

Fighting benzodiazepine misuse in Lithuania: detoxification treatment results in the single-centre toxicology department

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Abstract

Background. Chronic use of benzodiazepines frequently leads to physical dependence. In Lithuania, detoxification services are provided to individuals suffering from benzodiazepine addiction.

Aim. The purpose of our study was to find out the existing links and differences between patient gender, age, characteristics of benzodiazepine consumption, and the course of treatment.

Materials and methods. This retrospective study was conducted at Toxicology Centre of Republican Vilnius University Hospital. 48 patients who had been treated from 2011 January to 2018 March with the principal diagnosis of sedative, hypnotic or anxiolytic-related dependence (ICD-10 F13.2) were included in the final analysis. MS Excel and IBM SPSS 23.0 were used for data analysis, statistical significance was assumed when $p < 0.05$.

Results. An indirect intermediate correlation between benzodiazepine dose-at-arrival for treatment and age was found ($r_{\text{Phi}} = -0.16$, $p = 0.029$), as well as a direct weak link between dose-at-arrival and dose-at-discharge from the hospital ($r_{\text{Phi}} = 0.420$, $p = 0.005$). Male patients used higher doses of benzodiazepines ($p = 0.012$). Alcohol-consuming patients spent less time hospitalized ($p = 0.02$). Women were hospitalized longer than men ($p = 0.02$). Link between durations of inpatient treatment and benzodiazepine consumption was intermediate and direct (Spearman's $r = 0.310$, $p = 0.032$). An intermediate direct relationship between the duration of benzodiazepine consumption and number of additionally administered medicines was found (Spearman's $r = 0.420$, $p = 0.005$).

Conclusions. Men and younger patients had used higher doses of benzodiazepines. Patients, who had used higher doses, were prescribed a higher dose of benzodiazepines and a higher number of additional medicines at discharge. Inpatient treatment time was longer for women and for the patients, who had used benzodiazepines longer. Detoxification from benzodiazepines was shorter for alcohol-consuming patients.

Keywords: benzodiazepines; withdrawal; addiction; detoxification.

Piknaudžiavimas benzodiazepinų grupės vaistais Lietuvoje: detoksikacinio gydymo rezultatai

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Santrauka

Įvadas. Ilgai trunkantis benzodiazepinų vartojimas dažnai sukelia priklausomybę. Lietuvoje detoksikacijos paslaugos teikiamos asmenims, kenčiantiems nuo priklausomybės benzodiazepinams.

Tikslas. Šio tyrimo tikslas buvo išsiaiškinti egzistuojančius ryšius ir skirtumus tarp pacientų su TLK- 10 F13.2 diagnoze lyties, amžiaus, žalingų įpročių, vartojimo bei gydymo ypatumų.

Metodika. Šiame retrospektyviame tyrime dalyvavo 48 pacientai, kurie gydėsi 2011 m. sausio – 2018 m. kovo mėn. Respublikinės Vilniaus universitetinės ligoninės toksikologijos centre, turėję psichikos ir elgesio sutrikimai dėl raminamųjų ir migdomųjų medžiagų vartojimo, priklausomybės sindromo (F13.2) diagnozę, kaip pagrindinę. Statistinei analizei naudoti MS Excel ir IBM SPSS 23.0 programiniai paketai, duomenys laikyti statistiškai reikšmingais, kai $p < 0,05$.

Rezultatai. Atvirkštinė vidutinio stiprumo priklausomybė tarp benzodiazepinų dozės atvykus ir amžiaus, $r_{\text{Spearmano}} = -0,316$, $p = 0,029$, tiesioginė silpna priklausomybė tarp dozės atvykus ir išrašant, $r_{\text{Spearmano}} = 0,304$, $p = 0,036$. Vyrai vartojo didesnes benzodiazepinų dozes, $p = 0,012$. Vartojantys alkoholį pacientai stacionare išbuvo trumpiau $p = 0,02$. Ilgiau stacionare išbuvo moterys, $p = 0,02$. Nustatytas tiesioginis vidutinio stiprumo ryšys tarp hospitalizacijos ir vartojimo trukmės, $r_{\text{Spearmano}} = 0,310$, $p = 0,032$, tiesioginė vidutinio stiprumo priklausomybė tarp vartojimo trukmės ir papildomai skirtų medikamentų skaičiaus, $r_{\text{Spearmano}} = 0,420$, $p = 0,005$.

