doi: *Original scientific paper*

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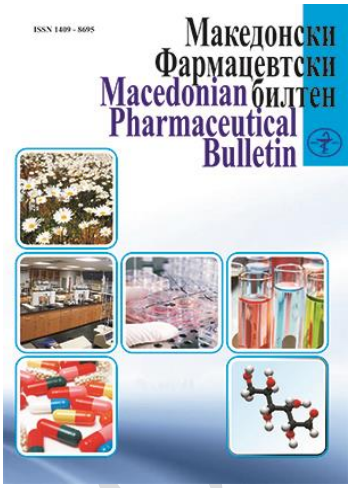
Accepted Manuscript



Title: Pattern of benzodiazepine use among death cases in Republic of North Macedonia

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DOI:
Received date: December 2021
Accepted date: January 2022
UDC:
Type of paper: Original scientific paper
Mac. Pharm. Bull. Vol. 67(2) 2021

Please cite this article as:

*Corresponding author e-mail: marija.bujaroska@medf.ukim.edu.mk

doi: *Original scientific paper*

Pattern of benzodiazepine use among death cases in Republic of North Macedonia

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Abstract

The aim of this study was to determine the pattern of benzodiazepine related deaths in Republic of North Macedonia. Retrospective survey of *post-mortem* toxicology data from eight-year period, obtained from Laboratory of Forensic Toxicology was performed, including cases with known gender, age, cause and manner of death and complete toxicology report. *Post-mortem* toxicology analyses were conducted with Fluorescence Polarization/Enzymatic Immunoassay and Biochip Array Technology method for screening of urine and blood respectively, and confirmation by GC-MS after solid phase extraction. Total of 1169 cases were investigated. Benzodiazepines were detected in 30.05% of the cases, with statistically significant difference between cases of natural and of violent cause of death, as well as between genders, but without statistically significant difference due to the age between both genders. Study revealed women were more likely to use benzodiazepines with the median age to be 52.88 and 49.87 for males and females, respectively. According to *post-mortem* toxicology data benzodiazepines are the most used drugs in our country. Of them, diazepam was found to be the most often used one. Data analyses have shown that benzodiazepines were often combined with alcohol, psychoactive medicines and drugs of abuse. In 46.6% of all cases with positive findings for

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benzodiazepines, use of drugs of abuse was detected, mostly heroine and methadone. Important note should be given to the simultaneous use of benzodiazepines with heroine and methadone, which have resulted in increased number of fatal intoxications. Further studies are needed to determine the reason for popular use of benzodiazepines among drug addicts.

Keywords: Abuse, diazepam, drug-related deaths, intoxication, *post-mortem*

Introduction

Benzodiazepines (BZDs) are widely prescribed medicines in treatment of anxiety, tension, insomnia, seizures, alcohol withdrawal, and also used for inducing amnesia during uncomfortable procedures, before surgery, panic attacks and stress reactions (Shumiala, 2018; UNODC, 2017).There are suggestions that a number of distinct mechanisms of action contribute to varying degrees of the sedative-hypnotic, muscle relaxant, anxiolytic and anticonvulsant effect of BZDs, but inhibitory neurotransmitter process by acting on GABA receptor is the main mechanism of action (Hobbs et al., 1996). BZDs are considered to be one of the safest psychotropic drugs, since there is basically no lethal potential to benzodiazepine overdose when drug is taken alone or in short-term occasional or intermittent use (Heather, 1995; Salzman and Freeman, 1998; Shumiala, 2018). However, there are recommendations for BZDs use as second-line agents for treatment of anxiety disorders due to their long-term side effect as abuse and dependence (Bystritsky et al., 2013). Long-term regular use in therapeutic doses, and abuse/recreational use in high doses can result with more serious adverse effects (Heather, 1995). Some experts divide the BZDs abuse in two groups: the first one is recreational abuse in purpose of getting high and the second one is unintentionally misuse over time, as a result of tolerance and dependence in regular users of BZDs, especially in high-dose therapy (Schmitz, 2016; Shumiala, 2018). According to current Global SMART Update, focus should be placed on the concomitant use of BZDs and opioids, because non-medical use of BZDs in combination with prescription opioids has resulted in a growing number of deaths in USA. BZDs are also the most common prescription medicines associated with acute intoxication cases in Europe

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(UNODC, 2017; WHO, 2017). Therefore, the purpose of this study was to determine the pattern of BZD related deaths in Republic of North Macedonia for eight years ranging from 2013 to 2020, using *post-mortem* toxicological data.

