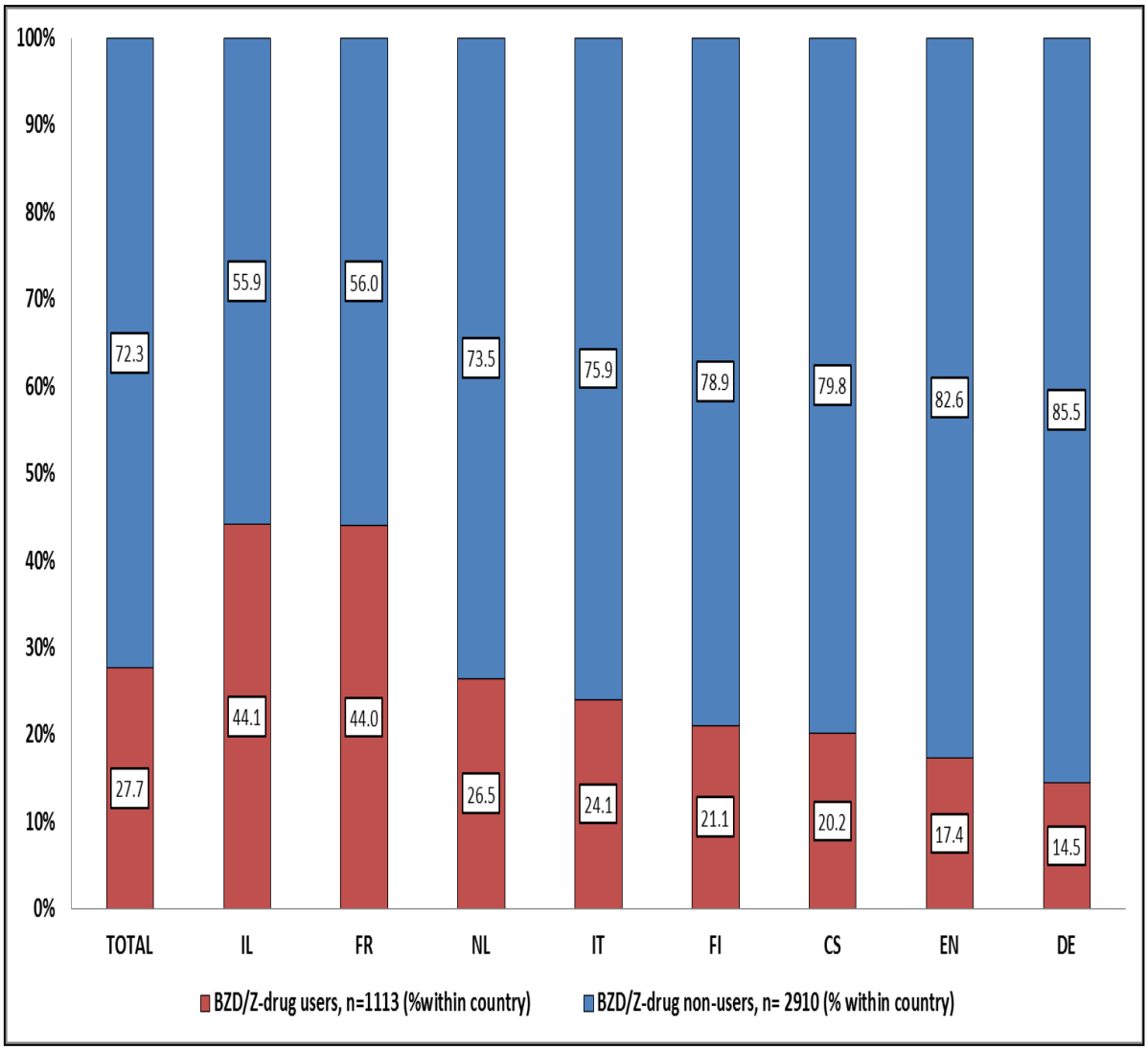
[c] Total number of BZDs/Z-drugs in this table is not mutually exclusive and contains of duplicities within and across particular drugs.

[d] The total percentage of BZDs/Z-drugs overtakes 100% due to duplicities within and across particular drugs.

[e] There was one triplicate in the sample represented by oxazepam. Total number of prescribed oxazepams in the sample was 195 = 182 single + 5 duplicities (10 oxazepams) + 1 triplicate (3 oxazepams).

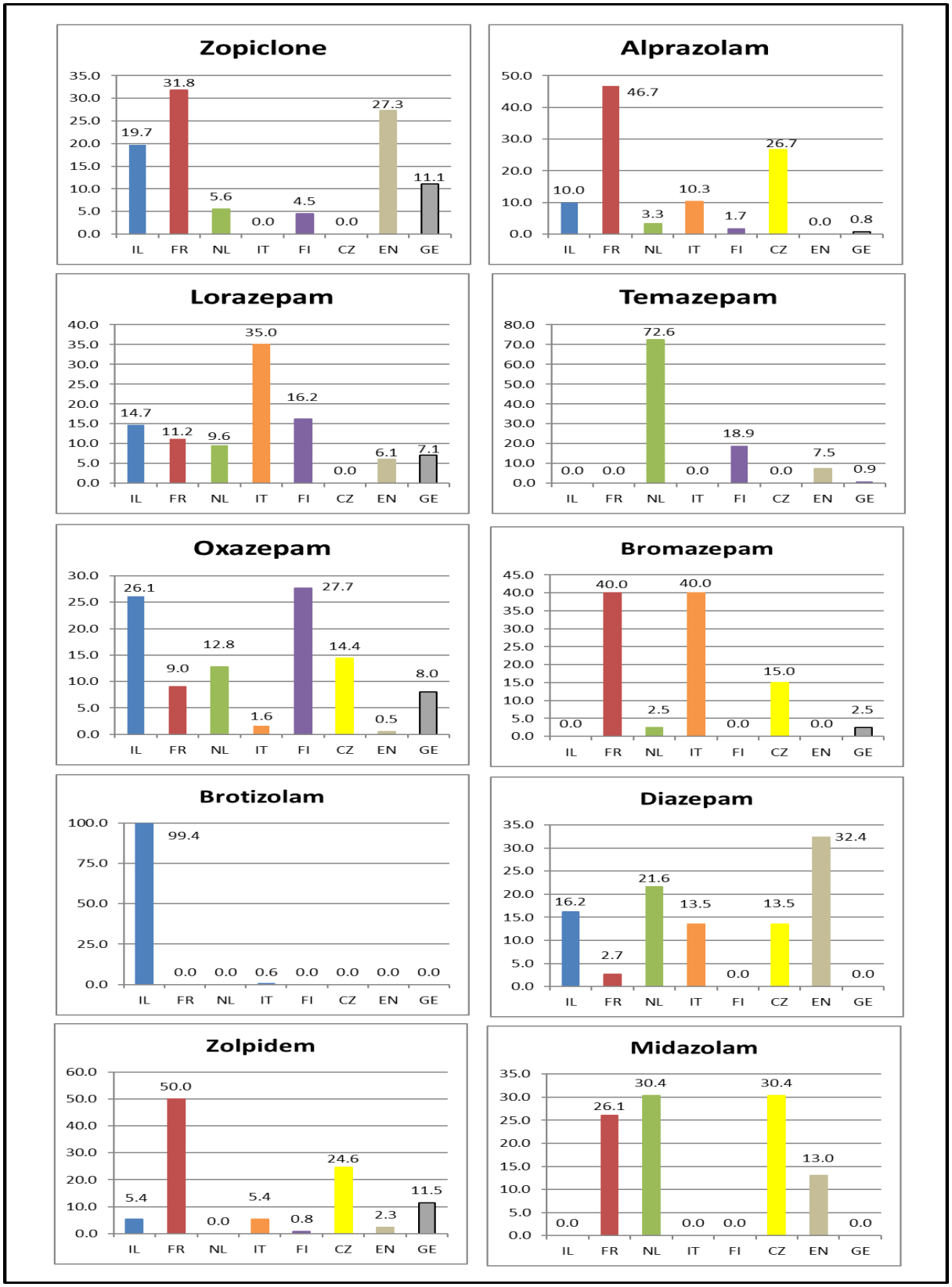
Figure 1 shows the prevalence of BZD/Z-drugs use in particular countries, with Israel having the highest (44.1%) and Germany the lowest (14.5%) prevalence. The differences in prescribing patterns of 10 most frequent BZDs/Z-drugs are showed in Figure 2. While lorazepam, oxazepam and diazepam were used in most countries; brotizolam, temazepam and zolpidem showed predominant use in Israel, The Netherlands and France; respectively. Figure 3 demonstrates prescribing patterns in all participating countries. Israel, Finland, The Netherlands, England and Italy had one dominant BZD/Z-drug exceeding 50% of use; however, in the rest of the countries a wider spectrum of BZDs/Z-drugs was found.

Figure 1. Prevalence (%) of BZD/Z-drug users across countries.



IL-Israel, FR-France, NL-The Netherlands, IT-Italy, FI-Finland, CS-The Czech Republic, EN-England, GE-Germany

Figure 2. Distribution (%) of 10 most frequent BZDs and Z-drugs across countries.



IL-Israel, FR-France, NL-The Netherlands, IT-Italy, FI-Finland, CS-The Czech Republic, EN-England, GE-Germany

Figure 3. Distribution (%) of BZDs and Z-drugs within users in particular country.

ZOPIC-zopiclone, ZOLPID-zolpidem, LORA-lorazepam, OXA-oxazepam, BROTI-brotizolam, ALPRA-alprazolam, TEMA-temazepam, BROMA-bromazepam, DIA-diazepam, MIDA-midazolam

The total percentage count can exceed 100 % of users due to multiple users within and across different BZD/Z-drug users in each country.

The comparison of basic characteristics between groups of users, non-users and multiple users of BZDs/Z-drugs is showed in Table 3. In general, any user of BZDs/Z-drugs (users and multiple users) was statistically significantly more likely to use more medications, to have more pain and more severe depression and to be less cognitively and functionally impaired compared to non-user of BZDs/Z-drugs. Similar results were found for the comparison of multiple users of BZDs/Z-drugs compared to non-users of BZDs/Z-drugs.

According to the univariate logistic regression (Table 4), every one-point increase on the CPS scale, ADLH scale, and Communication scale (denoting poorer performance) was associated with lower probability of use of BZDs/Z-drugs (risk decrease of 6.7%, 1.7%, and 0,6%; respectively). Patients with diagnoses and presence of anxiety and difficulty falling asleep had statistically significantly higher risk of using BZDs/Z-drugs.

Using Germany (country with the lowest BZDs/Z-drugs prevalence) as a reference and ordering countries according to the increasing prevalence of BZD/Z-drug use, the univariate logistic regression showed country of residence to be a strong factor influencing the use of BZDs/Z-drugs. Country of residence remained positively associated with use of BZDs/Z-drugs even after adjusting for all other covariates (Table 4).

Table 3. Characteristics of patients and comparison between particular groups of BZD/Z-drug users.

	All sample N=4,023 (%)	**All BZD/Z-drug users** N=1,113 (%)	**BZD/Z-drug non-users** N=2,910 (%)	**p value**	**Users of multiple BZDs/Z-drugs** N=111 (%)	**BZD/Z-drug non-users** N=2,910 (%)	**p value**	**Users of single BZD/Z-drug** N=1,002 (%)	**Users of multiple BZDs/Z-drugs** N=111 (%)	**p value**
Age, years mean ± SD	83.5±9.4	83.2±9.4	83.7±9.3	0.10	82.4±9.7	83.7±9.3	0.21	83.2±9.3	82.4±9.7	0.37
Gender Female	2,945(73.2)	822(73.9)	2,123(73.0)	0.57	81(73.0)	2,123(73.0)	0.99	741(74.0)	81(73.0)	0.82
Number of medications mean ± SD	7±3.6	8.3±3.3	6.5±3.6	<0.001	9.7±3.4	6.5±3.6	<0.001	8.1±3.3	9.7±3.4	<0.001
CPS[a] Mean ± SD Median (IQR)	2.9±1.9 3.0(1.0-5.0)	2.7±1.9 3.0(1.0-5.0)	3.0±1.9 3.0 (1.0-5.0)	0.002	2.4±2.0 2.0 (0.0-5.0)	3.0±1.9 3.0(1.0-5.0)	0.02	2.8±1.9 3.0 (1.0-5.0)	2.4±2.0 2.0 (0.0-5.0)	0.18
ADL scale[b] Mean ± SD Median (IQR)	5.6±4.3 6.0(1.0-9.0)	5.1±4.3 5.0(1.0-9.0)	5.7±4.3 6.0 (2.0-9.0)	<0.001	4.4±4.1 4.0 (0.0-8.3)	5.7±4.3 6.0(2.0-9.0)	<0.001	5.2±4.3 5.0 (1.0-9.0)	4.4±4.2 4.0 (0.0-8.3)	0.03
ADL Hierarchy scale[c] Mean ± SD Median (IQR)	15.2±9.5 16.0 (7.0-24.0)	14.2±9.7 15.0 (5.0-23.0)	15.5±9.5 17.0 (7.0-24.0)	<0.001	12.4±9.4 13.0 (3.0-20.0)	15.5±9.5 17.0(7.0-24.0)	<0.001	14.4±9.6 15.0 (6.0-23.0)	12.4±9.4 13.0 (3.0-20.0)	0.04
PAIN scale[d] Mean ± SD Median (IQR)	0.6±0.8 0.0 (0.0-1.0)	0.7±0.9 0.0(0.0-1.0)	0.5±0.8 0.0 (0.0-1.0)	<0.001	0.8±0.9 1.0 (0.0-1.0)	0.5±0.8 0.0(0.0-1.0)	<0.001	0.7±0.9 0.0 (0.0-1.0)	0.8±1.0 1.0 (0.0-1.0)	0.04
CAP Delirium[e] Mean ± SD Median (IQR)	0.3±0.8 0.0(0.0-0.0)	0.3±0.9 0.0(0.0-0.0)	0.3±0.8 0.0 (0.0-0.0)	0.18	0.4±1.0 0.0 (0.0-0.0)	0.3±0.8 0.0(0.0-0.0)	0.72	0.3±0.8 0.0 (0.0-0.0)	0.4±1.0 0.0 (0.0-0.0)	0.90

Table 3. Characteristics of patients and comparison between particular groups of BZD/Z-drug users. – *Continued.*

	All sample N=4,023 (%)	**All BZD/Z-drug users** N=1,113 (%)	**BZD/Z-drug non-users** N=2,910 (%)	**p value**	**Users of multiple BZDs/Z-drugs** N=111 (%)	**BZD/Z-drug non-users** N=2,910 (%)	**p value**	**Users of single BZD/Z-drug** N=1,002 (%)	**Users of multiple BZDs/Z-drugs** N=111 (%)	**p value**
Depression scale[f] Mean ± SD Median (IQR)	2.1±2.7 1.0(0.0-3.0)	2.6±2.9 2.0(0.0-4.0)	1.9±2.6 1.0 (0.0-3.0)	<0.001	3.4±2.8 3.0 (1.0-6.0)	1.9±2.6 1.0(0.0-3.0)	<0.001	2.5±2.9 2.0 (0.0-4.0)	3.4±2.8 3.0 (1.0-6.0)	<0.001
Communication scale[g] Mean ± SD Median (IQR)	3.0±2.9 2.0(0.0-6.0)	2.6±2.8 2.0(0.0-5.0)	3.1±2.9 2.0 (0.0-6.0)	0.05	2.2±2.6 1.0 (0-0-4.0)	3.1±2.9 2.0(0.0-6.0)	0.02	2.6±2.8 2.0 (0.0-5.0)	2.2±2.7 1.0 (0.0-4.0)	0.11

[a] CPS – Cognitive Performance Scale[38] was used to access cognitive status. It includes five items: cognitive skills for daily decision making, short-term memory problems, procedural memory problems, making self-understood, and eating ability. Scores of CPS items range from 0 (intact) to 6 (very severe impairment), and any score ≥2 indicates impairment.

[b] ADL scale – Activities of Daily Living scale[37] comprises four items: personal hygiene, locomotion, toilet use, and eating, while each item is scored from 0 = requires supervision to 4 = total dependence. The scale ranges from 0 to 16, with higher scores reflecting greater level of dependency and difficulties in performing activities.

[c] ADL Hierarchy scale –Activities of Daily Living Hierarchy scale[37] comprises 7 items: personal hygiene, dressing upper body, dressing lower body, locomotion, toilet use, bed mobility, eating, while each item is scored from 0 = requires supervision to 4 = total dependence. The scale ranges from 0 to 28, with higher scores reflecting greater level of dependency and difficulties in performing activities.

[d] Pain scale[40]- summarizes the reported presence and intensity of pain. The scores range from 0 = no pain to 4 = daily excruciating pain

[e] CAP Delirium[42] – this scale comprises 4 items: easily distracted, disorganized speech, mental function varies over day, change in decision making. The scale ranges from 0 to 4, with higher values indication increase likelihood of delirium.

[f] Depression scale[39] – is based on the self-reported mood items and indicates the presence of depressed mood and anxiety. It consists of 3 self-reported mood items, while each question can be scored from 0 to 2 with the maximum overall score of 6. The score of this scale range from 0 = no symptoms of depression to 6 = all symptoms present in last 3 days/24 hours: high likelihood of depression.