Išvados. Vyrai ir jaunesni pacientai buvo linkę vartoti didesnes benzodiazepinų dozes. Pacientams, vartojusiems didesnes benzodiazepinų dozes, buvo išrašytos didesnės dozės detoksikacinio gydymo tęsimui ambulatoriškai ir didesnis papildomų medikamentų skaičius. Moterims bei ilgiau benzodiazepinus vartojusiems pacientams, stacionarinis gydymas truko ilgiau. Vartojantiems alkoholį, priklausomybės gydymas nuo benzodiazepinų buvo trumpesnis.

Raktažodžiai: benzodiazepinai; abstinencija; priklausomybė; detoksikacija.

1. Introduction

Benzodiazepines (BZDs) are one of the most frequently prescribed drugs worldwide, primarily used for their anxiolytic properties. However, it should be noted that benzodiazepine prescriptions are suitable only in one-third of all cases [1]. BZDs are used to treat anxiety, seizures, withdrawal states, insomnia, agitation, and are commonly used for procedural sedation [2,3]. However, there is significant concern regarding overprescribing of benzodiazepines and the resultant harms, as evidence suggests that long-term use of benzodiazepines causes dependency, cognitive decline and falls [4].

In 2017, benzodiazepines and other tranquillizers were the third most commonly misused illicit or prescription drug in the United States [5]. In Lithuania, the use of anxiolytics was more than twice compared to Estonia and Latvia during the period 2010-2015 [6]. Even though in Lithuania the consumption of benzodiazepines showed a progressive decline from 40.781 defined daily doses (DDDs) per 1000 inhabitants in 2016 down to 29.610 DDDs per 1000 inhabitants in 2020, they are still widely prescribed despite guidelines [8].

Chronic use of benzodiazepines usually causes physical dependence. Importantly, upon discontinuation, withdrawal syndrome is observed in many long-term BZD users [9]. In Lithuania, detoxification and rehabilitation services are provided to individuals suffering from benzodiazepine addiction [10]. Therefore, the aim of our study was to find out the existing links and differences between patient gender, age, characteristics of benzodiazepine consumption, and the course of treatment.

2. Materials and Methods

2.1. Study population

The patient inclusion criteria were the following: diagnosed benzodiazepine addiction (ICD-10 code F13.2 Mental and behavioural disorders due to use of sedatives or hypnotics Dependence syndrome), being hospitalized at the Toxicology centre of Republican Vilnius University hospital for planned BZD detoxification and benzodiazepine use for at least six months. Acute BZD intoxication, addiction to other than benzodiazepine anxiolytics or hypnotics and addiction to more than one psychoactive substance (except for alcohol) were the reasons to exclude a patient from the study. There were 48 patients from the period of 2011 to March 2018 included in the final analysis.

2.2. Ethics

The research was carried out with the permission of the institutional Bioethics Committee of Republican Vilnius University Hospital, Vilnius, Lithuania, on 28th of February, 2018 (permission number 158200-18/3-1013-513).

2.3. Data collection

The data were collected retrospectively from medical documentation. Demographics, information about patient smoking status, alcohol use, earlier detoxification treatment, specialist referring for detoxification, used BZD types, their doses before and after the treatment, total duration of BZD use, withdrawal symptoms after one day of treatment, psychiatric comorbidities and other than BZD medicines prescribed for outpatient treatment after detoxification were gathered. Furthermore,

doses of various types of BZDs were converted into diazepam equivalents (DE) [5] (Table 1).

Table 1. Diazepam equivalents.

| Benzodiazepine | Dose equal to 5 mg of Diazepam (mg) |
|----------------|-------------------------------------|
| Alprazolam | 0.5 |
| Bromazepam | 3 |
| Clonazepam | 0.5 |
| Lorazepam | 1 |

2.4. Data analysis

MS Excel and IBM SPSS 23.0 were used for data analysis. Quantitative variables were tested for normality using the Shapiro-Wilk test. Mann-Whitney U test was used to compare not normally distributed variables in two independent samples. Spearman's correlation

coefficient was applied to assess the correlation between non-normally distributed data. To analyse the correlation between categorical variables χ^2 and Phi coefficient were used. Statistical significance was assumed when $p < 0.05$.