Materials and methods

The data used in this study were obtained from toxicology reports of autopsied cases at the Institute of Forensic Medicine, Criminology and Medical Deontology in Skopje, Republic of Macedonia, for duration of eight years (2013-2020).

The criteria for including data in this study are identified age, gender, cause of death, manner of death and complete toxicological analyses for each case. Only cases with available samples as blood, urine and humour vitreous, 1169 cases in total, were analysed. Toxicological analyses for determination of alcohol and general screening were performed within seven days after autopsy, and were stored in suitable containers at +4°C. In the cases where confirmatory analyses were not conducted immediately after screening, samples were stored at -20 °C until the time of analysis.

Screening for psychoactive substances and the most abused medicines was performed using Fluorescence Polarization/Enzymatic Immunoassay - FPIA/EIA (AxSYM /Architect c4000, Abbott) for urine samples, and Biochip Array Technology - BAT (Evidence investigator Randox), for blood samples. Confirmatory tests were conducted by Gas Chromatography with Mass Spectrometer (GC-MS QP2010 Shimadzu, Japan). Determination of alcohol concentration was performed using headspace Gas Chromatography with Flame Ionization Detection (GC-FID 2010Plus Shimadzu, Japan).

Statistics

In this paper following statistical tests were used: median, proportions (%) and Mann-Whitney U Test. A *p* value below 0.05 was considered as significant.

Limitations of the study

This study was elaborated using data from toxicology reports included only from autopsied cases at Institute of Forensic Medicine, Criminology and Medical Deontology,

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Skopje, Republic of North Macedonia, covering the area for about 1 000 000 - 1 200 000 inhabitants compared to about 2 000 000 inhabitants in all country. In this respect, the presented results cannot be considered as national. The real number of BZDs related deaths is much higher, but cases with lack of data for at least one of the including factors (age, gender, cause of death, manner of death and complete toxicological analyses) were not subjected to analysis in this study.

Results and discussion

The total number of 1169 cases was included in this study, of which 331 cases with natural cause of death, while the rest 838 cases with violent cause of death. Benzodiazepines were detected in 30.2% of all cases (n = 353), with the highest rate of 42.19% in 2017 (Fig. 1). Out of all BZDs registered in Republic of North Macedonia, diazepam was the most frequently detected.

Fig. 1

Age and gender distribution

In total autopsied cases, there were 950males and 219 females. Positive findings for BZDs were confirmed in 26.63% of males, and 44.95% of females. There were statistically significant differences between genders (Mann-Witney U Test = 2, Z = -3.09812, p = 0.00194) with a conclusion that women are more likely to use BZDs, which is in agreement with the data from other studies (Schmitz, 2016; Park et al., 2015; Vozoris and Leung, 2011). Gender distribution is presented in Fig. 2. The most of all BZDs-related cases were individuals over 65 years old, which is in accordance with the fact that tendency of BZDs use increases with age (Dermengiu et al., 2013; Schmitz, 2016). In addition, this population group is more susceptible to adverse effects of BZDs due to the decreased rate of metabolism, especially to over sedation. The median age of the positive cases detected was 50.8 years (52.88 and 49.87 for males and females, respectively). However, the difference between male and female BZD-related deaths related to their age was insignificant (Mann-Witney U Test = 10, Z = 0.41779, p = 0.67448). Higher median age was found in female

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cases compared to men subjects in 2017 (60.41 years and 48.3 years, respectively), but the analysis of data in 2015 showed completely different age distribution (43.21 years for female and 52.35 years for male cases).