[g] Communication scale[41] – consists of two items: making self-understood (expression) and ability to understand others (comprehension), while not taking directly into consideration hearing and visual impairment. It is primarily focused on dysphasia and similar syndromes. The scores ranges from 0 = intact to 8 = very severe impairment.

Table 4. Factors influencing prescription of BZDs/Z-drugs – results from univariate and multivariate logistic regression.

Factors influencing prescription	Unadjusted OR	95% CI	p value	Adjusted OR[g]	95% CI	p value
Age	0.994	0.987 - 1.001	0.10	0.993	0.985 - 1.002	0.14
Gender						
Male - reference	-	-	-	-	-	-
Female	1.047	0.895 - 1.225	0.57	1.063	0.885 - 1.277	0.51
Country ordered by prevalence of BZD/Z-drug use						
Germany - reference	-	-	-	-	-	-
England	1.237	0.881 - 1.737	0.22	1.532	1.070 - 2.193	0.02
Czech Republic	1.491	1.070 - 2.077	0.02	1.509	1.064 - 2.140	0.02
Finland	1.572	1.128 - 2.191	0.008	1.888	1.324 - 2.691	<0.001
Italy	2.226	1.645 - 3.122	<0.001	2.631	1.857 - 3.727	<0.001
The Netherlands	2.489	1.814 - 3.416	<0.001	2.424	1.738 - 3.381	<0.001
France	4.630	3.407 - 6.292	<0.001	5.250	3.473 - 7.936	<0.001
Israel	4.653	3.451 - 6.273	<0.001	6.660	4.823 - 9.198	<0.001
CPS[a]	0.933	0.900 - 0.968	<0.001	0.974	0.908 - 1.044	0.46
ADLH[b]	0.983	0.976 - 0.990	<0.001	0.992	0.981 - 1.003	0.15
Pain scale[c]	1.228	1.130 - 1.336	<0.001	1.113	1.004 - 1.234	0.04
CAP Delirium[d]	1.052	0.965 - 1.146	0.25	0.992	0.897 - 1.097	0.88
Depression scale[e]	1.088	1.061 - 1.115	<0.001	1.052	1.020 - 1.085	0.001
Communication scale[f]	0.994	0.921 - 0.968	<0.001	0.941	0.898 - 0.986	0.01
Anxiety						
Not present - reference	-	-	-	-	-	-
Primary diagnosis	1.627	0.909 - 2.913	0.10	1.171	0.608 - 2.252	0.64
Diagnosis present, treatment	2.956	2.308 - 3.785	<0.001	1.887	1.382 - 2.578	<0.001
Diagnosis present, monitored	1.367	0.944 - 1.980	0.10	0.820	0.525 - 1.280	0.38

Table 4. Factor influencing prescription of BZDs/Z-drugs – results from univariate and multivariate logistic regression. – *Continued.*

Factors influencing prescription	Unadjusted OR	95% CI	p value	Adjusted OR[g]	95% CI	p value
Difficulty falling asleep						
Not present - reference	-	-	-	-	-	-
Present, not exhibited	2.519	2.026 - 3.134	<0.001	2.687	2.098 - 3.443	<0.001
Exhibited 1 of 3 days	2.106	1.483 - 2.990	<0.001	1.953	1.315 - 2.901	0.001
Exhibited 2 of 3 days	1.830	1.208 - 2.770	0.004	1.777	1.118 - 2.824	0.01
Exhibited daily of 3 days	3.244	2.549 - 4.129	<0.001	3.274	2.481 - 4.320	<0.001

[a] CPS– Cognitive Performance Scale[38] was used to access cognitive status. It includes five items: cognitive skills for daily decision making, short-term memory problems, procedural memory problems, making self-understood and eating ability. Scores of CPS items range from 0 (intact) to 6 (very severe impairment), and any score ≥2 indicates impairment.

[b] ADLH scale –Activities of Daily Living Hierarchy scale[37] comprises 7 items: personal hygiene, dressing upper body, dressing lower body, locomotion, toilet use, bed mobility, eating, while each item is scored from 1 = requires supervision to 4 = total dependence. The scale ranges from 0 to 28, with higher scores reflecting greater level of dependency and difficulties in performing activities.

[c] Pain scale[40] - summarizes the reported presence and intensity of pain. It comprises two items: pain symptoms-frequency and pain symptoms-intensity of highest level of pain present. The scores range from 0 =no pain to 4 =daily excruciating pain

[d] CAP Delirium[42] - this scale comprises 4 items: easily distracted, disorganized speech, mental function varies over day, change in decision making. The scale ranges from 0 to 4, with higher values indication increase likelihood of delirium.

[e] Depression scale[39] - is based on the self-reported mood items and indicates the presence of depressed mood and anxiety. It consists of 3 self-reported mood items, while each question can be scored from 0 to 2 with the maximum overall score of 6. The score of this scale range from 0 = no symptoms of depression to 6 = all symptoms present in last3 days/24 hours: high likelihood of depression.

[f] Communication scale[41] – consists of two items: making self-understood (expression) and ability to understand others (comprehension), while not taking directly into consideration hearing and visual impairment. It is primarily focused on dysphasia and similar syndromes. The scores ranges from 0 = intact to 8 = very severe impairment.

[g] Adjusted for all factors in univariate logistic regression: age, gender, functional and cognitive status, anxiety, insomnia, depression, delirium, pain, and communication problems

Discussion

This large cross-sectional study gives a comprehensive evaluation of prevalence of BZD/Z-drug use across European countries and Israel. It demonstrates the differences in prescribing patterns between countries and shows substantial variance in proportion of use of individual drugs. Overall prevalence of BZD/Z-drug use of 27.7% found in this study correlates with findings of other studies[8,16-23]. The present study also denotes that beside known factors associated with BZD/Z-drug use, such as age and gender[16,44,49], there is a significant difference in prescribing patterns between countries, presumably allied with other influencing factors not yet described.

Countries with the highest prevalence of BDZ/Z-drug use

The highest prevalence of BZD/Z-drug use in this study was documented in Israel (44.1%). Few studies previously reported the prevalence or prescribing patterns of BZDs/Z-drugs in NHs in Israel; however, studies in community dwelling older people show similar results. Overall health status, health care use, and institutionalization seems to be strongly influenced by the differences between the Jewish and the Arab older population.[45] Blumstein et al. 2014[46] showed an overall 20.2% and 21.6% prevalence of BZD-only use and anxiolytic and sedative/hypnotic use, respectively, in community dwelling older Jewish population in Israel. The prevalence of use of anxiolytics and sedatives/hypnotics in the age group of 80-94 years old was 26.5%.[46] Another study in primary care found Israeli Arabs being significantly less likely to purchase BZDs (Odds Ratio [OR] 0.38, 95% confidence interval [CI] 0.27-0.53) compared to Israeli Jews, while Jews born in Russia or East Europe and Europe or America (OR 1.70, 95% CI 1.41-2.06; OR 1.32, 95% CI 1.02-1.71; respectively) were more likely to purchase BZDs.[47] Authors postulated that these disparities might be attributed to the past post-traumatic experience during the Holocaust in Jews born in Russia, East Europe, Europe or America.[47] It is of importance to mention that symptoms of posttraumatic stress disorder accompanied by sleep, anxiety, and depressive disorders in the Holocaust survivor population were extensively investigated.[48] In 2008 about 7% of Holocaust survivors were institutionalized with estimates being up to 19% in year 2025.[48] Lower purchase of BZDs by Israeli Arabs and Israeli Jews might be associated with the

stigmatizing character of mental illnesses and stronger reliability on informal support in these groups.[47]

A study of Russian-speaking immigrants in Israel (represent 20% of all older people in the country) residing in the independent living facilities showed that 69% use BZDs, while 45% of these was on a daily basis.[49] In our study 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 sample. After adjusting for confounders, the country of residence remained a strong predictor of BZD/Z-drug use: in case of Israel adjusted OR 6.660; 95% CI 4.823-9.198. Unfortunately, in our study it was impossible to get information on the ethnicity of Israel NH residents. Therefore, further studies are needed to investigate differences in BZD/Z-drug use in Israel NH residents and association with their ethnicity.

The second highest prevalence of BZD/Z-drug use in this study was found in France (44.0%). This corresponds with findings of 53.4% prevalence of BZD/Z-drug use in residents of NHs in France in 2011.[50] In the present study, zopiclone together with zolpidem were the most frequently BZDs/Z-drugs used. Differences in BZD/Z-drug prescribing pattern in France may be explained by their availability on the market.[50] For example the most prevalent BZD brotizolam in Israel is currently not available in France, therefore no brotizolam use was identified in France in our study. On the other hand, in spite of availability in France, our study did not find any use of temazepam compared to The Netherlands where temazepam represents the most frequently used BZD (53.1%). This result correlates with the study of de Sousto Barreto et al. 2013[50] that found the prevalence of temazepam to be 0.02%. In response to the high consumption of BZDs/Z-drugs in France and concern about their AEs, there have been a number of warnings and campaigns against use of these drugs.[15] Detailed recommendations on how to help patients to withdraw from BZDs were published by the Haute Autorité de Santé (HAS) in 2008.[51] However, overall consumption of BZDs/Z-drugs remained stable after the HAS recommendation: sales of BZDs decreased by 6.0% and sales of Z-drugs increased by +4.7%, giving a global variation of +1.8%.[15] Even after the introduction of non-BZD hypnotic prolonged-release (PR) melatonin in 2008, the consumption of BZDs/Z-drugs did not change significantly.[15] This might be a consequence of poor promotion of melatonin, lack of reimbursement compared to BZDs,

high price (eight times higher than a mean price of BZDs in France), and unwillingness of French patients to pay "out-of-pocket" money.[15] The most recent attempt to reduce the consumption of BZDs in France was made with introduction of the pay-for-performance intervention; however this did not succeed in reducing the use of BZDs neither in the general population nor in patients >65 years.[52]

Countries with the lowest prevalence of BZD/Z-drug use

The second lowest prevalence of BZD/Z-drug use in our study was reported in England (17.4%). A large study of older patients aged 65-104 years in England during 2008 to 2009 showed a 7.4% and 14.5% prevalence of BZD use in community and NHs; respectively.[18] Following the recommendations to restrict BZD and Z-drug use in 2004 made by the Department of Health[53], the consumption of BZDs decreased between 2005 and 2010 by 31.7%[15]. On the other hand, despite the recommendations given by the National Institute for Health and Care Excellence (NICE) on Z-drugs in 2004[54], there was an increase of 7.3% in prevalence of Z-drug use[15]. The launch and reimbursement of PR melatonin in 2008 did not changed the figures of BZD/Z-drug consumption.[15] The shift of use of BZDs in favour of increased use of Z-drugs during years 2005 to 2010[15] corresponds with findings of our study, where zopiclone represented 61.4% of BZD/Z-drug use in England.

In our study, Germany was the country with the lowest prevalence of BZD/Z-drug use (14.5%). Another study of NH residents in Germany reported a 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.[55] Since 1980s the German Federal Institute for Drugs and Medical Devices restricted the BZD use to a maximum standard period of 2-4 weeks.[56] 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.[57] In contrast, the prevalence of Z-drug use was relatively stable, with change from 3.2% to 3.0% between 2006 and 2010, in those aged 60-74 years, and from 2.1% to 2.0% for those aged >75 years.[57] A study of the impact of PR melatonin launch on the German market found that 31% of BZD/Z-drug users (mean age ± SD = 63 ± 14 years) discontinued BZD/Z-drug use after the PR melatonin initiation; however 10% of patients not previously

using BZDs/Z-drugs received BZD/Z-drug during the follow-up period after the initiation of PR melatonin.[58]

The above described information on particular countries involved in 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.

Study strengths and limitations

This study has several strengths. It comprised a large sample of older people residing in NHs in different European countries and Israel. It applied a standardized and accurate method of data collection using a validated interRAI LTCF assessment, enabling a comprehensive cross-country comparison. Our study provides a unique insight in BZD/Z-drug prescribing patterns that might be explained by specific non-clinical factors.

Limitations of this study include the cross-sectional design that does not allow identification of a causal relationship. Secondly, this study reports analyses of only baseline data. Therefore, it is not possible to evaluate the use of BZDs/Z-drugs over time. However, as all the BZDs/Z-drugs described as “use as needed” were excluded from the analyses, the potentially non-regular use of BZDs/Z-drugs was eliminated. As the main focus of this study was to describe the use of BZDs and Z-drugs inducing similar health concerns, other drugs used in hypnotic indication (e.g., mirtazapine, trazodone, antipsychotics, etc.) were not analysed.

Finally, the possibility of selection bias should be acknowledged. Residents enrolled in the SHELTER study must not be considered randomly selected and the sample was not intended to be fully representative of all NHs in each country.[35] Thus the residents´ characteristics cannot necessarily be generalized to all NH residents in participating European countries.

Conclusions

This study showed significant differences in prevalence of BZD/Z-drug use across European countries and Israel. It documented specific prescribing patterns in particular countries and association of different factors with BZD/Z-drug use. Except for the well-established factors influencing the prescription of BZDs/Z-drugs such as age, female gender, anxiety, insomnia and depression, the current study found an important association with country of residence, suggesting that non-clinical factors may significantly contribute to BZD/Z-drug use. However; more studies are needed to define other 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.

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Chapter 3

Association between benzodiazepine use and falls

Full text of Chapter 3 was published as an original study:

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Abstract

Background

Hypnosedatives are commonly prescribed for anxiety and sleep problems. Changes in pharmacokinetics and pharmacodynamics of BZDs during ageing may increase their potential to cause adverse outcomes.

Objective

This study aimed to investigate the use of BZDs in acute care settings and explore their association with falls.

Methods

A prospective cohort study was undertaken of patients aged over 70 years consecutively admitted to 11 acute care hospitals in Australia. Data were collected using the interRAI AC assessment tool. Falls were recorded prospectively (in hospital) and retrospectively (in the 90 days prior to admission).

Results

Of 1,412 patients, 146 (10.3%) were taking BZDs at admission and 155 (11.3%) at discharge. 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 than all other BZD users (70.8 vs. 36.1%; p=0.002), particularly when compared with 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 (odds ratio 3.0; 95% CI 1.1–8.5; p=0.036).

Conclusions

Different BZDs may vary in their propensity to predispose to falls, with diazepam having the strongest association. The selection of particular BZDs for older patients should be carefully evaluated.

Introduction

BZDs are prescribed for a number of conditions, including anxiety disorders, insomnia, alcohol withdrawal, depression, and muscle spasms.[1] BZDs are widely used among older community-dwelling people, with estimated prevalence varying from 10 to 32%.[2-5] A recent Australian study of 337 community-dwelling people over 75 years found a prevalence of long-term BZD use of 16.6% at first assessment and 19.6% at 3- and 4.5-year follow-up.[3] Smith and Tett[6] conducted a study of changes in utilization of antidepressants and BZDs between different age groups within the general Australia population from 2003 to 2006, and found a decrease in overall utilization of BZDs by 2%. However, individuals aged ≥85 years had the highest use of BZDs within the group aged ≥65 years.[6] The utilization of BZDs by concession beneficiaries in people aged ≥85 years was approximately 120 DDDs/1,000 concession beneficiaries/day, while in the group aged 65–74 years it was approximately 50 DDDs/1,000 concession beneficiaries/day.[6] They also showed that while younger age groups were more likely to use anxiolytic BZDs such as diazepam and alprazolam, the older group (≥65 years of age) frequently used hypnotic BZDs such as temazepam.[6]

Changes in pharmacokinetics and pharmacodynamics in the aging human body are well reported.[7-11] Body fat increases with chronological age and this can affect the distribution of lipophilic drugs such as diazepam.[11,12] The pharmacological profile of BZDs in older people may be influenced by changes in activity of CYP enzymes[13], as well as by decrease in albumin plasma levels and therefore higher free fractions of BZDs[14]. The increased sensitivity of an ageing CNS to BZDs[9, 10, 15] coupled with age-related changes in BZD pharmacodynamics are important from the clinical perspective because of the observed relationship of BZD use with falls and hip fractures[16-21].

Among people aged 65 years and older, epidemiological studies show that falls are the leading cause of both fatal and non-fatal unintentional injuries, accounting for 40% of all injury-related deaths and over 80% of all injury admissions to hospital.[22] The incidence of falls differs across settings. In a Swedish prospective study of hospital settings, the incidence

rate of 92 (95% CI 72–112) falls per 10,000 patient-days has been reported for geriatric rehabilitation wards, and 171 (95% CI 146–196) falls per 10,000 patient-days for psychogeriatric wards.[23] In nursing home settings the incidence of falls is reported to be about three times higher than in the community, with incidence rates of 1.5 falls per bed per year (range from 0.2 to 3.6).[24] A systematic review of risk factors and risk assessment tools for falls in hospital inpatients identified a number of significant risk factors: gait instability, agitation, confusion, urinary incontinence or frequency and need of assisted toileting, previous falls history and prescription of drugs exerting effects on the central nervous and cardiovascular systems, in particular sedative hypnotics.[25]

BZDs belong to the group of so-called 'fall-risk increasing drugs'[26], which are associated with falls and hip fractures in older adults[16-21]. In a recent meta-analysis, use of BZDs was associated with a 40% increased risk of falls in older individuals.[21] In another analysis, use of BZDs was associated with a 2.2-fold (95% CI 1.4–3.4) increased risk of injurious falls in people aged ≥80 years.[20] A few studies have focused on the association between the biological half-life of BZDs and falls, with conflicting results[27-29], while some authors suggest a strong dose-response relationship for falls among users of BZDs[30,31]. Few studies have evaluated the relationship between specific BZDs and falls.