3. Results

48 patients were included in the study. The age median was 46 years (range 40-63 years) and there was no significant age difference between male and female subjects, $p = 0.191$ (table 2). There was a weak positive correlation between gender and smoking suggesting that males had been more likely to smoke than females, $\chi^2 = 4.286$, $r_{\text{Phi}} = 0.299$, $p = 0.038$. Also, a positive intermediate relationship between gender and alcohol use was found indicating that males of this sample were more likely to use alcohol than females, $\chi^2 = 5.943$, $r_{\text{Phi}} = 0.352$, $p = 0.015$. Smoking and alcohol use frequencies are shown in table 2.

Table 2. Distribution of patient characteristics according to gender.

| | Males | Females | Total | p |
|---------------------------------|--------------|--------------|---------------|-------|
| Number (%) | 20 (41.7) | 28 (58.3) | 48 (100) | |
| Age median, years | 45 | 46 | 46 | 0.191 |
| Smoking, n* (%) | 7 (35) | 2 (7.1) | 9 (18.75) | 0.038 |
| Alcohol use, n* (%) | 10 (50) | 6 (21.4) | 16 (33.33) | 0.015 |
| BZD use duration median, years | 12 | 12.5 | 14 | 0.36 |
| Duration quartiles, years | 8-18.5 | 9.5-21 | 9-20 | 0.9 |
| Psychiatric comorbidity, n* (%) | 12 (60) | 16 (57.1) | 28 (58.3) | 0.84 |

| | | | | |
|--|-----------|-------------|--------------|-----------|
| Depression spectrum, n* (%) | 5 (25) | 11 (55) | 16 (33.3) | 0.30 1 |
| Alcohol dependence (F10.2) frequency (%) | 6 (30) | 5 (17.9) | 11 (22.9) | 0.32 4 |
| Hospitalization median, days | 7 | 10 | 9 | 0.02 |

* n – number of patients

** mg – milligram

The study revealed that patients were referred for the detoxification treatment mostly by family practitioners (37.5%, n=18) and psychiatrists (35.42%, n=17), while others were referred following the consultation by clinical toxicologist (27.02%, n=13). For 22.9% of patients (n=11), the detoxification treatment, included in this study, was not the first one, however, there was no data on how many hospitalisations a patient has previously had.

BZD use duration median was equal to 14 years (range 9-20 years) and it did not differ significantly between males and females. Diazepam equivalent dose median before the treatment was 58 mg (range 30-90 mg). In this sample, males have been consuming

significantly higher doses than females (p=0.012). Moreover, younger patients have been using higher DE doses, as a negative intermediate correlation between age and DE dose at arrival was observed, $r_{\text{Spearman's}} = -0.316$, p=0.029.

It was found that before arriving for the detoxification patients have been using five different types of BZDs: lorazepam was the most common one (n=21), meanwhile bromazepam was used only in combinations with other benzodiazepines. It should be noted that 14 patients (29.17%) have been combining two different benzodiazepines. The evidencing results are given in Fig. 1.

Figure 1. Use of different BZDs.