Fig. 2

Distribution according to manner of death

BZDs were detected in 22.05% of cases with natural cause of death, and 33.65% of cases with violent cause of death. Violent death is any non-natural death, occurred as a result of homicide, suicide or accident. There was statistically significant difference in BZDs presence between the two groups (natural and violent cause of death) (Mann-Witney U Test = 10, Z = 2.25795, p = 0.02382). BZDs were detected in 25.74% (n = 125) of cases classified as accidents including accidental intoxications, falls from high, drowning and traffic accidents. Over sedation related to BZDs use is often associated with serious traffic accidents, as well as dose-related impairment of reaction time and psychomotor function (Barbone et al., 1998; Heather, 1995). Memory impairment is another adverse effect of BZDs that occurs even in patients who use oral therapeutic doses, but this effect was more frequently observed in heavy alcohol drinkers (Curran, 1992; Nicholls et al., 1993). Since 2015 BZDs are listed as substances with regulated use in drivers in our country, as a result of European study for Driving under Influence of Drugs, Alcohol and Medicines (DRUID). The final report of this study has shown that BZDs are the second most detected substances in blood of traffic accident victims, immediately after alcohol (Schulze et al., 2012). Except for traffic accidents, the both substances are related with violent events and suicide (Guo et al., 2016). BZDs use can cause depression, especially in long-term users (alcohol and barbiturate-dependent patients), or aggravate this condition, which may increase the risk of suicidal tendencies in such patients (Ashton, 1987; MHRA, 2015; Nutt, 1990). In our study BZDs were detected in 26.04% (n = 25) of homicides and in 48.71% (n = 132) of the suicide cases (Table 1).

Table 1

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Distribution of death cases associated with the combined use of benzodiazepines

Long-term BZD users are at risk to develop tolerance and dependence. Despite these well-known BZD's effects, in *post-mortem* toxicology they are rarely identified as the only drug involved in the death case, which is confirmed in other studies (Abrahamsson et al., 2017; Sun et al., 2017). In many fatal cases, the use of BZDs was generally therapeutic. Out of all BZD-related deaths, in 48.15% BZDs were the only detected substances in analysed samples (biological fluids), while in 51.85% other substances as alcohol, drugs of abuse and psychoactive medications have been also identified. Distribution of the BZDs combined use through the time was 58.82%, 62.86%, 42.86%, 52.83%, 43.6%, 45.45%, 45% and 43.42% in 2013, 2014, 2015, 2016, 2017, 2018, 2019 and 2020, respectively. These data are summarized in Fig. 3. Combination of BZDs and alcohol can be very dangerous, because both substances are central nervous system (CNS) depressants and their concomitant use can lead to respiratory depression, coma or death (UNODC, 2017; White and Irvine, 1999). In our study concurrent use of BZDs and alcohol was found in 54 cases, which is 29.67% of the BZD-related deaths, with the highest rate of 44% in 2017. Antidepressants, antipsychotic and other psychoactive medicines were detected in 24.7% of BZD-related deaths with the highest rate of 36.36% in 2014. Concomitant use of BZDs and barbiturates was found in only two of all analysed cases. Nowadays, BZD use/abuse as a recreational drug is a growing problem, mainly among poly-drug and illicit drug abusers. According to EMCDDA, 12% of all opioid users who entered the treatment program in 23 European countries, reported use of certain BZDs as secondary drug problem. Drugs of abuse were found in 46.6% of all BZD-related deaths, with the highest rate of 60% in 2018. The reason for concurrent use of opioids and BZDs sometimes is therapeutic, because these medications are used for managing the mental health issues of opioid users. Two studies have reported that 47% of the patients in Spain, and 52% of Swiss patients in methadone treatment were BZDs users (Fernández Sobrino et al., 2009; Meiler et al., 2005). Similar results are found in studies conducted among opioid users in prisons. Namely, high risk opioid users self-medicate BZDs to potentiate opioids effects achieving euphoria, or to treat anxiety and insomnia, adverse effects and withdrawal symptoms of substances like cocaine and alcohol (Salzman and Freeman, 1998). Combined use of BZDs with opioids, and other CNS depressants increases the risk of non-fatal and fatal overdose, which is more