The aims of our study were to investigate the relationship between in hospital use of BZDs and falls occurring in hospital (determined prospectively), and between pre-hospital use of BZDs and falls occurring in the 90 days prior to admission (determined retrospectively) in a population of patients aged over 70 years admitted to hospital. Our study also focused on evaluating differences between use of particular BZDs and their association with a history of falls.

Methods

Study design and participants

In this study we undertook secondary data analyses of all patients recruited as three separate prospective cohorts in studies originally designed to investigate prevalence of geriatric syndromes and quality of care in acute care settings.[32-34] In total, 1,418 patients aged over 70 years admitted to general medical, orthopaedic and surgical wards in 11 acute care hospitals in two states of Australia were included in the study. The hospitals included secondary care centres (with 120–160 beds) as well as major metropolitan teaching hospitals (with more than 700 beds). Patients within each cohort were recruited consecutively between July 2005 and May 2010. Patients were excluded if they were admitted to coronary or intensive care units, were receiving terminal care only, or were transferred out of the acute ward within 24 h of admission. Recruitment methodology has been described in detail elsewhere.[32-34]

Ethical approval was obtained from each participating hospital's Human Research and Ethics Committee and the University Medical Research Ethics Committee.

Data collection

The interRAI AC was used to collect data on each patient at both admission and discharge. This tool, one of a suite of instruments to support assessment and care planning of persons across care settings[35], was developed specifically for use in acute care settings to support comprehensive geriatric assessment of older inpatients[35,36]. For the collection of interRAI AC data, eligible participants, who were likely to stay in hospital for at least 48 h, were invited at admission to enrol in the study. Personal or proxy consent was obtained in writing prior to study commencement.

The interRAI AC comprises 62 clinical items across 11 domains, including ADLs, instrumental ADLs (IADLs), cognitive function, communication, mood and behaviour, continence, nutrition, falls, medical diagnoses, medications, advance directives, and discharge potential.[36] A number of scales are embedded in the interRAI AC, combining multiple items

belonging to a single domain, such as ADLs or cognition, that can be used to describe the presence and extent of deficits in that domain.[33] A number of studies have been conducted to test the performance of the interRAI instruments[37], with a 12-country study showing substantial reliability (overall kappa mean value of 0.75 for 161 core items)[37].

Data were collected by trained nurse assessors relating to three time points: the pre-morbid period, admission and discharge. Pre-morbid data relevant to the interRAI AC tool were collected retrospectively at admission assessment by assessors who asked questions relating to the 3 days prior to the onset of the acute illness for all variables, except for a history of falls, which was ascertained over the preceding 90 days. Admission data, collected at admission assessment, comprised information relating to the first 24-h of the patient's stay on the ward. Discharge data, collected at discharge assessment, comprised information relating to the remainder of the hospital stay. All data were collected using multiple information sources and combining subject interview, care providers and family interview.

All medications that patients were receiving at admission and at discharge, as listed on the inpatient medication chart, were recorded. Names of medications, ATC codes, doses, routes of administration and dosing regimens were entered by pharmacists or pharmacy students and subsequently verified by a second pharmacist or geriatrician. Medications of interest were those taken on a regular, long-term basis. All medications taken 'as needed' on or during the admission and at discharge, including BZDs, were excluded from analyses. In collecting data within 24 h of hospital admission, it was assumed that BZD use, if recorded on the in-hospital medication chart, reflected regular use during the pre-morbid period.

Outcome measures

The outcome measure was the number of individuals who had experienced a fall prior to admission, or during the period of hospitalization. A fall, as defined in the interRAI AC Assessment Form and User's Manual[38] was any unintentional change in position where the person ends upon the floor, ground, or other lower level, and included falls that occurred while being assisted by others.

For prior history of falls, a faller was defined as having had at least one fall in the 90 days prior to admission, these data being collected retrospectively at admission assessment. For in-hospital falls, a faller was defined as having had at least one fall during the period of hospitalization. These data were collected prospectively by daily chart reviews and ward visits by the research nurses using all available sources of information (interviewing the patient and medical staff, reviewing the medical records, and checking the forms or systems for recording adverse events). The process of data collection was based on the detailed instructions provided in the tool manual.[38]

Statistical analyses

Descriptive statistics were used to define characteristics of the sample population. The relationships between use of BZDs, recorded at admission and at discharge, and characteristics of the sample population were assessed by univariate analysis, using parametric (t-test) or non-parametric (Mann–Whitney U test) methods for normally or nonnormally distributed data; respectively. Pearson's Chisquare test was used for categorical data. The significance levels were set at $p<0.05$ and all proportions were calculated as percentages of all patients with available data.

In regard to the outcome of *in-hospital falls*, the incidence rates and incidence rate ratios (IRR) of in-hospital fallers were estimated for different categories of BZD users: *never users*—patients not using BZDs at admission and at discharge; *stop users*—patients using BZDs at admission but not at discharge; *new users*—patients not using BZDs at admission but using BZDs at discharge; and *continuous users* - patients using BZDs at admission and at discharge. A collapsed category of *ever users* was created by summing stop, new and continuous users, to represent those patients who had used or been prescribed BZDs at any time during the period of hospitalization. For the outcome *history of falls*, the prevalence of falls in the 90 days prior to admission was estimated for users and non-users of BZDs based on medications recorded at admission.

For both outcomes, multivariate logistic regression models were performed to assess their relation with BZD use, this being expressed as an adjusted OR with 95% CI, and adjusted for age, gender, premorbid cognitive status [premorbid Cognitive Performance Scale (CPS)]

and premorbid functional status [premorbid Activities of Daily Living scale (ADL)]. These co-variates, discussed in more detail below, had been showed in the literature to have a significant association with the outcome of falls[39, 40], as well as with the predictor – use of BZDs[2, 21, 41-43]. The logistic regression models were also adjusted for other medication groups associated with increased risk of falls in older people — opioids, antipsychotics, antidepressants, nitrates, diuretics, b-blockers, and angiotensin-converting enzyme inhibitors (ACEIs)[21, 44-46].

For the outcome of *history of falls*, two different multivariate logistic regression models were conducted. To assess the relationship between history of falls and users versus non-users of BZDs, both overall and for specific BZDs, the dichotomous variables (use/non-use of a particular drug) were entered into the model. In the second multivariate logistic model, dummy variables were used as independent predictors of outcome of history of falls in order to compare the effect of specific BZDs within the BZD users group. Dummy variables were created for the mutually exclusive groups of BZD users (diazepam users, oxazepam users, other BZD users, BZD non-users) to compare each category with the reference category — diazepam users.

Analyses were performed using SPSS® IBM Version 20 (SPSS, Inc., Chicago, IL, USA) and using Stata Statistical Software, Release 9 (StataCorp. 2005; StataCorp LP, College Station, TX, USA).

Results

Patients with missing medication records at admission (n=6) and at discharge (n=42) were excluded from the analyses, leaving an evaluable sample of 1,412 patients at admission and 1,376 at discharge. Baseline data showed their mean age ± SD was 81.0 ± 6.8 years, the majority (55.1%) were women, and most (87.8%) were admitted from the community. The median [interquartile range (IQR)] length of stay in hospital was 6 (4–11) days. The mean ± SD number of regular medications at admission was 8.3 ± 3.9, ranging

from 0 to 24 medications. The mean ± SD number of comorbidities was 6.1 ± 2.3, ranging from 0 to 10 diagnoses.

Associations between BZD use and patient characteristics

Overall, 146 patients (10.3%) were receiving BZDs at the admission assessment, and 155 patients (11.3%) at discharge assessment. There was no statistically significant difference in age or gender between BZD users and nonusers (Table 1). Patients taking BZDs at both assessments (admission and discharge) compared with non-users were significantly more likely to have more medications and more comorbidities. The mean score of the premorbid ADL short-form scale, as well as the mean score of the premorbid performance IADL scale, was significantly higher (denoting poorer performance) in the group of BZD users compared with non-users at admission. Patients using BZDs at admission were significantly more likely to have severe impairment of premorbid cognitive status than BZD non-users. At discharge, BZD users had a significantly higher score of ADL short-form scale and IADL capacity scale compared with non-users. There was no statistically significant difference in the discharge cognitive status of patients using BZDs compared with non-users.

Table 1. Characteristics of the sample population and their association with use of BZDs at admission and at discharge.

	Total sample[a] n = 1412 (%)	**BZDs users n = 146 (%)**	**BZDs non-users n = 1266 (%)**	**p value[*]**
Age, years mean ± SD[1]	81.0 ± 6.8	81.7 ± 6.6	80.9 ± 6.8	0.172
Gender Female	778 (55.1)	90.0 (61.6)	688 (54.3)	0.093
Admission assessment				
No. of medications mean ± SD	8.3 ± 3.9	10.5 ± 3.8	8.1 ± 3.9	≤0.001
No. of comorbidities mean ± SD	6.1 ± 2.3	6.5 ± 2.1	6.0 ± 2.3	0.021
Premorbid ADL short form scale[c,d] mean ± SD median, IQR[2]	1.3 ± 2.9 0.0 (0.0 – 1.0)	1.5 ± 3.1 0.0 (0.0 - 2.0)	1.3 ± 2.9 0.0 (0.0 - 1.0)	0.035
Premorbid IADL performance scale[c,e] mean ± SD median, IQR	22.7 ± 15.5 22.0 (9.0-36.0)	26.3 ± 14.8 27.0 (13.3 - 39.8)	22.3 ± 15.5 22.0 (8.0– 36.0)	0.002
Premorbid cognitive status[f] 0-1 = intact 2 – 4 = mild to moderate 5 – 6 =severe	1045 (76.0) 275 (20.0) 55 (4.0)	101 (71.1) 29 (20.4) 12 (8.5)	944 (76.6) 246 (20.0) 43 (3.5)	0.015
Discharge assessment				
	Total sample[b] n = 1376 (%)	**BZDs Users n = 155 (%)**	**BZDs non-users n = 1221 (%)**	**p value[*]**
No. of medications mean ± SD	8.1 ± 3.9	9.7 ± 3.8	7.9 ± 3.8	≤0.001
Discharge ADL short form scale[c,d] mean ± SD median, IQR	2.3 ± 3.9 0.0 (0.0 – 3.0)	2.9 ± 4.2 1.0 (0.0 – 4.0)	2.2 ± 3.8 0.0 (0.0 – 3.0)	0.010
Discharge IADL capacity scale[c,g] mean ± SD median, IQR	21.5 ± 16.2 21.0 (6.0 – 36.0)	24.1 ± 14.8 28.0 (14.0 – 40.0)	20.1 ± 16.2 20.0 (6.0 – 36.0)	≤0.001
Discharge cognitive status[f] 0-1 = intact 2 – 4 = mild to moderate 5 – 6 =severe	958 (73.9) 263 (20.3) 75 (5.8)	102 (72.3) 26 (18.4) 13 (9.2)	856 (74.1) 237 (20.5) 62 (5.4)	0.170

*Comparing BZD users and non-users, with p values for trend noted for multiple comparisons pertaining to one variable.

[1] SD refers to standard deviation

[2] IQR refers to Interquartile Range

[a] 6 patients at admission with missing medications records were excluded.

[b] 42 patients at discharge with missing medications records were excluded.

[c] Mann – Whitney non-parametric test was used.

[d] ADL (Activities of Daily Living) short form scale comprises 4 items: personal hygiene, walking, toilet use, and eating, while each item is scored from 1 = requires supervision to 4 = total dependence. The scale ranges from 0 to 16 with higher scores reflecting greater level of dependency.[33]

[e] Premorbid IADL (Instrumental Activities of Daily Living) performance scale constitutes of 7 items (meal preparation, ordinary housework, managing finances, managing medications, using the telephone, shopping, and transportation), scores of ≥2 points indicate IADL impairment. It is calculated at admission to the hospital and it reflects the pre-morbid period only.[33]

[f] Cognitive Performance Scale (CPS) includes 5 items: cognitive skills for daily decision-making, short-term memory problems, procedural memory problems, making self-understood and eating ability. Scores of CPS items range from 0 to 6 and any score ≥2 indicate impairment.[33] For the purposes of our analyses a categorical variable *premorbid cognitive status* and *discharge cognitive status* with categories 0–1 = intact, 2–4 = mild to moderate impairment, 5–6 = severe impairment, was created.

[g] IADL capacity scale is calculated at discharge assessment and reflects assessor's judgement of patients' capacity in different activities. It consists of 7 items (meal preparation, ordinary housework, managing finances, managing medications, using the telephone, shopping, and transportation), ranging from 0 to 42 with higher scores representing poorer functional status.

Associations between BZD use and in-hospital falls

The numbers of patients in the different categories of BZD users and the corresponding numbers of in-hospital fallers are given in Table 2. Table 3 lists the incidence rate of fallers in particular BZD user categories and compares the IRR of those exposed to BZDs (new users, continuous users, and stop users) and those not exposed (never users). There were 7.1 in-hospital fallers per 1,000 person-days among ever users (collapsed group of new users, continuous users and stop users), while among never users there were 6.9 in-hospital fallers per 1,000 person-days. The corresponding IRR was non-significant: 1.030 (95% CI 0.583–1.818; p = 0.894). Similarly, no significant differences were seen between any subgroup of ever users or between subgroups of ever users and never users. Univariate and multivariate analyses showed no statistically significant association between in-hospital falls and any of the BZD user categories (data not shown).

Table 2. Frequency of different categories of BZD users and corresponding numbers of in-hospital fallers.

BZDs user categories	**No. of patients** **(% of all sample)**	**No. of in-hospital fallers** **(% of the category)**
Never users	1228 (87.0)	79 (6.5)
Ever users[a]	184 (13.0)	14 (7.6)
= stop users	29 (2.1)	4 (13.8)
= new users	38 (2.7)	3 (7.9)
= continuous users	117 (8.2)	7 (6.0)
All sample	1412 (100.0)	93 (6.6)

[a] Ever users represent a collapsed group of new users, continuous users and stop users who comprise all patients who had used BZD during the study period.

Table 3. Incidence rates and incidence rate ratios of in-hospital fallers in different BZDs user categories.

BZD user categories	Incidence rate of in-hospital fallers per 1000 person-days	Incidence rate ratios of in-hospital fallers	95%CI[b]	p value (2-tailed)
Ever users[a] vs. Never users	7.1 / 6.9	1.030	0.583 – 1.818	0.894
New users vs. Never users	6.7 / 6.9	0.980	0.309 – 3.103	1.000
Continuous users vs. Never users	5.8 / 6.9	0.851	0.393 – 1.842	0.718
New users vs. Stop users	6.7 / 11.9	0.565	0.129 – 2.477	0.478
Continuous users vs. Stop users	5.8 / 11.9	0.509	0.147 – 1.635	0.277

[a] Ever users represent a collapsed group of new users, continuous users and stop users. This group consists of those patients who had used BZD during the study period.
[b] CI refers to 95% Confidence Interval

Associations between BZD use and pre-morbid history of falls

The three most frequently used BZDs at admission were oxazepam (33.6% of BZD users), temazepam (32.3%) and diazepam (16.8%). Within the group of oxazepam users, 95.5% were on a ≤30 mg daily dose; within temazepam users, 89.1% were on a ≤10 mg daily dose; and within diazepam users, 62.5% were on a ≤5 mg daily dose. These doses fall within the recent recommendations for use of potentially inappropriate medications in older patients.[47-50] Daily doses higher than 30 mg for oxazepam, 10 mg for temazepam and 5 mg for diazepam were considered as high doses.

Results of analyses of an association between the use of specific BZDs at admission and a history of falls in the previous 90 days are shown in Figure 1. There was no statistically significant association between the use of BZDs overall and a history of falls, comparing BZD users and non-users (41.8% vs. 37.8%; p = 0.369). However, analyses involving specific BZDs

revealed that patients on diazepam at admission were significantly more likely to have a fall compared with BZD non-users (70.8% vs. 37.8%; p = 0.001), and with all other BZD users (70.8% vs. 36.1%; p = 0.002). There was no significant association between the use of temazepam and falls when compared with either BZD non-users or all other BZD users. In contrast, patients taking oxazepam at admission were significantly less likely to have a fall in the previous 90 days compared with all other BZD users (25.0% vs. 49.0%; p = 0.007), although there was no significant difference in history of falls between oxazepam users and all BZD non-users.

Figure 1. Association between use of particular BZDs at admission and history of falls in previous 90 days.

Table 4 compares the different BZDs at admission in terms of their association with a history of falls. Oxazepam users were significantly less likely to have a fall in the previous 90 days compared with temazepam users (23.3% vs. 48.1%; p = 0.012), while no statistical difference was seen between diazepam and temazepam users (68.2% vs. 47.2%; p = 0.097). Users of long-acting diazepam were significantly more likely to have had a fall than users of short-acting oxazepam (70.8% vs. 25.0%; p≤0.001). In analysing the association between BZD dose and a history of falls for each of the different BZDs, there was no statistically significant association between higher daily dose and a history of falls for any of the different BZDs (data not shown).

Table 4. Relationship between history of falls and use of particular BZDs at admission.