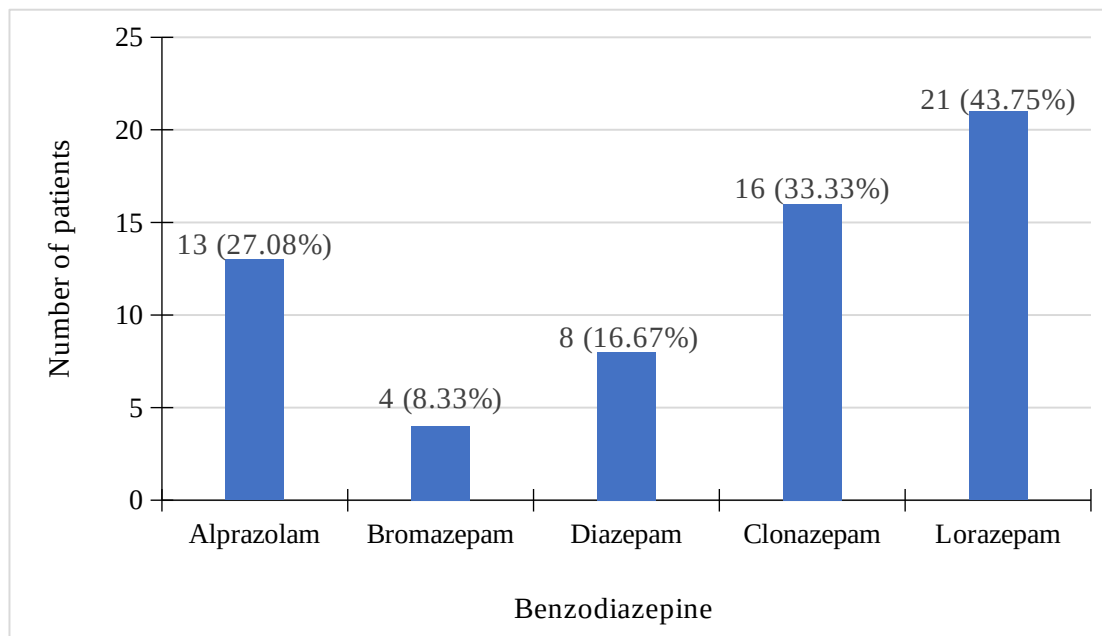


Table 3. Withdrawal symptoms and lorazepam use.

| | Lorazepam users | Non- users | Total |
|--------------------------------|--------------------|---------------|-------|
| Withdrawal symptoms, median | 2 | 1 | 1 |
| Quartiles | 1 - 2 | 1 - 2 | 2 - 2 |
| p | 0.018 | | |

After the first hospitalization day, patients experienced the following withdrawal symptoms: anxiety, insomnia, headache, tremor and increased sweating. However, the number of symptoms differed between the patients. Importantly, lorazepam users, n=21 (43.75%), had slightly more withdrawal symptoms than others, p=0.018 (Table 3).

The study revealed that 58.3% (n=28) of the patients had been diagnosed with psychiatric comorbidities, and 9 subjects were diagnosed with two different comorbidities. It should be noted that comorbidity prevalence did not differ significantly between females and males, p=0.301. 22.9% (n=11) of the patients had F10.2 diagnosis – mental and behavioural disorders due to alcohol use, alcohol dependence. The results demonstrated that prevalence of alcohol dependence (F10.2) did not differ significantly between males (30%, n=6) and females (17.9%, n=5), p=0.324 (table 2) in this study. Other comorbidities included

depression spectrum disorders (F32, F33) and their frequency did not differ significantly by gender (Table 2).