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remarkable with increasing the dose of each drug (Nicholls et al., 1993; Park et al., 2015; UNODC, 2017). Despite this fact, the *post-mortem* concentration of both drugs in drug related deaths (DRDs) is often in therapeutic range (Hakkinen et al., 2014). Some studies reported that BZDs are one of the most common prescription medicines associated with intoxication cases and they are involved in nearly 30% of opioid overdose cases (Morasco et al., 2010; Saunders et al., 2012; UNODC, 2017). In our study BZDs were identified mostly in combination with heroine and methadone. Similar results have been reported in many other countries. Namely, BZDs were identified in 67% of methadone and 31% of heroine/morphine deaths in Slovenia, in 88% of DRD cases in Finland, and 73% of DRD cases in Scotland (EMCDDA, 2018; Karlovsek, 2004). We have found that diazepam is the most often used BZDs in all DRD cases. Comprising this pattern, the analysed cases in our study were correspondent to about 90% of the results reported in the Slovenian study (Karlovesk, 2004). On the opposite, alprazolam has been reported to be often used in combination with illicit drugs (Jones and Holmgren, 2013). Diazepam and alprazolam were found among the most frequently involved drugs in drug overdose cases in the USA (Hedegaard et. al., 2018). However, both BZDs are highly prevalent in multi-drug deaths, together with other BZDs with higher lipophilicity and shorter half-lives (Schmitz, 2016). The concomitant use of BZDs and opioids has resulted in increased number of fatalities in Europe and North America (UNODC, 2017). Moreover, the spread of BZDs on the illicit market as legitimate trade medicines, as well as new psychoactive substances (NPSs) which belong to this group, sold under street names “legal BZDs”, “research chemicals” and “designer BZDs” is a serious concern. These substances may have been produced, but not approved by pharmaceutical companies, or have been made by structure modification in clandestine laboratories. Due to the variety of still unknown pharmacological and toxicological properties of these substances (Moosmannet al, 2015; UNDOC, 2016a, 2017b), a lot of challenges have been raised yet to be analysed and answered.

Fig. 3

Conclusion

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Considering the few limitations of this study, it can be concluded that BZDs are the most used drugs in our country according to the *post-mortem* toxicology data. These medicines are frequently used by elderly, but it should not be neglected that they are often detected in cases with violent cause of death, regardless of age. Especially notable is their simultaneous use with heroin and methadone may result in fatal intoxications. Further studies are needed in order to determine whether these drugs are part of the treatment for solving the withdrawal symptoms of patients enrolled in maintenance program or drug addicts are regularly abusing them. In our country there is no data for benzodiazepine type of NPSs entered on the illicit market yet, but abuse and misuse of prescribed BZDs remain to be sustainable problem needed profound investigating approach.

Compliance with ethical standards

Conflict of interest There are no financial or other relations that could lead to a conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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Резиме

Анализа на употреба на бензодиазепини кај смртни случаи во Република Северна Македонија

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Клучни зборови: злоупотреба, диазепам, смртност поврзана со дроги, интоксикација, постмортални

Со цел да се анализира употребата на бензодиазепини кај смртните случаи во Република Северна Македонија, спроведена е ретроспективна студија на постмортални токсиколошки податоци во период од осум години, добиени од лабораторијата за форензична токсикологија при Институтот за судска медицина, криминалистика и медицинска деонтологија, вклучувајќи податоци за пол, возраст, причина за смрт, начин на настанување на смрт и комплетен токсиколошки наод. Токсиколошките анализи на постморталните примероци беа спроведени со примена на флуоресцентно полазирачки/ензимски имунотестови и метод на биочип технологија за скрининг на примероци урина и крв соодветно, како и потврдни анализи со примена на гасна хроматографија со масена спектрометрија по цврсто-фазна екстракција на примероците. Во студијата беа вклучени вкупно 1169 смртни случаи. Присуство на бензодиазепини беше

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определено кај 30,05% од случаите, со статистички значајна разлика помеѓу случаите на природна и насилна смрт, како и помеѓу половите, но без статистички значајна разлика во возраста помеѓу двата пола.Од добиените резултати може да се заклучи дека жените почесто употребуваат бензодиазепини, а средната возраст на починатите за кои е добиен позитивен наод за бензодиазепини е 49,78 години кај жените и 52,88 години кај мажите. Со анализата на податоците беше забележано дека оваа група лекови често се употребува во комбинација со етил алкохол, психоактивни лекови и психоактивни супстанции кои подлежат на злоупотреба. Кај 46,6% од случаите со позитивен наод за бензодиазепини беше забележана употреба на психоактивни супстанции кои подлежат на злоупотреба, најчесто хероин и метадон. Според постморталните податоци, бензодиазепините претставуваат најупотребувана група лекови во нашата земја, а диазепам е најупотребуваниот претставник од оваа група. Особено важно е да се истакне дека заедничката употреба на бензодиазепините со хероин и метадон може да доведе до зголемување на бројот на интоксикации со летален исход. Потребни се понатамошни детални студии за да се дефинира причината за широката употреба на бензодиазепини, особено меѓу зависниците од психоактивни супстанции.