	No fall in previous 90 days (%)	**At least one fall in previous 90 days (%)**	**p value**
Oxazepam users n = 43 (%)	76.7	23.3	0.012
vs.			
Temazepam users n = 54 (%)[a]	51.9	48.1	
Diazepam users n = 22 (%)	31.8	68.2	0.097
vs.			
Temazepam users n = 53 (%)[b]	52.8	47.2	
Diazepam users n = 24 (%)	29.2	70.8	≤0.001
vs.			
Oxazepam users n = 44 (%)	75.0	25.0	

[a] 1 patient taking both oxazepam and temazepam at admission was excluded.
[b] 2 patients taking both diazepam and temazepam at admission were excluded.

Statistically significant associations between users of diazepam and oxazepam at admission and a history of falls noted in the univariate analyses were further tested in multivariate logistic regression models which adjusted for age, gender, premorbid CPS, premorbid ADL and other medications potentially associated with falls. As shown in the first logistic regression model (Table 5), the use of diazepam continued to be positively associated with a history of falls independently of the effect of other covariates (OR 3.3; 95% CI 1.3–8.2; p=0.012). When using the dummy variables to perform the comparison between particular groups of BZD users in the second model (Table 6), diazepam users remained independently positively associated with a history of falls compared with BZD non-users (OR 3.3; 95% CI 1.3–8.3; p=0.012) and all other BZD users (OR 3.0; 95% CI 1.1–8.5; p=0.036). Diazepam users compared with oxazepam users, in particular, were about seven times more likely to have a fall in the previous 90 days (OR 6.8; 95% CI 2.1–22.0; p=0.001).

Table 5. Multivariate analysis of the association between history of falls and BZDs users at admission compared to non-users.

History of falls (at least 1 fall in previous 90 days)	**Adjusted Odds Ratio***	**p value**	**95% Confidence Interval**
Diazepam users at admission vs. Diazepam non-users at admission[a]	3.269	0.012	1.298 – 8.230
Oxazepam users at admission vs. Oxazepam non-users at admission[b]	0.481	0.054	0.229 – 1.011

*Adjusted for age, gender, premorbid cognitive performance (CPS – Cognitive Performance Scale), premorbid functional status (ADL – Activities of Daily Living), opioids, antipsychotics, antidepressants, nitrates, diuretics, beta-blockers, and ACEIs (Angiotensin Converting Enzyme Inhibitors).

[a] Diazepam non-users at admission represent all BZDs non-users and users of BZDs other than diazepam.

[b] Oxazepam non-users at admission represent all BZDs non-users and users of BZDs other than oxazepam.

Table 6. Multivariate analysis of the association between history of falls and particular drugs within the group of BZDs users

History of falls (at least 1 fall in previous 90 days)	**Adjusted Odds Ratio***	**p value**	**95% Confidence Interval**
Diazepam users vs. all BZDs non-users[a]	3.288	0.012	1.305 – 8.281
Diazepam users vs. all other BZDs users[a]	3.022	0.036	1.077 – 8.478
Diazepam users vs. Oxazepam users[a]	6.796	0.001	2.100 - 21.985

*Adjusted for age, gender, premorbid cognitive performance (CPS – Cognitive Performance Scale), premorbid functional status (ADL – Activities of Daily Living), opioids, antipsychotics, antidepressants, nitrates, diuretics, beta-blockers, and ACEIs (Angiotensin Converting Enzyme Inhibitors).

[a] Variables were entered to one multivariate logistic regression model as dummy variables in order to allow comparison between particular BZDs users groups. As a baseline group (comparator group) the diazepam users were chosen and assigned value of 0 in each of the dummy variables. Other user groups (oxazepam users, others BZDs users, and BZDs non-users) were subsequently assigned value of 1 to be compared with the diazepam users group.

Discussion

This large study of older patients admitted to acute care Australian hospitals using rigorous methods of data collection of comprehensive geriatric assessment is, as far as we are aware, the first study to evaluate the associations between BZD use — both overall and for specific BZDs — and in-hospital falls and a prior history of falls.

BZD use and association with in-hospital falls

Despite incidence rates of falls in hospitals ranging from 2.9 to 13 falls per 1,000 bed-days[25], studies focusing on BZD use as a risk factor of in-hospital falls have yielded conflicting results. The authors of one negative study 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.[51] In contrast, a population-based case-control study examining in-hospital hip fractures reported an adjusted OR of 2.05 (95% CI 1.05–3.77; p=0.035) in BZD users compared with nonusers.[52] An observational prospective study of hospitalized older patients showed an increased risk of falls in association with use of short half-life BZDs (OR 1.8; 95% CI 1.2–2.8), as well as very short half-life BZDs (OR 1.8; 95% CI 1.03–3.3).[29]

We found no statistically significant difference between incidence rates of in-hospital fallers among users of BZDs (ever users) versus non-users (never users). Non-significant differences in incidence rates of in-hospital fallers in our study population 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.

It is important to note that of 146 BZD users at admission, 29 had discontinued use by discharge. Of 155 BZD users at discharge, 38 commenced these medications during hospitalization—that is, they were not using BZDs at admission assessment but were using BZDs at the discharge assessment. Because medications were recorded at admission and discharge, the number of patients who were prescribed BZDs during hospitalization but had ceased by discharge is unknown.

BZD use and association with past history of falls

A comprehensive meta-analysis of studies published between 1966 and 1999 which studied the association of drugs with falls reported a pooled OR for any BZD use of 1.48 (95% CI 1.23–1.77),[53] while a more recent meta-analysis of nine medication classes involving older individuals reported a Bayesian pooled OR of 1.41 (95% CI 1.20–1.71)[21]. In one study in this meta-analysis[21], which showed no relationship between antipsychotic drugs (including BZDs) and a history of falls[54], its authors conjectured this negative finding was probably due to a very low prevalence of BZD use in their sample (3.5 %), and the relatively healthy and mobile status of the sample population[54].

Contrary to previous studies[21,29,53,55-57], our present study found no statistically significant differences in history of falls between users and non-users of BZDs overall. In subgroup analyses of outcome history of falls, no statistically significant relationships were found between temazepam users compared with BZD non-users, nor between oxazepam users compared with BZD non-users. However, there was a significant association with diazepam users. The non-significant association between all BZDs users and falls in our study may be attributed to the fact that temazepam and oxazepam users represent the majority of the BZD users in the sample (oxazepam: 33.6% of BZD users; temazepam: 32.3% of BZD users).

Association between half-life of BZDs and falls

Research evidence of differences between particular BZDs and falls according to their biological half-life is mixed[19,27-29,31,58]. Using multivariate analyses, Ensrud et al.[19] showed trends toward increased risk of falls in older community-dwelling women taking either long-acting or short-acting BZDs compared with non-users (OR 1.42, 95% CI 0.98–2.04; and OR 1.56, 95% CI 1.00–2.43, respectively)[19]. Other authors have found associations between current use of long-acting BZDs (in this case those with a half-life >24 h) and hip fractures (adjusted OR 1.6; 95% CI 1.1–2.4) when compared with current non-users of BZDs.[58] A case-control study designed to examine the association between use of BZDs and risk of hospitalization for femur fractures resulting from accidental falls showed a significantly increased risk with BZDs having a half-life ≤24 h (OR 1.5; 95% CI 1.1–2.0) but not with BZDs having a half-life >24 h (OR 1.3; 95% CI 0.7–2.4).[31] In another prospective observational study of the use of BZDs and subsequent falls in hospitalized older patients, the authors

reported an increased risk of falls in patients taking short-acting and very-short-acting BZDs compared with untreated populations (OR 1.8, 95% CI 1.2–2.8; and OR 1.9, 95% CI 1.03–3.3, respectively).[29] Groups of BZDs in this study were defined as long half-life >24 h, short half-life 12–24 h, and very-short half-life <6 h.[29] Exposure to long half-life BZDs did not show a statistically significant association with falls in this study, with the authors suggesting this may have resulted from random error due to the small number of patients in this subgroup.[29] A prospective study of community-dwelling older people concluded that occasional as well as regular users of long-acting BZDs had higher risk of falls compared with non-users.[27] In a cohort study of residents of nursing homes, the incidence of falls increased as the elimination half-life of BZDs increased: for BZDs with a half-life of 12–23h, the rate ratio (RR) was 1.43 (95% CI 1.29–1.59), while for those with a half-life ≥24 h, the RR was 1.77 (95% CI 1.38–2.26).[28] In addition, when oxazepam was excluded from the group of BZDs with a short half-life, the adjusted RR for night-time falls increased from 2.19 (95% CI 1.59–3.03) to 2.82 (95% CI 2.02–3.94).[28]

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. Temazepam and diazepam are drugs subject to 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.[59] One study of drug-metabolizing enzyme content in liver biopsies, particularly CYP, found that CYP content declines at a rate of approximately 0.07 nmol/g per year after 40 years of age.[13] However, other studies report inconsistent results, with some showing reduction, paradoxical increase, or no significant change in hepatic clearance of low hepatic clearance drugs in older people.[59] In contrast, oxazepam is extensively metabolized by UGT enzymes.[60] Drug metabolism by glucuronidation involving UGT appears to be preserved in otherwise fit and well older people, although it might be affected by frailty.[59] Old age may also alter the plasma protein binding of BZDs as most of the BZDs are highly bound to albumin, the levels of which decline with ageing.[14] Other possible mechanisms to account for the differences in

falls risk between different BZDs may include changes in receptors, neurotransmitters, and second-messenger systems in the brain[15], which remain to be accurately defined for specific BZDs.

Association between doses of BZDs and falls

Few studies have focused on dose-related associations between BZD use and falls.[28, 31] In one study of falls leading to hospitalization for femur fractures, standardized doses, defined as DDD equivalents per day, were calculated and it was shown that patients exposed to BZD doses >0.74 DDD equivalents per day incurred the highest risk of fracture—related falls, independent of biological half-life or the mode of use (new exposure or regular user).[31] In another study, adjusted RRs of falls increased according to increasing dose equivalent of diazepam: RR of 1.30 (95% CI 1.12–1.52) for a dose equivalent to ≤2 mg of diazepam and RR of 2.21 (95% CI 1.89–2.60) for a dose equivalent to >8 mg of diazepam.[28] In our study, we did not identify any significant relationships between a history of falls and different doses of different BZDs. Most of the doses of BZDs used in the study fell within the recent recommendations for use of potentially inappropriate medications in older patients.[47-50]

Study strengths and limitations

Our study has several strengths. It comprised a large sample of older people admitted to acute care at multiple sites and employed a standardized, accurate method of data collection using the validated interRAI AC assessment tool, with verification of accuracy of medication data by a second pharmacist or geriatrician. We used multivariate regression to analyse associations between falls history and individual BZDs, in addition to BZDs as a group, independently of other confounders.

Limitations of our study include lack of data on time sequence between in-hospital fall events and starting or stopping of BZD use. We could not be certain that BZD prescription at admission to hospital reflected regular use in the pre-morbid period. We assumed that the majority would have been regular users; however, we acknowledge that some BZDs may have been newly prescribed on admission due to presentations for conditions such as acute

neurological or confusional syndromes. Also, our reliance on patient self-report in gathering data on past falls may have biased our estimates of falls risk due to retrospective recall, but this would have likely led to under-estimates rather than over-estimates.[61] Moreover, the interRAI AC tool provides some multilevel validation of the data, as trained assessors collected information using the combination of patient and primary caregiver interviews and interrogation of chart records.[36] Our subgroup analyses of BZDs which yielded positive associations with falls compared with the null findings from whole-group analyses may invoke scepticism, but the level of statistical significance was high in univariate analyses ($p<0.01$) and the associations persisted in multivariate analyses.

Other limitations of the study include the possibility of selection bias from several sources, including the requirement that patients have an expected hospital stay of at least 48 h and the recruitment of participants on weekdays only. However, to minimize selection bias, a computer program was used to select patients randomly when there were more than three eligible patients on the one day at each hospital. Another potential source of bias derives from the sizeable number of patients who declined to participate in the study. However, there was no difference in the length of admission between participants and non-participants, suggesting no difference in terms of illness severity[34].

Conclusions

This study of older hospitalized patients showed no significant differences in the incidence rates of in-hospital fallers between groups of users and non-users of BZDs. However, the overall low incidence of in-hospital fallers among patients who stayed in hospital for a relatively short time and other factors that predispose to falls, probably account for this negative finding. Therefore, further investigations in this patient-specific setting should be carried out.

Our study did document differences in the association between different BZDs and a history of falls according to their biological half-life. Diazepam use was shown to be an independent risk factor of a history of falls when compared with BZD non-users, all other BZD users and, in particular, with oxazepam users. Our study confirms 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.

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Chapter 4

Prevalence of benzodiazepine use in the Czech Republic

Full text of Chapter 4 is prepared for submission as manuscript:

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Abstract

Background

Benzodiazepines (BZDs) are commonly prescribed for anxiety disorders and sleep problems and are widely used in younger adults as well as in the older population. Utilization of BZDs and prescribing patterns can substantially differ between age groups reflecting specific indications for use as well as resulting in different potential adverse effects.

Objective

This study aimed to evaluate the trends in utilization of BZDs between years 2009 and 2013 in the Czech Republic (CZ), with particular focus on describing the age structure of BZD users and source of BZD prescriptions.

Methods

Three different databases were used as primary data sources: (1) the State Institute for Drug Control (Státní ústav pro kontrolu léčiv - SUKL) medication database; (2) the database of reimbursed medicinal products of the General Health Insurance Company (Všeobecná zdravotní pojišťovna České republiky - VZP); and (3) the database of the medicinal product delivery reporting system (DIS-13) conducted by the SUKL. Data about utilization of BZDs (in DDDs), number of patients using BZDs, and prescribers' specializations in the CZ in the study period 2009-2013 were analysed retrospectively using descriptive statistical methods.

Results

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 highest average proportion of BZD users was documented in the age group of 85+ years (17.6% of the persons). The proportion of particular BZD users did not change rapidly between 2009 and

2013. The most frequently used BZD was alprazolam (62.2% of BZD users), followed by diazepam (22.1%) and oxazepam (11.0%). BZDs were most often prescribed by general practitioners (45.8%) followed by psychiatrists (38.9%) and neurologists (3.7%).

Conclusions

This study provided comprehensive information on BZD utilization and prescription patterns in the CZ and unique insight into the consumption of particular BZDs in this country. Results of the study open opportunities for further in-detail clinical studies on rationality of BZDs´ use and for international cross-sectional comparisons.

Introduction

Since 1960s, after the introduction of chlordiazepoxide as the first BZD, there have been more than 30 other substances from this drug class used all around the world.[1] During so called "Age of Anxiety" in 1960s and 1970s in the United States, BZD use rapidly increased while dramatically replacing older substances from the barbiturates group.[1] BZDs are widely prescribed in treatment of anxiety disorders, insomnia, and they are commonly used as muscle relaxants, adjuvant therapy for depression or schizophrenia.[2,3] Different studies estimated the long term use of BZDs in general population to be from 2% to 8.9%[4-8], while the proportion of BZD users in the older population reaches up to 13% to 54%[9-16]. However, also a concern about the use of BZDs due to their addictive potential and propensity to cause many adverse drug outcomes (such as fall and fractures, cognitive impairment, functional decline, and delirium), particularly in older population, has been well described.[17-24] BZDs were included in the Schedule IV of the United Nations Convention on Psychotropic Substances.[25] They are also listed in the internationally acknowledged and widely used list of potentially inappropriate medications in older people called the Beers criteria.[26] Considering above mentioned safety concerns, recommendations and policies have been established in many European countries to reduce the prescription and consumption of substances from this drug class.[27-31]

Selective benzodiazepine receptor agonists commonly called as Z-drugs (zolpidem, zopiclone, zaleplone and eszopiclone) were introduced in late 1980s and 1990s.[32] Compared to BZDs substances, Z-drugs 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.[30] 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.[33,34] Concerns related to Z-drugs potential of abuse and dependence have risen in some studies as well.[35-37] Zolpidem was included on the Schedule IV of the United Nations Convention on Psychotropic Substances due to abuse and dependence

potential.[25] The prevalence of Z-drug use in general population reaches up to 50%[38,39] and up to 25% in older patients[40-43].

Use of BZDs in the CZ was documented in a few studies mainly focusing on general misuse of various addictive substances[44,45] or in specific population of NH residents[46]. As far as we are aware, there is no study that would describe the prevalence of BZD use or their prescription patterns in the CZ in general population. Thus, this study aimed to evaluate the trends in utilization of BZDs, with particular focus on describing the age structure of BZD users and source of BZD prescriptions.

Methods

Data sources

Three different nationwide databases were used as primary data sources:

(1) the State Institute for Drug Control (Státní ústav pro kontrolu léčiv - SUKL) medication database;

(2) the database of reimbursed medicinal products of the General Health Insurance Company (Všeobecná zdravotní pojišťovna České republiky - VZP); and

(3) the database of the medicinal product delivery reporting system (DIS-13) conducted by the SUKL.

In the CZ the reimbursement process of medications used in outpatient setting is in responsibility of the SUKL. In outpatient settings the reimbursement of medicinal products is covered by health insurance companies on the basis of prescriptions provided by pharmacies. The SUKL medication database gives comprehensive list of medicinal products that hold marketing authorisation for use in the CZ and provides their status of reimbursement. This database was searched for all existing ATC codes based on the WHO Collaborating Centre for Drug Statistics Methodology available for BZDs (see Table 1 in Chapter 2).[47] As a result, a list of ATC codes of active substances of medicinal products with market authorisation and with and without reimbursement was created (Table 1). The list of BZDs given in the Table 1 was thereafter used for search within above mentioned databases.