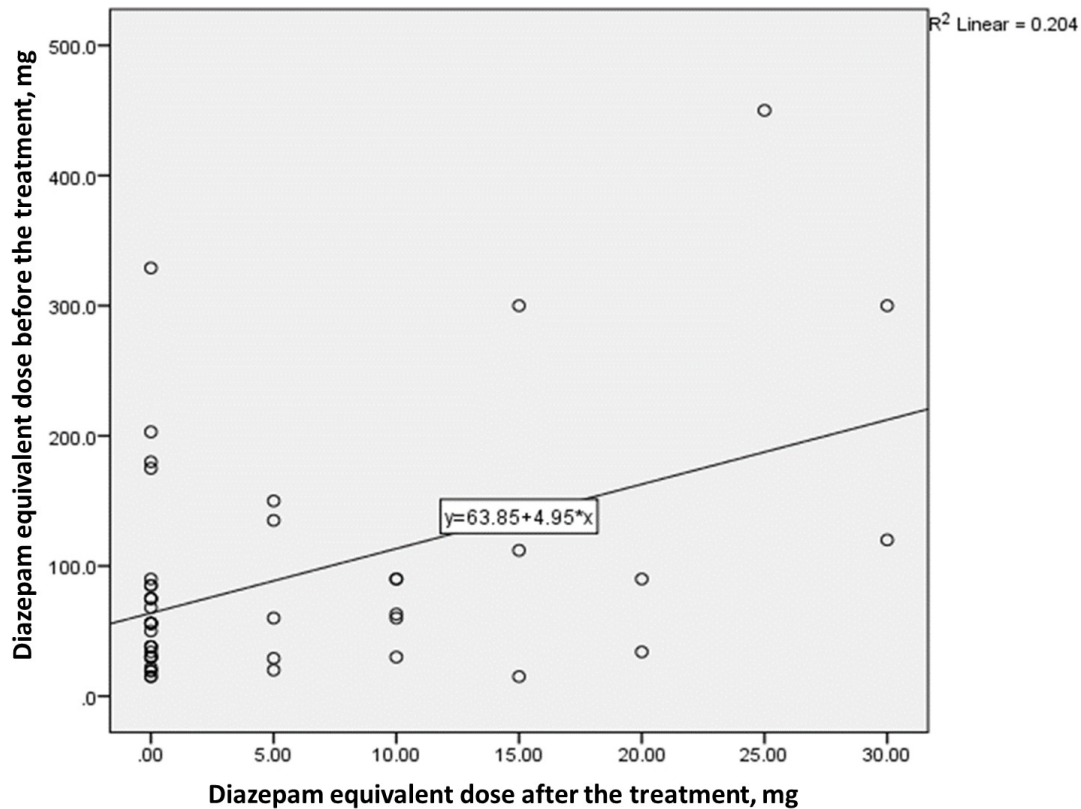
The median of hospitalization days was equal to 9 days (range 6.5-11 days). Hospitalization of female patients was significantly longer than males, p=0.02 (Table 2). In addition, alcohol users have been hospitalized for a longer period than non-users, p=0.02 (Table 4). What is more, it was found that longer BZD use is significantly correlated with longer hospitalization, $r_{\text{Spearman's}}=0.310$, p=0.032 (Table 4).

After the detoxification, 62.5% (n=30) of the patients were able to discontinue BZD use. The remaining 37.5% of the subjects had been discharged with DE doses ranging from 5 to 30 mg. These patients were suggested to continue outpatient detoxification treatment. There was a weak positive correlation between DE dose before and DE dose after the treatment, $r_{\text{Spearman's}}=0.304$, p=0.036 (Figure 3).

Table 4. Hospitalization days and alcohol use.

| | Alcohol users | Non- users | Total |
|------------------------------|------------------|---------------|-------------|
| Hospitalization days, median | 6.5 | 9 | 9 |
| Quartiles | 5 – 8.5 | 7 – 11 | 6.5 – 11 |
| p | 0.012 | | |

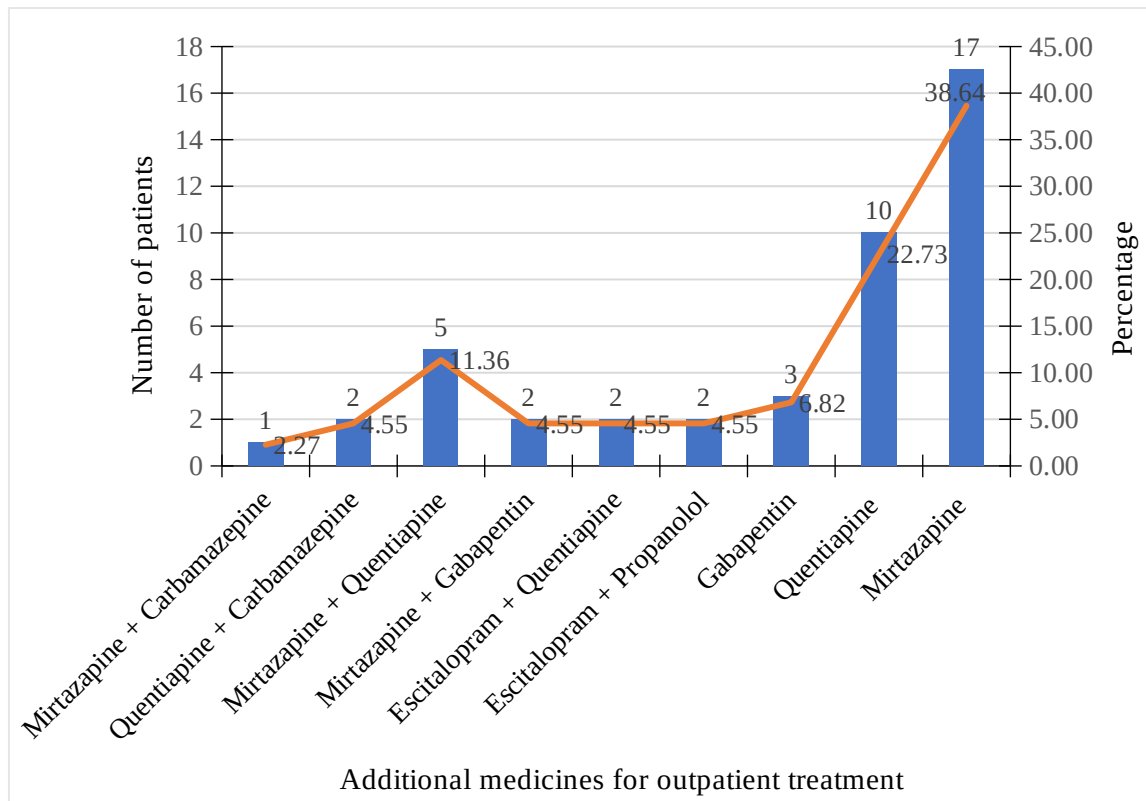
Figure 2. The relationship of diazepam equivalent dose before and after the detoxification treatment.