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Table 1. Case distribution according to manner of death for 8-year period (2013-2020)

	Natural cause of death		Violent cause of death		Homicides		Suicides		Accidents	
Year	All cases	BZD positive cases	All cases	BZD positive cases	All cases	BZD positive cases	All cases	BZD positive cases	All cases	BZD positive cases
2013	54	10	134	44	14	1	39	16	81	27
2014	30	7	85	28	17	6	26	15	42	7
2015	39	8	105	20	24	0	33	11	48	9
2016	63	11	119	42	8	1	41	22	70	19
2017	39	9	89	46	17	8	32	19	40	19
2018	35	6	91	27	6	4	23	7	62	16
2019	40	15	117	45	6	3	41	23	70	19
2020	31	7	98	30	4	2	36	19	58	9
Total	331	71	838	282	96	25	271	132	471	125
%		22.05		33.65		26.04		48.71		25.74

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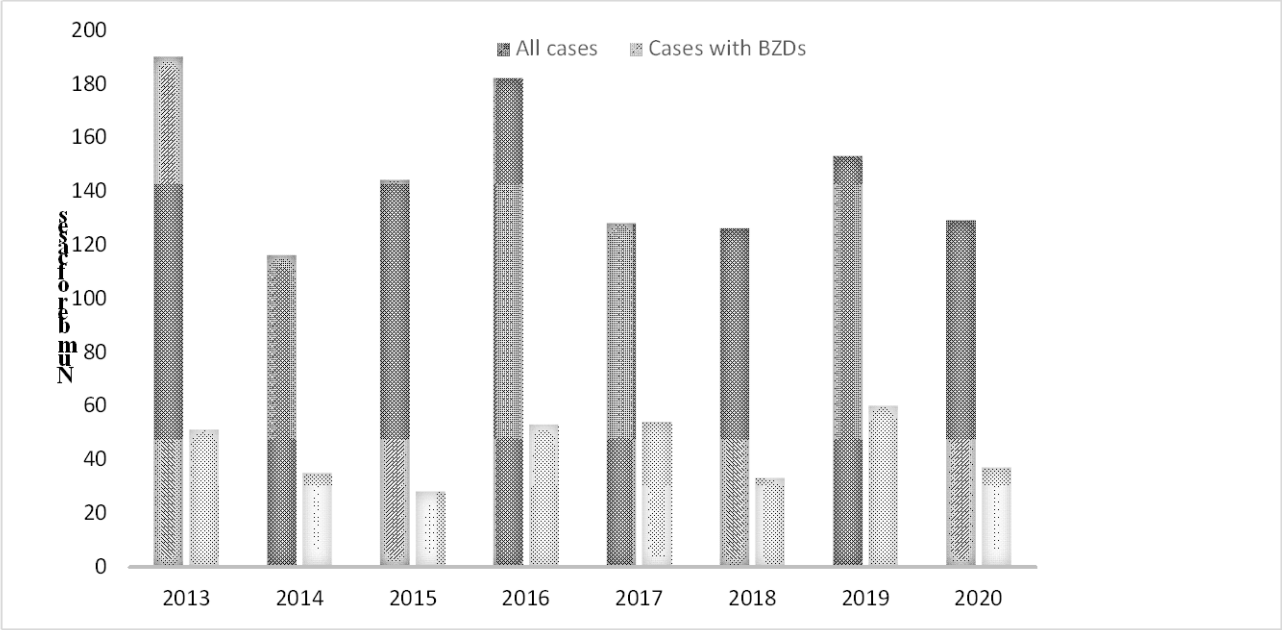

Fig. 1. BZDs-related deaths presented relative to total number of cases for 8-year period (2013-2020).