Table 1. BZDs and Z-drugs with/without market authorisation and reimbursement in the Czech Republic (valid on 25 May, 2016)

Active substances in medicinal products with market authorisation in CZ		**Active substances in medicinal products <u>with</u> reimbursement in CZ[1]**		**Active substances in medicinal products <u>without</u> reimbursement in CZ[2]**	
Benzodiazepines					
ATC code	**Name**	**ATC code**	**Name**	**ATC code**	**Name**
N05BA01	Diazepam	N05BA01	Diazepam	N05BA08	Bromazepam[3]
N05BA02	Chlordiazepoxide	N05BA02	Chlordiazepoxide	N05BA23	Tofisopam[3]
N05BA03	Medazepam	N05BA03	Medazepam	N05CD08	Midazolam[4]
N05BA04	Oxazepam	N05BA04	Oxazepam	N05CD13	Cinolazepam
N05BA08	Bromazepam	N05BA09	Klobazam		
N05BA09	Klobazam	N05BA12	Alprazolam		
N05BA12	Alprazolam	N05CD08	Midazolam[4]		
N05BA23	Tofisopam				
N05CD08	Midazolam				
N05CD13	Cinolazepam				
Z-drugs[5]					
N05CF01	Zopiclone			N05CF01	Zopiclone
N05CF02	Zolpidem			N05CF02	Zolpidem
N05CF03	Zaleplone			N05CF03	Zaleplone

[1] ATC codes for all substances with reimbursement were searched within the VZP and DIS-13 databases

[2] ATC codes for substances which do not possess reimbursement were not searched within the VZP and DIS-13 databases

[3] Medicinal products containing bromazepam and tofisopam were reimbursed until 2009 and 2011, respectively. Thus these ATC codes were searched in both databases.

[4] Midazolam is reimbursed just in parenteral forms, per oral forms of medications containing midazolam are not reimbursed. Because parenteral forms of midazolam are in Czech clinical practice prescribed and used mainly in preoperative care, these ATC codes were not searched in neither of databases.

[5] None of the Z-drugs has reimbursement in the CZ. ATC codes for these substances were searched just in the DIS-13 database in order to provide comparison to overall BZD distribution in the CZ.

The VZP is the largest public health insurance company in the CZ providing health insurance for almost 60% of the Czech population (i.e. approximately 6 million people).[48] The large market share of the VZP represents a great majority of the CZ population and relative shares of patients according to their age and their gender within the VZP has been stable over years.[49] Because in the CZ the public health insurance is compulsory by law for all citizens, information about use of medicinal products with reimbursement provided by the VZP database illustrates well the real-world prescribing practice. The VZP database provides

information on medicinal products reimbursed, age structure of patients and source of prescription (the clinicians' specialization).

All distributors of medicinal products or manufacturers distributing their own products must report on a monthly basis all the deliveries of human medicinal products within the CZ.[50] The database of DIS-13 provides information on all deliveries to pharmacies, vendors of selected medicinal products, healthcare professionals providing health care, health care facilities, veterinarians, marketing authorisation holders (MAH) or sales representatives authorised by MAH, and to other distributors.[50] Deliveries of human medicinal products to European Union Member States and abroad should be reported as well.[50] The DIS-13 database was used to evaluate an overall distribution of BZDs in order to compare to the amount of BZDs that were reimbursed. It is not possible to distinguish which medicinal products within the distributors´ reports were reimbursed by insurance company or paid on 'out-of-pocket' bases. Therefore, the information about BZD use from this database can substantially differ from those reported in the VZP database.

The DIS-13 database was used also to obtain data about Z-drugs. This analysis was conducted in order to compare use of BZDs with Z-drugs, as they have a common indication of insomnia and the research shows that they may cause the same AEs. As none of the medicinal products containing Z-drugs are reimbursed in the CZ and therefore no data about these substances are available within the VZP database, the age stratification cannot be obtained from this database. There are also no other resources that would allow to comprehensively analyse the use of Z-drugs and their prescribing patterns in the CZ. Therefore, further analyses were not conducted for this drug class.

Demographic data about the Czech population stratified by age were obtained from the Czech Statistical Office.[51]

As all of the accessed data from all databases were de-identified, ethics committee approval was not required for these analyses.

Data analysis

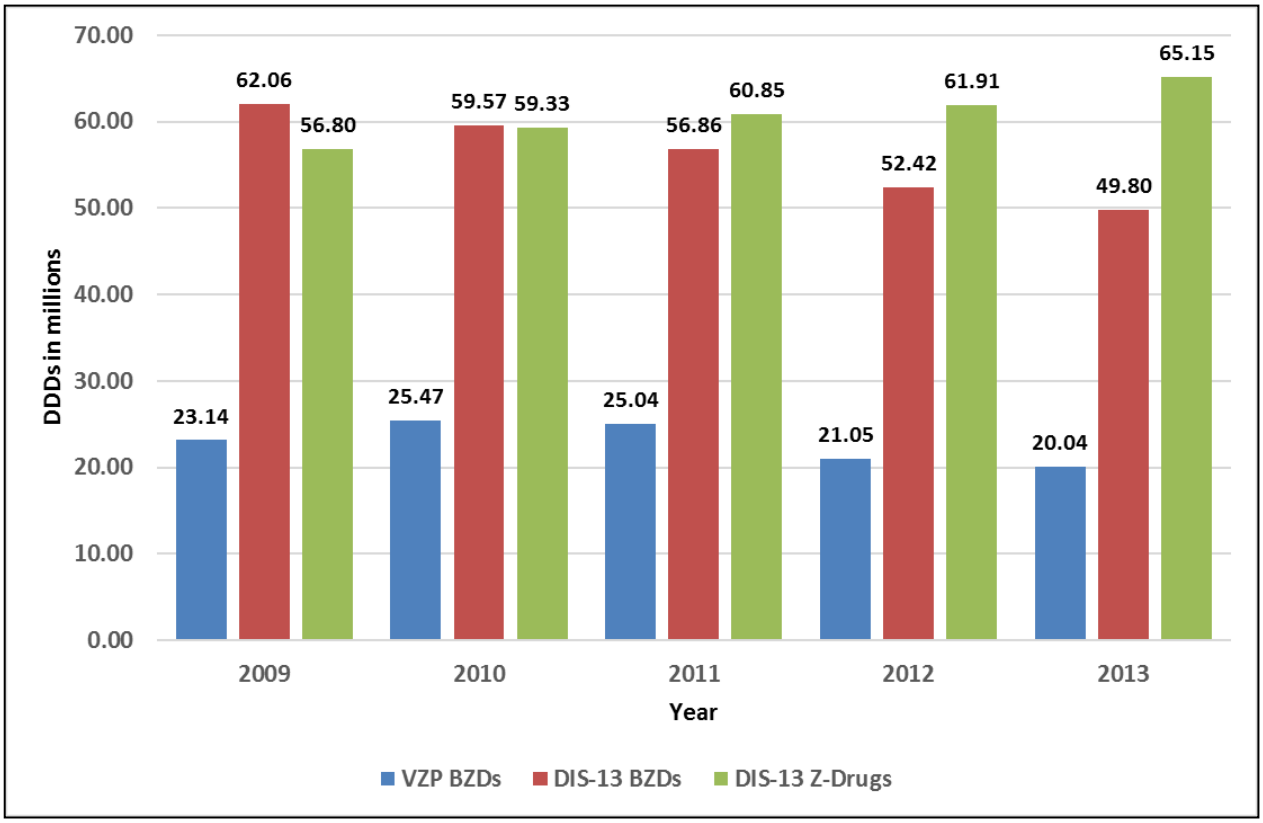
Data from the VZP database were obtained for all BZDs (using the list of ATC codes from Table 1) that were reimbursed according to medical prescriptions during years 2009 to 2013. The data were stratified by age into five-year intervals. Prescriptions were converted into DDDs that represent assumed average maintenance dose per day for a drug used in its main indication in adults.[52] The approach of using DDD measure overcomes difficulties in comparing prescriptions of different medicinal products, different package sizes and dosage as well as it allows for comparison over time and place.[53] Utilization of BZDs (stratified by age and year) was expressed in DDDs and in number of patients who were prescribed BZDs. To evaluate the proportion of BZD users within the persons insured by the VZP, information on numbers of persons insured from annual VZP reports[49] were used. The information about specialization of clinicians prescribing BZDs was evaluated and data were expressed as percentage of DDDs of BZDs prescribed.

The data obtained from the DIS-13 database were expressed only in DDDs, as this database provides simple data about the amount of distributed medicinal products.

Results

Overall consumption of BZDs and Z-drugs during years 2009 and 2013 stratified by the origin of data sources is shown in Figure 1. According to the data from the DIS-13 database the number of DDDs of BZDs decreased from 62.1 million in 2009 to 49.8 million in 2013 (by 19.8%), while the number of DDDs of Z-drugs increased from 56.8 million in 2009 to 65.1 million in 2013 (by 14.7%). The analysis of the VZP database showed that prescription of BZDs decreased approximately by 13.4%.

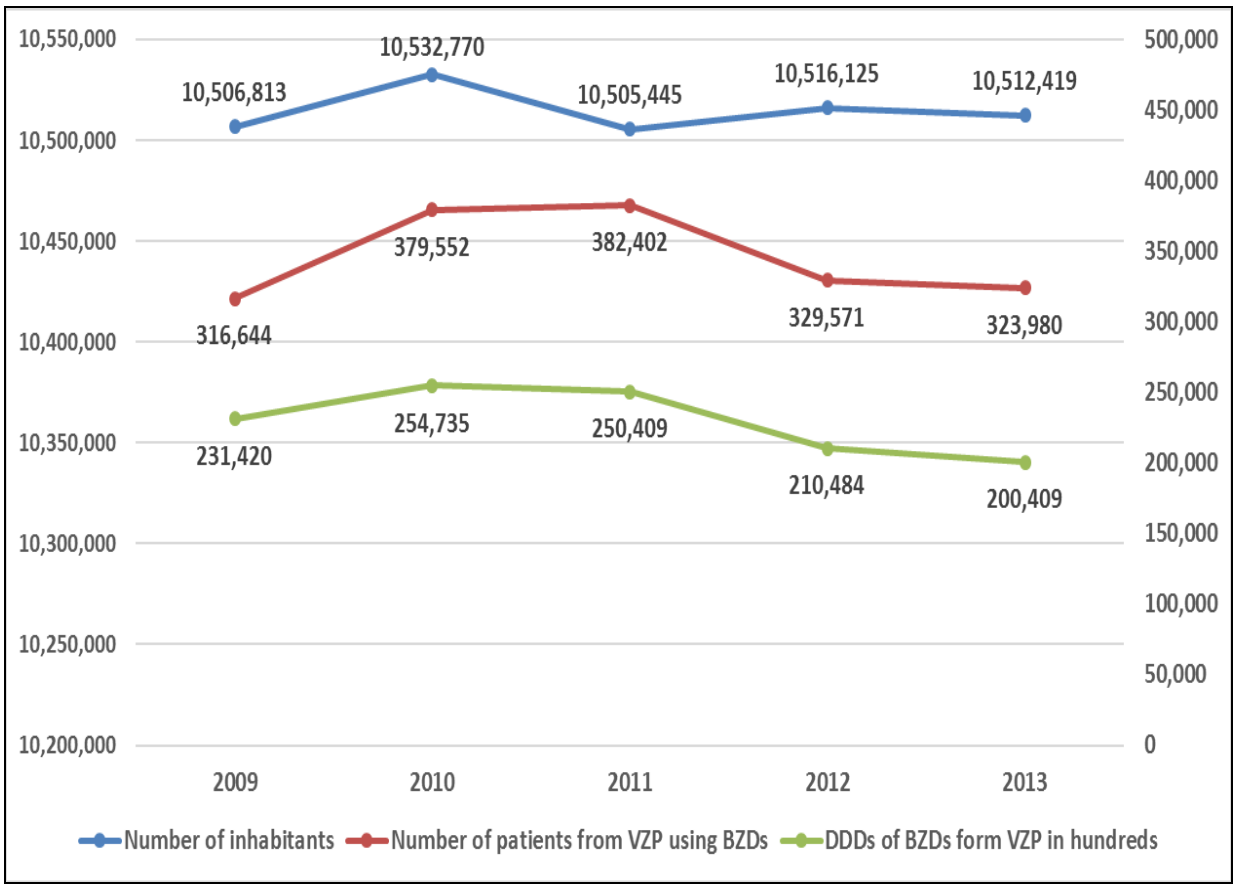
Figure 1. Consumption of BZDs and Z-drugs (in millions of DDDs) in the Czech Republic (2009-2013) stratified by year and dataset source.



VZP BZDs – consumption of BZDs according to the VZP database
DIS-13 BZDs – consumption of BZDS according to DIS-13 database
DIS-13 Z-drugs – consumption of Z-drugs according to DIS-13 database

Figure 2 shows changes during 2009 and 2013 in the total Czech population, number of patients using BZDs and DDDs of BZDs utilized (according to VZP database). The number of BZD users from VZP database represented approximately 3.3% of the Czech population and this proportion did not change substantially during 2009 to 2013 (3.01% to 3.08% in 2009 and 2013; respectively). Considering the 60% of market share of VZP in the CZ, the calculated proportion of all BZD users in the Czech population would be 5.5% on average for years 2009 to 2013.

Figure 2. Comparison of trends in demographic statistics and consumption of BZDs (in hundreds of DDDs) in the Czech Republic, 2009-2013.



Number of inhabitants in the CZ was derived from the Czech Statistical Office[51]
Number of patients form VZP using BZDs – number of BZD users according to the VZP database
DDDs of BZDs from VZP – consumption of BZDs according to the VZP database

The consumption of BZDs during years 2009 and 2013 according to the VZP database is described in Figure 3. While the number of DDDs in the youngest groups (0-19 years) was relatively stable, in young adult groups (20-39 years) and in middle age groups (40-54 years) it decreased between 2009 and 2013. The number of DDDs in older adults (55-84 years) showed steep increase in 2010 and 2011 with swift decrease in subsequent year 2012. The number of DDDs in the oldest group of 90-94 years was constantly increasing during years 2009 and 2013. In comparison, Figure 4 shows number of patients who were prescribed BZDs during years 2009 and 2013. The trends in numbers of patients in age groups correspond with trends in number of DDDs; except for the youngest group of patients (0-4 years).

Figure 3. Consumption of BZDs (in DDDs) stratified by age and year in the Czech Republic, 2009-2013 (VZP database).

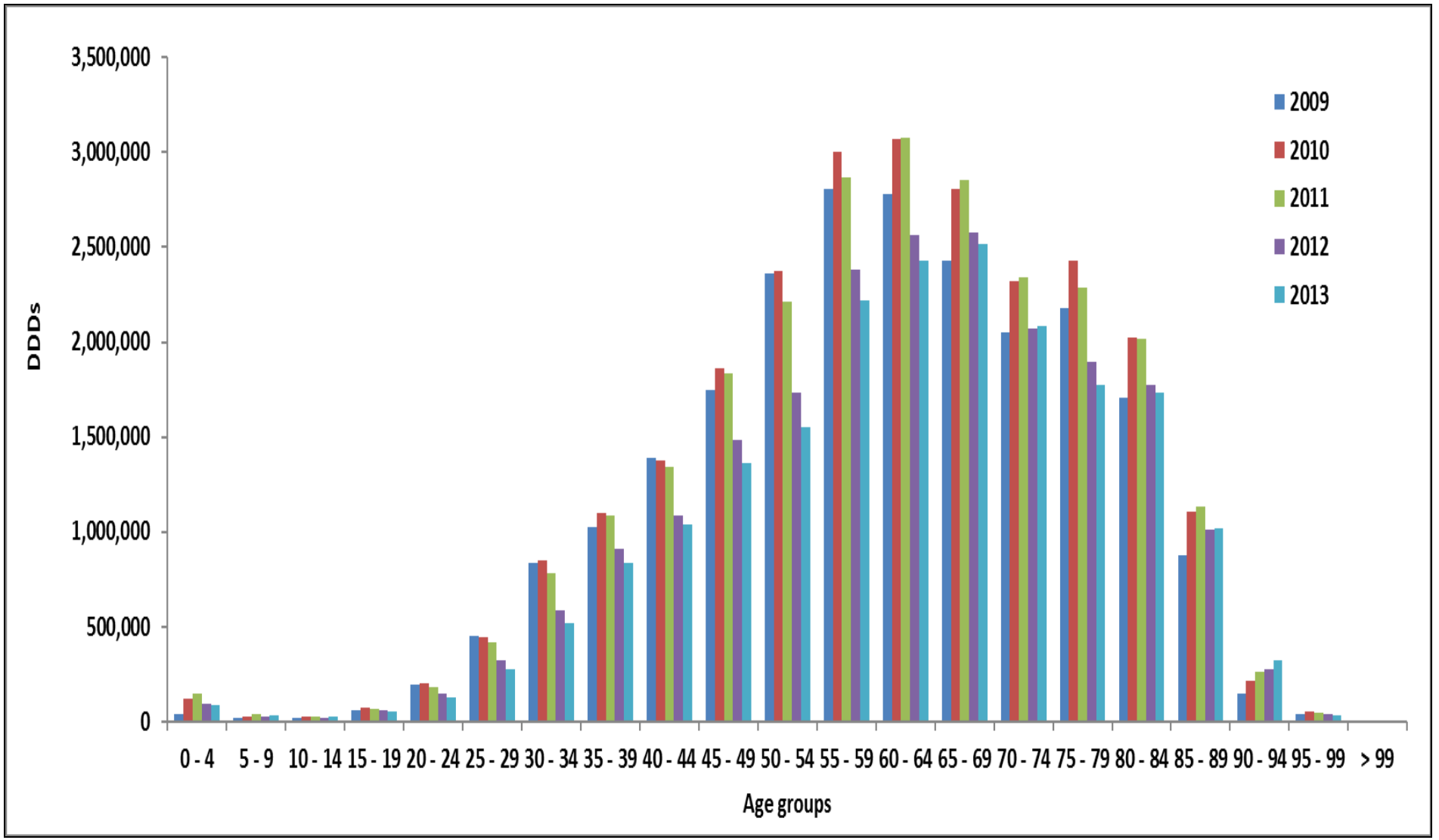
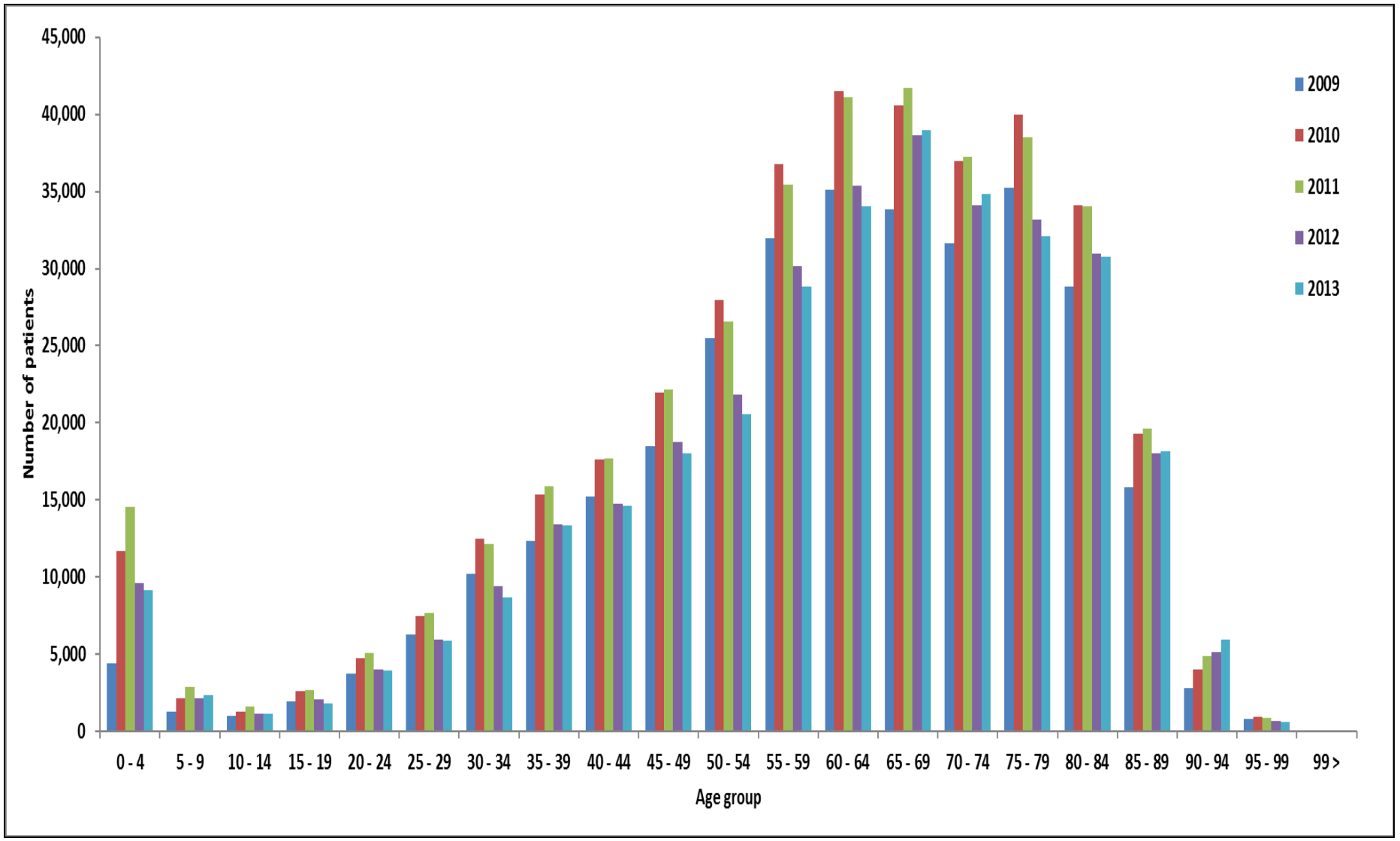
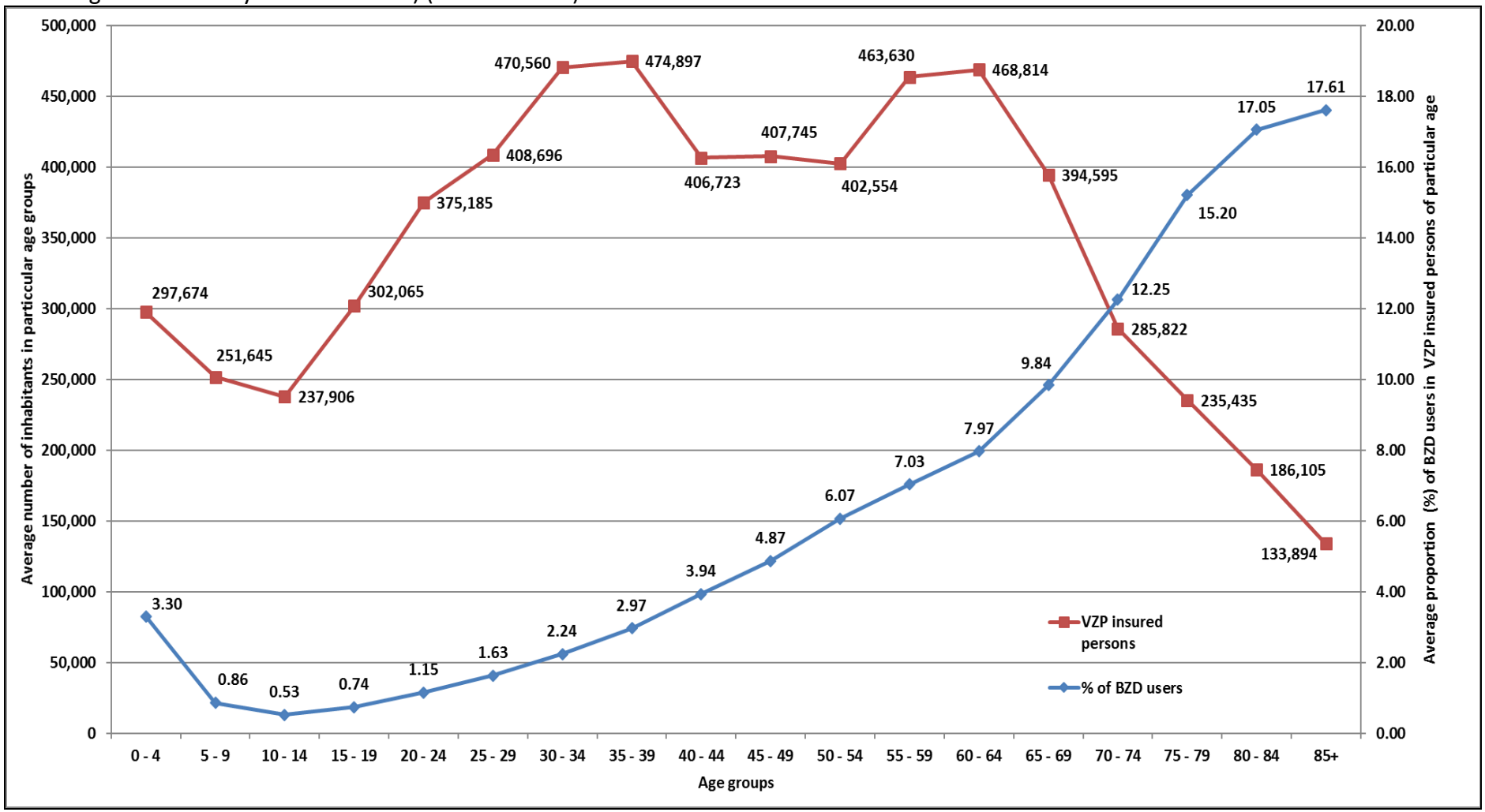


Figure 4. Absolute number of patients prescribed BZDs stratified by age and year in the Czech Republic, 2009-2013 (VZP database).



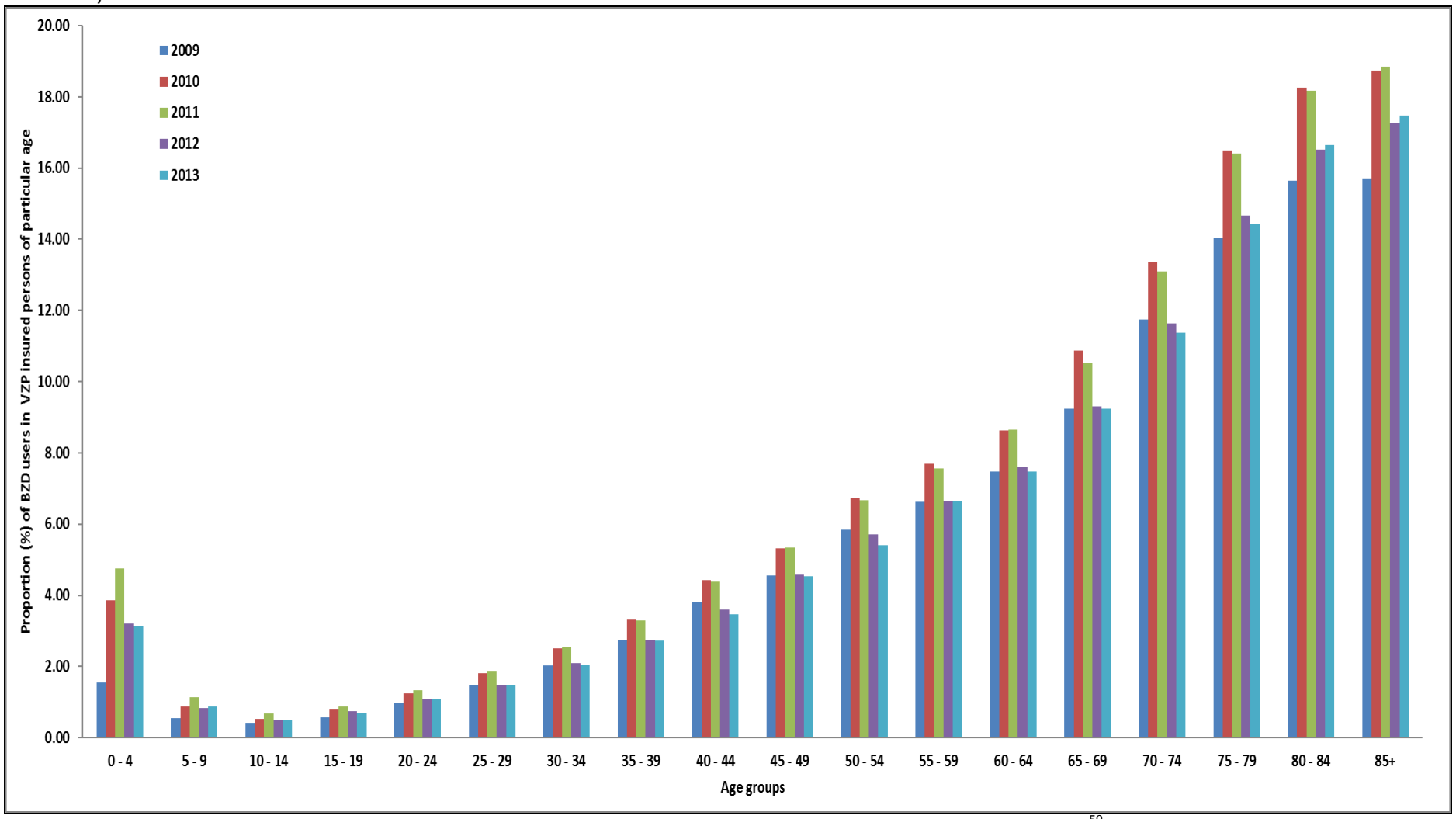
According to analyses related to the number of persons insured by the VZP, the proportion of BZD users within the persons insured by the VZP was 5.6% on average for the period 2009 - 2013. The highest proportion of BZD users was identified in the age group of 85+ years (17.6% average for years 2009-2013 in the population of 85+ years old persons insured by the VZP) followed by age group of 80-84 years (on average 17.1%) and 75-79 years (on average 15.2%). Figure 5 shows proportions of BZD users within the population of persons insured by the VZP stratified by age and number of persons insured by the VZP in each age group (both given as average numbers for years 2009-2013). Age groups accounting for the smallest number of persons represent at the same time groups with the highest proportion of BZD users. The changes in the proportion of BZD users within persons insured by the VZP in particular age groups are given in Figure 6. These results correlate with results given in Figure 3 and 4 describing steep increase in proportion of users among older adults (55-84 years) in 2010 and 2011 years and swift decrease in this proportion in a subsequent year 2012.

Figure 5. Number of persons insured by the VZP vs. proportion of BZDs users in the Czech Republic 2009-2013, stratified by age groups (given as average number for years 2009-2013) (VZP database).



Data about persons insured by the VZP were obtained from Annual Report of the General Health Insurance of the Czech Republic[50]. The age stratification was available only up to age group of 85+. The data about number of BZD users from the VZP database were therefore amended accordingly.

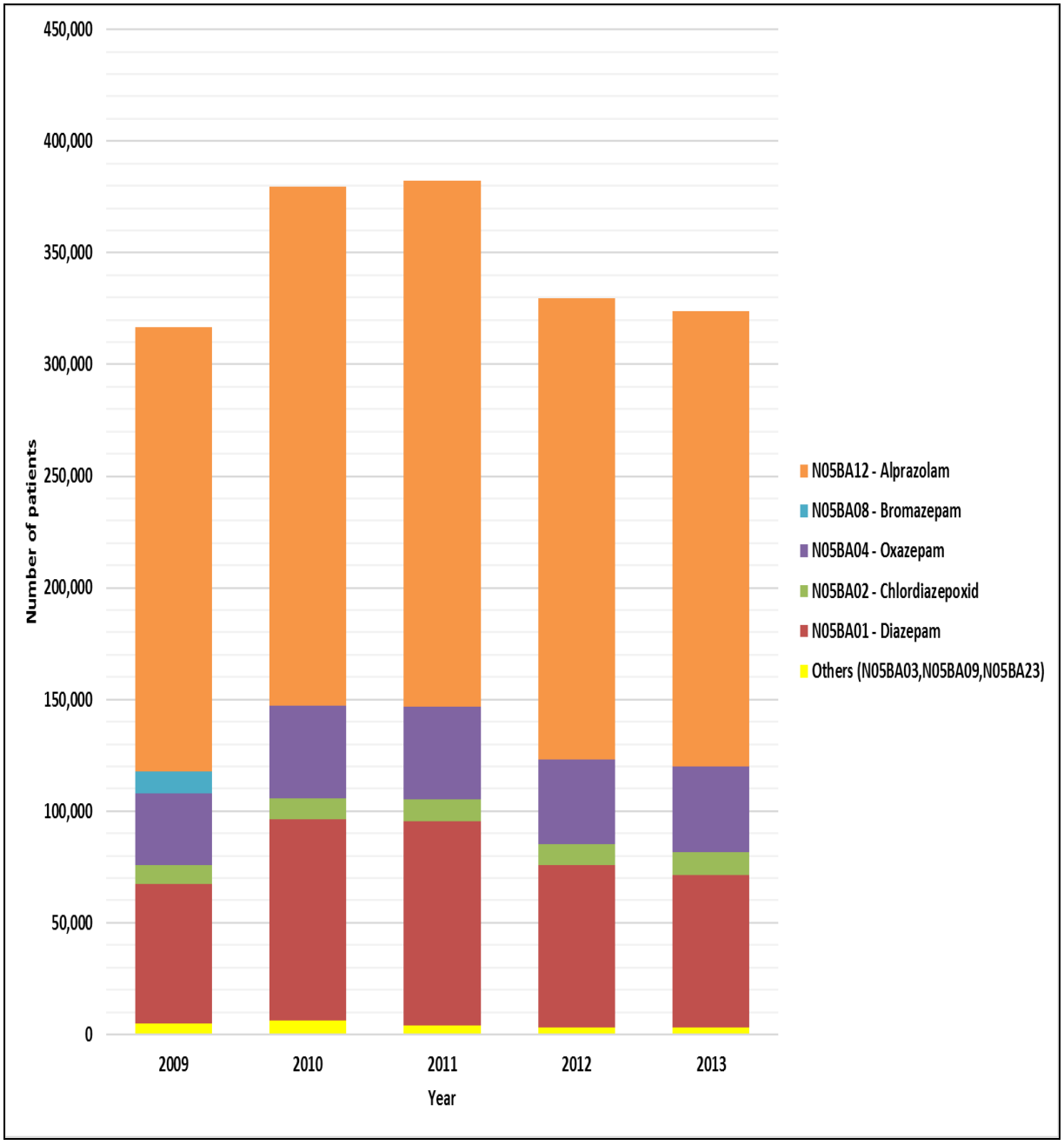
Figure 6. Trends in proportion of BZD users within persons insured by the VZP in the Czech Republic, 2009-2013, stratified by age groups (VZP database).