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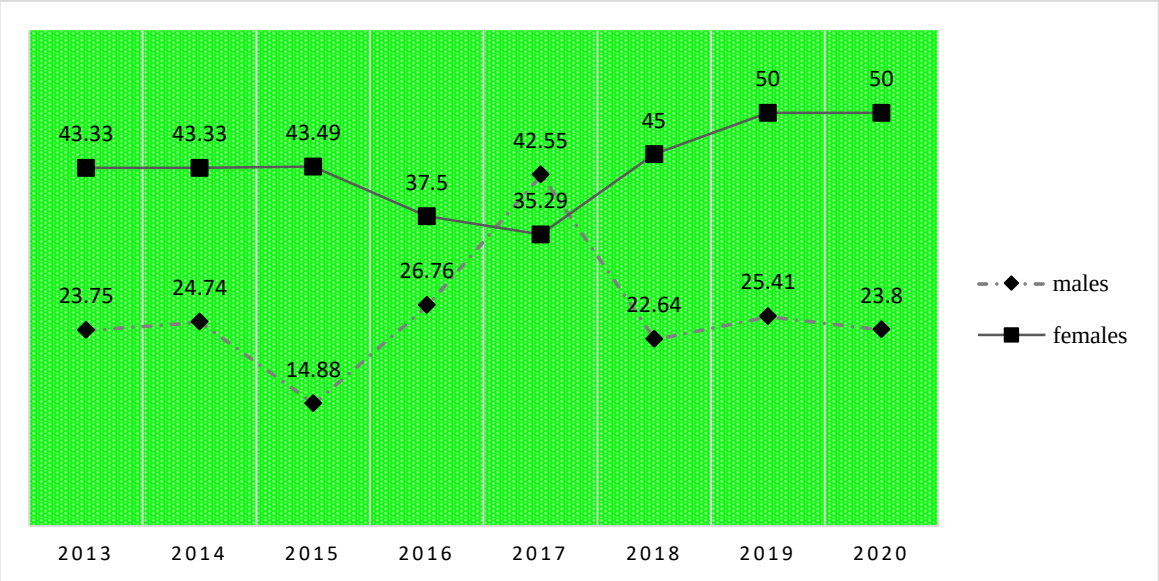

Fig. 2. Gender distribution of BZDs-related deaths (%) for 8-year period (2013-2020).

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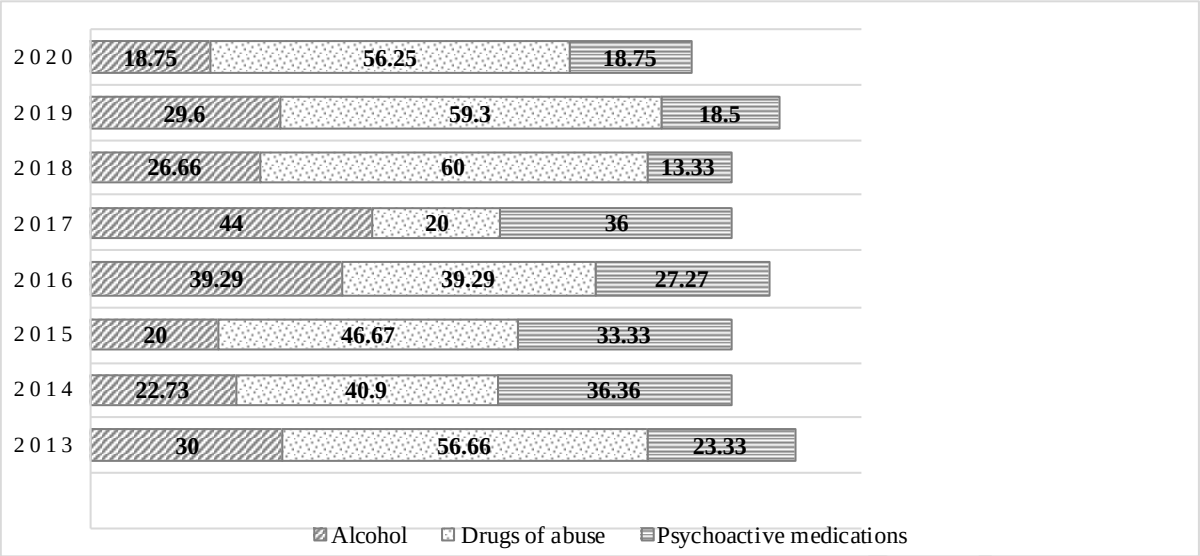

Fig. 3. BZD-related deaths distribution (%) in combination with alcohol, drugs of abuse and psychoactive medications.

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