Data about persons insured by the VZP were obtained from Annual Report of the General Health Insurance of the Czech Republic[50]. The age stratification was available only up to age group of 85+. The data about number of BZD users from the VZP database were therefore amended accordingly

The proportion of particular BZD users has not changed rapidly during years 2009 and 2013 (Figure 7), with alprazolam being the most frequently used BZD (average proportion of 62.2% of BZD users in 2009-2013 years) followed by diazepam (22.1%) and oxazepam (11.0%).

Figure 7. Number of users of particular BZDs in the Czech Republic during years 2009 and 2013 (VZP database).



Medicinal products containing bromazepam (N05BA08) and tofisopam (N05BA23) were reimbursed by 2009 and 2011, respectively. Thus there are no users according to the VZP database of these BZDs in 2013. However, the market authorization of these medicinal products continued, they might be still prescribed and paid from patients' out of pocket money.

Proportions of users of particular BZDs are shown for 2009 and 2013 years in Figure 8 and Figure 9. The proportions of patients using particular BZDs in different age groups did not change substantially in consequent 5 years, thus detailed results are given only for year 2013 (Figure 10). After the age stratification, alprazolam remained the most frequently used BZD in all age groups (53.9%, 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).

Figure 8. Age stratification of particular BZD users in the Czech Republic in 2009.

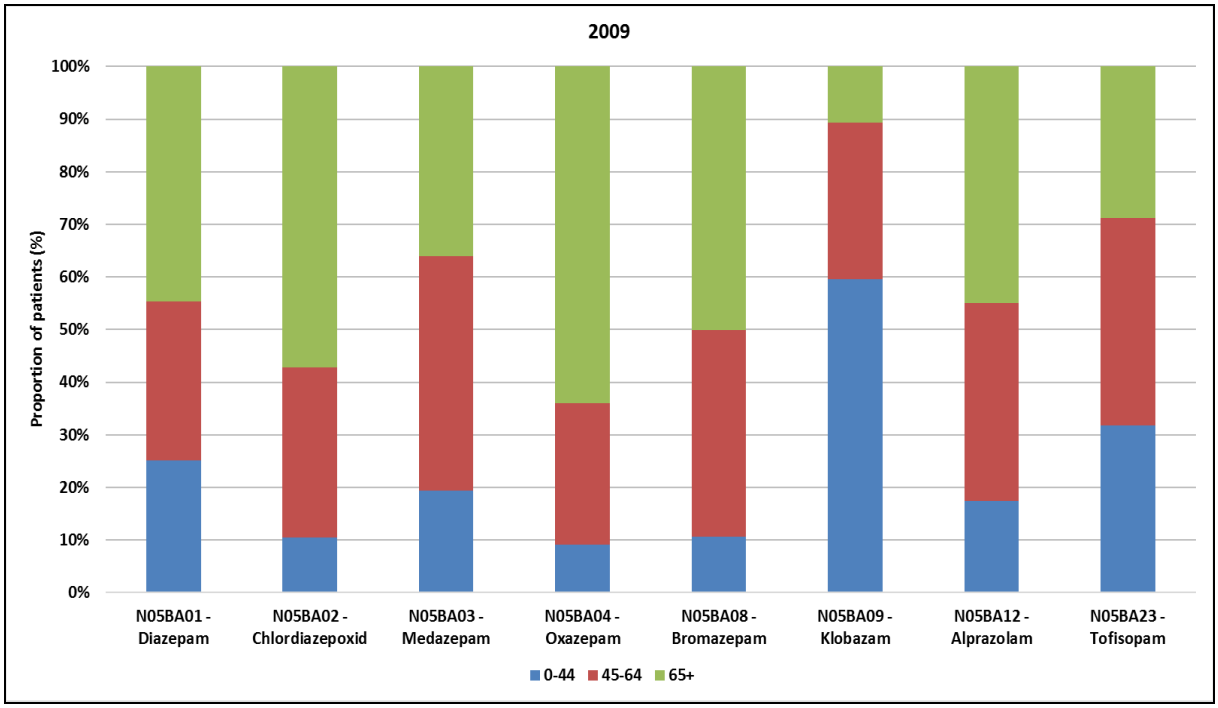
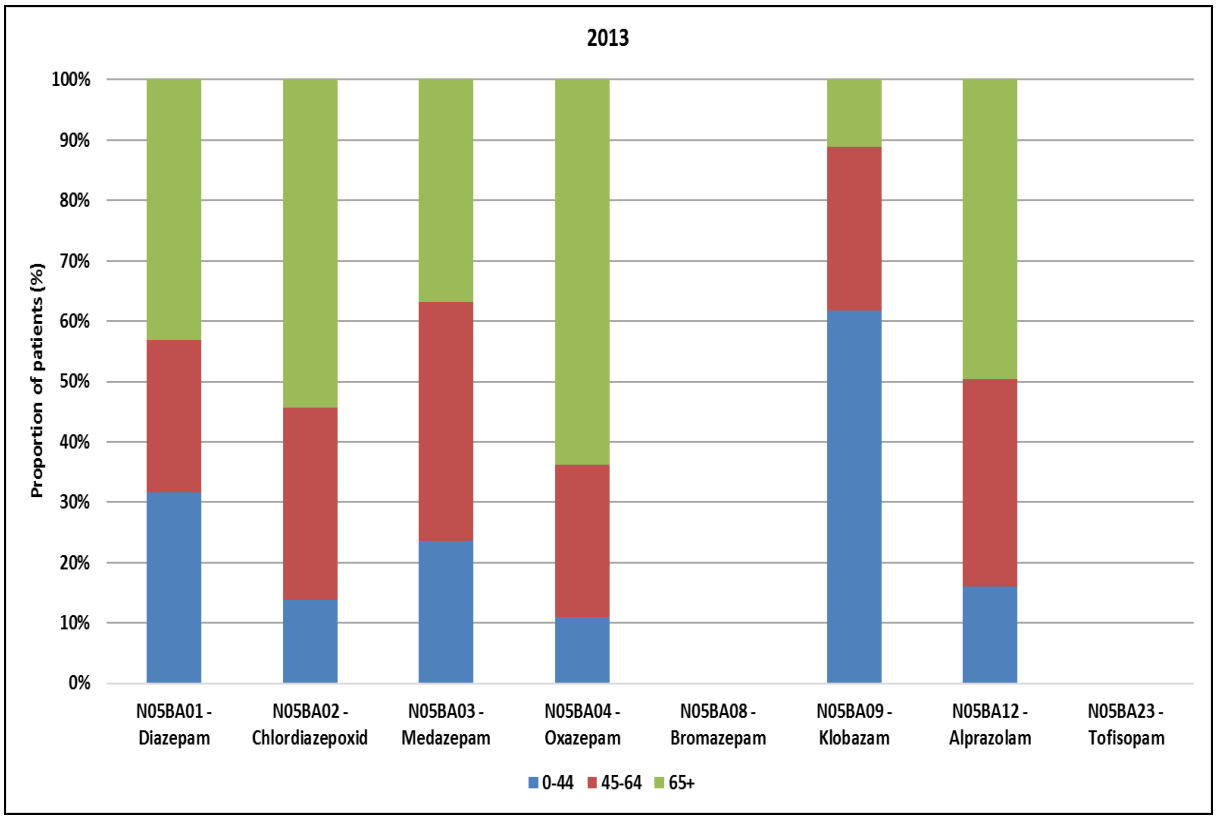
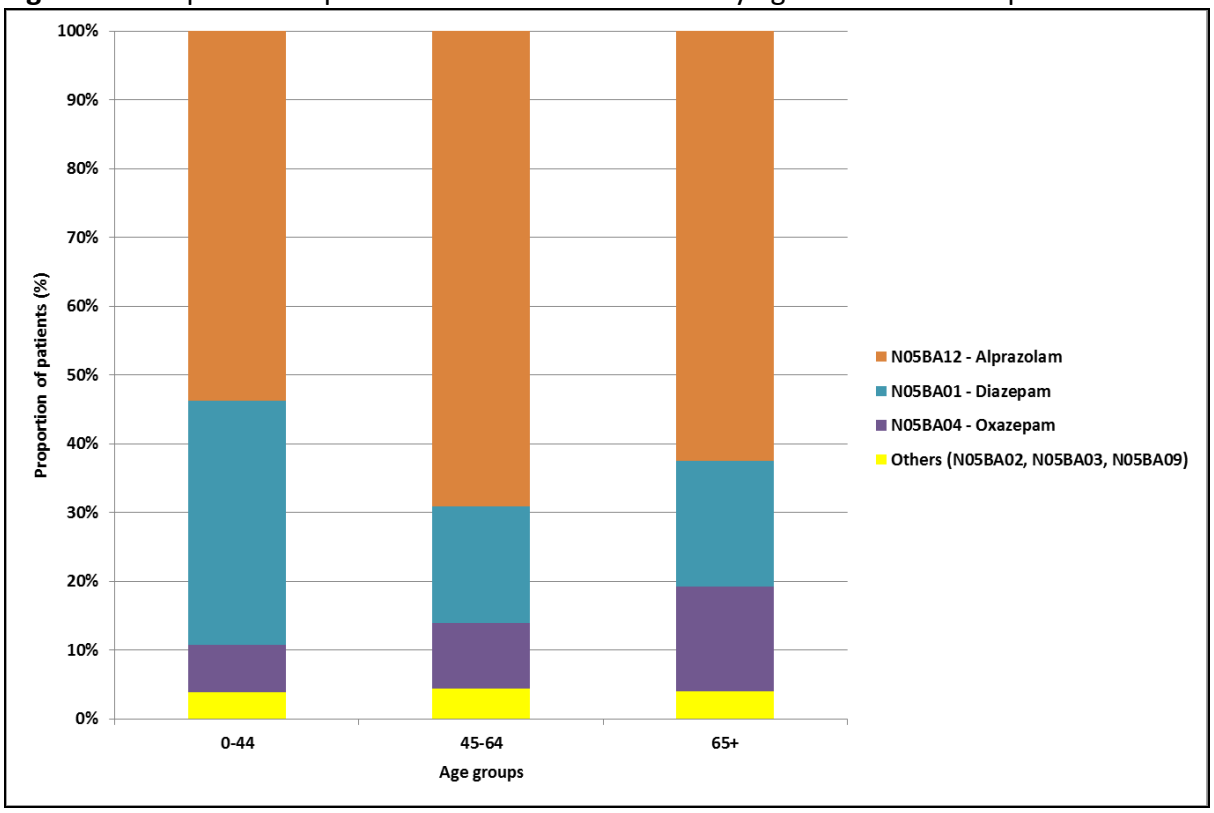


Figure 9. Age stratification of particular BZD users in the Czech Republic in 2013.



Medicinal products containing bromazepam (N05BA08) and tofisopam (N05BA23) were reimbursed only by 2009 and 2011, respectively. Thus there are no users according to the VZP database of these BZDs in 2013. However, the market authorization of these medicinal products continued, they might be still prescribed and paid from patients' out of pocket money.

Figure 10. Proportion of particular BZD users stratified by age in the Czech Republic in 2013.



Medicinal products containing bromazepam (N05BA08) and tofisopam (N05BA23) were reimbursed by 2009 and 2011, respectively. Thus there are no users according to the VZP database of these BZDs in 2013. However, the market authorization of these medicinal products continued, they might be still prescribed and paid from patients' out of pocket money.

Analyses showed that the proportion of different medical specialization prescribing BZDs did not change substantially during years 2009 and 2013 (Figure 11). Therefore, only the prescription pattern in terms of specialist prescribing BZDs in year 2013 is presented (Figure 12). Most of the prescriptions were prescribed by general practitioners (45.8%) followed by psychiatrists (38.9%) and neurologists (3.7%).

Figure 11. Prescribers of BZDs (in % proportion of DDDs) stratified by year.

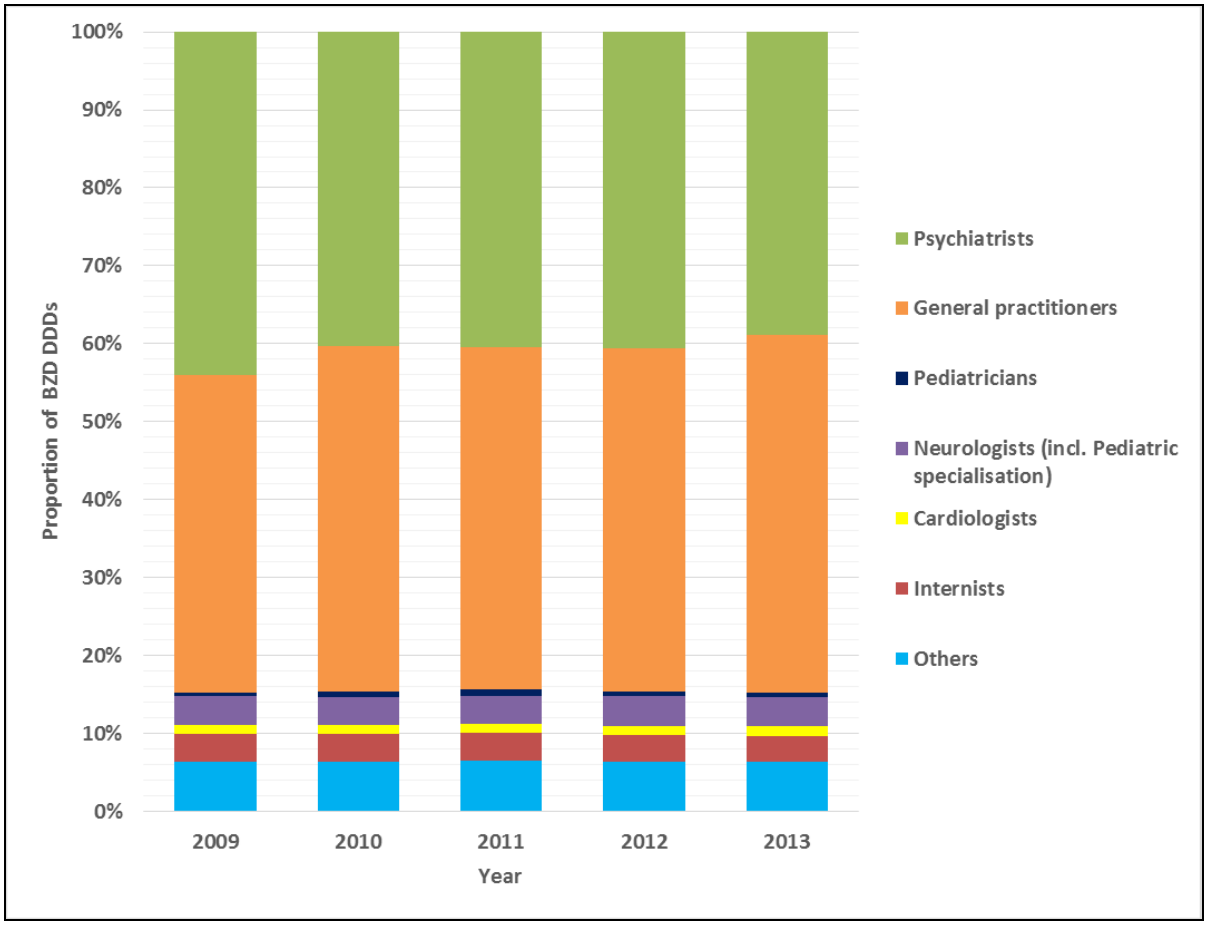
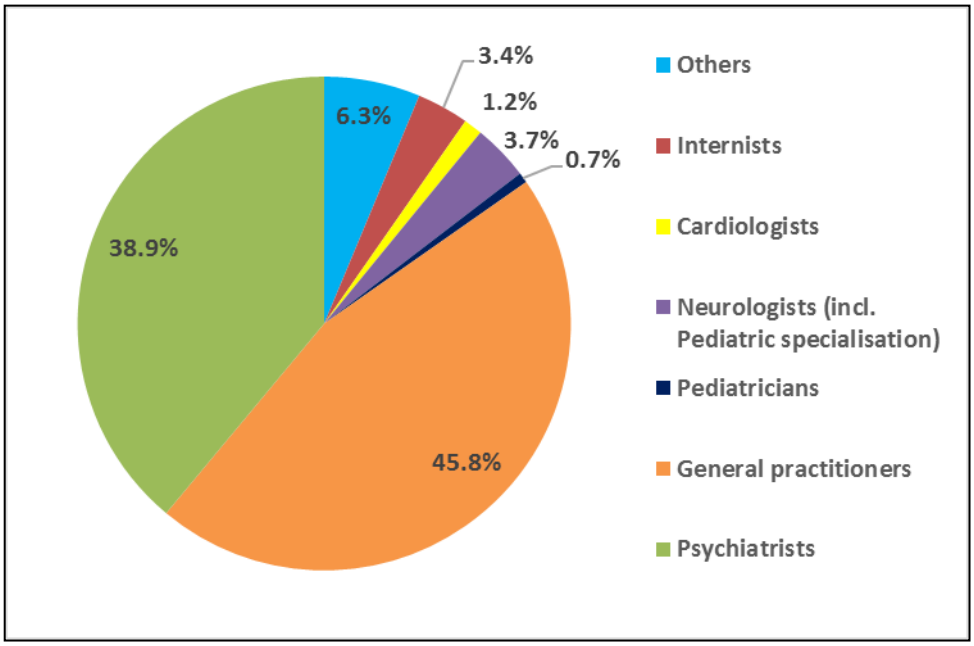


Figure 12. Proportion of BZDs (in % proportion of DDDs) prescribed by different medical specialists in 2013.



Discussion

Use of BZDs in general population

There is no other study to our knowledge that would comprehensively evaluate the evolution of BZD utilization in the CZ. Concerns regarding the addictive potential and safety issues of BZDs were first mentioned in the Czech scientific literature during early 1970s.[45] The majority of reports related to the use of BZDs in the CZ are connected with abuse of these substances solely or in combination with other drugs with abuse potential. BZD abuse was reported already in the communist period.[54] Flunitrazepam, one of the well-known abused substances of the BZD drug class, caused 27 fatal overdose cases (out of 49 cases of BZD overdose) in 2002.[45] Since 2003 there was a steep decrease of fatal overdose cases as a result of restriction of prescription of this substance within a special regimen for addictive substances, and in 2007 its marketing authorisation in the CZ was canceled.[45] Following the unavailability of flunitrazepam on the Czech market, clonazepam has become the most frequently abused BZD in the CZ nowadays.[45] According to a large cross-sectional multicentre study, BZDs (namely diazepam and chlordiazepoxide) belong to the 10 most common drugs inappropriately prescribed to older patients residing in nursing homes in the CZ.[46] In 2008 the European Health Interview Survey in the CZ, evaluating almost 2,000 respondents in age of 15+ years, showed that 2.1% of respondents suffered from chronic anxiety disorder and 68.2% of them were currently using medications for this condition.[55]

Our study 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). Furthermore, our analyses showed that approximately 5.6% of persons insured by the VZP were users of BZDs. When stratified by age, the highest proportion of BZD users was found in the 85+ years old persons insured by the VZP.

Results of studies focusing on the use of BZDs in general population vary from 2% to 8.9%.[4-8] A 10-years follow-up cohort study in the French population found 3.9% of occasional BZD users and 7.5% of long-term BZD users.[6] According to the retrospective analyses of BZD

prescriptions in the US, there were 5.2% of BZD users in general population.[8] Zandstra et al. showed that 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.[7]

In our study, a visible difference between utilization of BZDs and Z-drugs was captured. While the number of DDDs of BZDs continued decreasing through years 2009-2013 (by 19.8% according to DIS-13), the number of DDDs of Z-drugs continuously increased (by 14.7% according to DIS-13). These findings for BZDs and Z-drugs correspond with results of other utilization studies. The study of the Canadian population showed that the incidence of BZD use decreased from 55.5 to 30.3 users per 1,000, whereas the incidence of Z-drug use increased from 7.3 to 20.3 users per 1,000 over the 16-year period.[56]

Although the current study did not aim to evaluate the appropriateness of BZD use or the abuse/misuse of these substances, the numbers of their consumption (in general population and especially in older adults) are alarming, particularly in the light of recent surveys in the CZ showing that 18.3% of adults (of those prescribed sedatives and hypnotics or opioid containing medicinal products) were non-adherent with doctors' recommendation[44].

Use of BZDs stratified by age

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 connected with long-term continuous use, preferences and prescribing conventions of clinicians.

In terms of BZD users, our study outlined the use of BZDs as 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. The community-based 12-years cohort study of individuals aged 65+ years showed that 5.5% of men and 9.8% of women used benzodiazepines initially, while approximately 50.0%, 44.0%, and 25.0% of these users aged 65-74, 75-84, and 85+, respectively, were sustained users at follow-up.[57] The prevalence of BZD use in a study of the United States (US) population increased with age from 2.6% (18-35 years), 5.4% (36-50 years) and 7.4% (51-64 years) to 8.7% (65-80 years).[8] Similarly the proportion of long-term BZD use increased with age from 14.7% (18-35 years) to 31.4% (65-80 years).[8] The proportion of BZD use in older population, particularly in long-term care setting (e.g., NHs, long-term care facilities) can reach up to 54%.[9-16] Research showed that a longer use or higher dose of BZDs increases the odds for developing BZD addiction.[58] In addition, the knowledge of association between BZD use and risk of AEs such as falls and fractures, cognitive impairment, functional decline, and delirium[17-24], resulted in recommendations and policies in many countries to reduce the prescription and consumption of BZDs.[27-31] In the CZ no official policy decisions or recommendations have been issued in terms of reduction of prescription or use of BZDs. However, the Czech Gerontology and Geriatrics Association has been continuously educating general practitioners, geriatricians as well as other specialists in proper use of PIMs such as BZDs and delivers recommendations through their local guidelines.[59] There have been a few safety warnings about BZDs from the SUKL within its periodical pharmacovigilance information, with the latest in beginning of 2016 pointing out the BZD abuse and addiction potential in respond to series of cases reported in older patients.[60] The SUKL suggests to adequately evaluate the risk/benefit ratio of BDZ use and recommends continuous use no longer than 4 weeks.[60]

Use of particular substances from the BZD drug class

The most frequently prescribed substances in our study were alprazolam, diazepam and oxazepam. In comparison, other studies yielded mixed results that can be caused by different availability of BZDs on the local market, differences in national recommendations and guidelines, drug policies as well as reimbursement and price issues. While in the study of the US population the most frequently used BZDs were alprazolam and lorazepam[57], the evaluation of the French population showed bromazepam being the most commonly used BZD, followed by Z-drugs zolpidem and zopiclone[6]. In the study of the Canadian

population the most frequently prescribed BZDs were lorazepam, clonazepam, diazepam and alprazolam.[56]

There were no changes observed in the proportion of overall prescription of BZDs between 2009 and 2013 in our study. To the contrary, the study of general US population during 1987 and 2002 found an increase in the number of patients taking alprazolam and lorazepam from 22% to 37%, and from 18% to 36%; respectively.[57] Over the study period of 1996/97 – 2011/12 in the Canadian population, there was an increase in prevalence of lorazepam (from 33.4 to 41.5 per 1,000 population), clonazepam (from 5.6 to 15.8 per 1,000 population) and temazepam (from 8.1 to 12.0 per 1,000 population) recorded; while diazepam showed a decrease (from 10.5 to 5.8 per 1,000 population) and alprazolam prevalence remained stable (about 7.0 per 1,000 population).[56] The stable prevalence of particular BZDs in our study might be associated with long-term use of BZDs over time by the same patients as well as with no significant interventions in terms of policy, reimbursement or prices. Also a conservative approach and prescription conventions from the side of clinicians may play an important role.

When stratified by age, there were differences in BZDs used in particular age groups in our study. Alprazolam remained the most frequently used BZD in all age groups, while 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 pediatric population (0-4 years). We assume that BZDs are used in this population mainly for acute indications where diazepam is the drug of choice. In contrary, the Australian study of BZD utilization showed that the younger population (35-44 years) was much more likely to use anxiolytic BZDs such as diazepam, oxazepam and alprazolam, the older age group (65+ years) was more likely to use sedative BZDs such as temazepam.[61] This difference cannot be seen in our study, as no primarily sedative or hypnotic BZD is available on the Czech market. All three most frequent BZDs in our study (alprazolam, diazepam and oxazepam) can be indicated both in anxiolytic as well as sedative/hypnotic indication. Moreover, temazepam is currently not available on the Czech market.

Prescription of BZDs by different specialist

Almost half of the prescription of BZDs in our study were prescribed by general practitioners (45.8%), followed by psychiatrists (38.9%) and neurologists (3.7%). This finding is consistent with other studies. The study of the US population showed that most of long-term BZD prescriptions, in 9 out of 10 older adults, were prescribed exclusively by primary care physicians or other nonpsychiatrists.[8] A Norwegian study of psychotropic drug utilization (including antipsychotics [ATC code N05A], anxiolytics [N05B], hypnotics [N05C] and antidepressants [N06A]) outlined that these drugs were prescribed by general practitioners in 80% of cases, and by psychiatrists and other prescribers in 5% and 15% of cases; respectively.[62] According to the results of our study, 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.

Strengths and limitations

Our study has several strengths. The data sources used in our study represent the most reliable sources of information about drug consumption in the CZ. Analyses were undertaken for 5 subsequent years, so trends in utilization and prescription patterns could be described. Finally, the size and character of the VZP database allowed for analyses of age groups and prescription specialists, resulting in better understanding of differences between younger and older population.

The most important limitation of our study is unavailability of certain type of data about BZDs that are not reimbursed from the health insurance system in CZ. These out-of-pocket-paid BZDs must be still prescribed on medical prescription, however, such a prescription is not received and archived by insurance companies for reimbursement, thus detailed information about age of patients and prescription patterns are not available. Another limitation can be seen in the fact that utilization data were used just from the VZP database and not from the other health insurance companies. However, as VZP provides health insurance for almost 60% of the Czech population[48] and its relative shares of patients

according to their age and their gender has been stable over years[49], the results of our study can illustrate well the real-world prescribing practice.

Conclusions

This study of prescription and distribution databases captures the development of BZDs utilisation in the CZ during 5 consequent years. 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 on proportion of different clinical specialists prescribing BZDs together with the age stratification of BZD users give an insight into the clinical practice that may be unique across countries.

There is no other study to our knowledge that would comprehensively evaluate the development in consumption of BZDs in the CZ. In sight of their potentially inappropriate use in geriatric population, propensity to cause AEs and addiction, there should be other studies conducted to evaluate the appropriateness and quality of prescription of BZDs in different age groups, particularly in older adults.

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Overall results and discussion

This chapter provides a summary and overall discussion of main findings presented in previous chapters based on original research conducted by the author of the thesis and her co-authors of particular publications and manuscripts.

Chapter 1

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. The potential consequences of such changes include increased potential to cause AEs particularly in older adults, such as daily sleepiness, fatigue, falls, cognitive impairment, and confusion. Chapter 1 focuses mainly on falls in older people as multifactorial AEs, where use of BZDs plays an important role. Mixed evidence from different studies on BZD association with falls still gives an open field for research in this area. It is of importance to mention that differences between particular substances from BZD drug class should be further evaluated to identify and establish the risk/benefit ratios of their use to provide recommendations for appropriate indications and rational selection of BZDs in older adults suffering from multiple comorbidities in daily clinical practice.

Chapter 2

The study introduced in Chapter 2 showed important differences in use of BZDs and Z-drugs among several European countries (7) 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[1-9]. 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. The description of differences in spectrum of BZDs and Z-drugs used in the study uncovered the existence of factors influencing the uniqueness of prescribing patterns in particular European countries. Using the multivariate logistic regression models, a strong association between excessive use of BZDs/Z-drugs and country of residence was discovered. This finding suggests that country of residence plays an important role beneath well know clinical factors such as age, gender and (unknown) appropriateness of indication[2,10,11].

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 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 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 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[11-13]. 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.[14] Unfortunately, in our study it was impossible to get information about the ethnicity of Israeli NH residents. Therefore, further studies are needed to investigate differences in BZD/Z-drug use in Israel NH residents and association with their ethnicity.

The second highest prevalence of BZD/Z-drug use in this study was found in France (44.0%). This corresponds with findings of 53.4% prevalence of BZD/Z-drug use in residents of NHs in France in 2011.[15] In the present study, zopiclone together with zolpidem were the most frequently used BZDs/Z-drugs. Differences in BZD/Z-drug prescribing pattern in France may be explained by their availability on the pharmaceutical market.[15] In response to the high consumption of BZDs/Z-drugs in France and concern about their adverse effects, there have been a number of warnings and campaigns against frequent use of these drugs[16]; however, these did not succeed in reducing the use of BZDs neither in the general population nor in patients >65 years[16,17].

The second lowest prevalence of BZD/Z-drug use in our study was reported in England (17.4%), which corresponds with findings of a large study of older patients aged over 65 years in England showing a 7.4% and 14.5% prevalence of BZD use in community and NHs, respectively.[4] After the attempts to restrict BZD and Z-drug use in 2004 made by the Department of Health[18] the consumption of BZDs decreased between 2005 and 2010 by 31.7%[15]. On the other hand, despite the recommendations given by the NICE on Z-drugs in 2004[19], there was an increase of 7.3% in prevalence of Z-drug use[16]. The shift of use of BZDs in favour of increased use of Z-drugs in England during years 2005 to 2010[16]

corresponds with findings of our multicentric study, where zopiclone represented 61.4% of BZD/Z-drug used in England.

In our study, Germany was the country with the lowest prevalence of BZD/Z-drug use (14.5%). These findings are consistent with another study of NH residents in Germany that reported a 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.[20] Since 1980s the German Federal Institute for Drugs and Medical Devices restricted the BZD use to a maximum standard period of 2-4 weeks.[21] 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.[22] 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.[22]

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. Further studies are needed to investigate detailed interactions and associations across above mentioned potential factors of excesive BZD/Z-drug use.

Chapter 3

The study of acutely hospitalized older adults in Chapter 3 showed that association with falls differs significantly between particular substances of the BZD 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. 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.[23] 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.[24] An observational prospective study of hospitalized older patients showed an increased risk of falls in association with use of short half-life BZDs (OR 1.8; 95% CI 1.2–2.8), as well as very short half-life BZDs (OR 1.8; 95% CI 1.03–3.3).[26]

Contrary to previous studies[25-30], our present study found no statistically significant differences in history of falls between users and non-users of BZDs overall. A comprehensive meta-analysis of studies published between 1966 and 1999, which studied the association of drugs with falls, reported a pooled OR for any BZD use of 1.5 (95% CI 1.2–1.8)[27], while a more recent metaanalysis of nine medication classes involving older individuals reported a Bayesian pooled OR of 1.4 (95% CI 1.2–1.7)[26].

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[25,31-35]. 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.[36] One study of drug-metabolizing enzymes found that CYP content declines already after 40 years of age.[37] In contrast, oxazepam is extensively metabolized by UGT enzymes[38] that appears to be preserved in fit older people, although it might be affected by frailty[36]. Other possible factors contributing to differences in falls risk between individual active substances from the BZD drug group may include age-related changes in receptors, neurotransmitters, and second-messenger systems in the brain[39], which are not yet accurately described for specific BZDs.

This study documented differences in the association between different BZDs and a history of falls according to their biological half-life. Diazepam use was shown to be an independent risk factor of a 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

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). Furthermore, our analyses showed that approximately 5.6% of persons insured by the VZP were users of BZDs. In comparison, results of studies focusing on the use of BZDs in general population vary from 2.0% to 8.9%[40-44]; 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[45].

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 connected 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%[44,45], while in the proportion of BZD uses in older population, residing in long-term care setting can reach up to 54%[1-8]. It is of importance to mention that the research showed that a longer use or higher dose of BZDs increases the odds for developing BZD addiction.[46]

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 US population the most frequently used BZDs were alprazolam and lorazepam[45], the evaluation of the French population showed bromazepam being the most commonly used BZD, followed by Z-drugs zolpidem and zopiclone[42]. In the study of the Canadian population the most frequently prescribed BZDs were lorazepam, clonazepam, diazepam and alprazolam.[47] These differences can be caused by different availability of BZDs on the local market, differences in national recommendations and guidelines, drug policies as well as reimbursement and price issues. There were no changes observed in the proportion of overall prescription of BZDs between 2009 and 2013 in our study. The stable prevalence of particular BZDs in our study might be associated with long-term use of BZDs over time by the same patients as well as with no significant interventions in terms of policy, reimbursement or prices. Also a conservative approach and prescription conventions from the side of clinicians may play an important role.

When stratified by age, there were differences in BZDs used in particular age groups in our study. 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). 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 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.[44,48] 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.

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Overall conclusions

This doctoral thesis provides comprehensive overview of information and current knowledge on pharmacological profile, clinical use and AEs of BZDs as well as overview of results from studies performed on datasets of real geriatric patients using BZDs (in the practical part of this doctoral thesis). 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 of BZDs.

By providing the unique insight into the differences in prevalence of BZD/Z-drug use across 7 European countries and Israel together with the comprehensive background for 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 other 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. 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 patients.

The final part of this thesis describing prevalence of BZDs use in the CZ presents substantial differences across age groups in quantity and patterns of prescription with a higher proportion of BZD users among geriatric patients. 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 the CZ and provides an opportunity for comparison with other countries.

Considering the frequent inappropriate use of BZDs in geriatric population and higher propensity of these drugs to cause AEs and addiction in older patients, this doctoral thesis comprehensively summarizes characteristics of different BZDs, associated problems of BZD use in older adults and the situation with prescription and use of BZDs in the CZ and other mostly European countries. Results of this thesis are consistent with overall research

findings in the scientific literature. Moreover, it uncovered new information on prevalence of BZDs across different countries, described association of individual substances from BZD drug class with the risk of falls as well as novel facts about the current situation in utilization of these drugs on the Czech pharmaceutical market.

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