It was found that 91.67% (n=44) of the patients have been prescribed additional non-benzodiazepine medicine for outpatient treatment after hospitalization. These prescriptions included escitalopram, mirtazapine, quetiapine, carbamazepine, gabapentin and propanolol. 14 patients out of

44 have been prescribed two different drugs. According to the data, longer BZD use was significantly positively correlated with the number of additional non-BZD drugs prescribed after the detoxification, $r_{\text{Spearman's}} = 0.420$, $p = 0.005$ (moderate correlation strength). Figure 3 shows additional medicines, their combinations and distribution in the sample.

Figure 3. Medicines for outpatient treatment after the BZD detoxification.



4. Discussion

According to the earlier study, conducted in Lithuania, it might be argued that the largest amount of BZDs is prescribed by family practitioners [11]. Our study revealed that most of the patients have been referred for the detoxification treatment by a family practitioner. This shows the importance of primary health care in solving the BZD-related problem. It is important to note that certain actions in Lithuanian health care system have been taken to improve regulations and decrease misuse of BZDs. Since 1st of July, 2021, benzodiazepines can only be prescribed by an electronic prescription or a special controlled drugs form [12]. This has replaced earlier paper prescriptions and should prevent fake prescriptions. Furthermore, as electronic prescriptions are easier to track, this should decrease “doctor shopping” and limit the BZD total that can be bought by one patient. Also,

following new regulations, benzodiazepines can only be prescribed for 30 days of use and the patient must buy them within 10 days of prescription. The aforementioned restriction should encourage BZD-using-patients to visit their family practitioners or psychiatrists more often, thus, acquiring more medical attention, while using benzodiazepines. Overall, primary medical care remains one of the main targets for BZD addiction and misuse prevention in Lithuania.

It is suggested that long-term BZD use should be defined as the use for six months or more. In our study, the shortest duration of BZD use was 9 years, therefore, all the subjects can be considered as long-term users. Quite a few studies state that in general population females are more likely to use BZDs [11–15]. Our study is in compliance with the findings of earlier studies, concluding that general determinant of BZD use cannot be applied to long-term BZD

users [15], since no significant differences in BZD use duration were found between male and female patients.

Although the duration of use did not differ between genders, DE doses before the detoxification treatment were slightly higher in males than in females. This result might coincide with findings that women have higher GABAA-BZ receptor availability than men, which means that they are more sensitive to BZD effects [13]. Age-determined (younger patients use higher DE doses before detoxification) DE dose differences might be seen due to age-related pharmacokinetic and neuronal changes, therefore, younger people are able to consume higher doses with less undesirable effects [16–18]. In addition, it has been noted, that recreational BZD use is very common among young adults [19,20]. These results bring out the significance of benzodiazepine representation in popular media: glorification of benzodiazepines among the youth might be highly affected by social media, as there is a bulk of popular songs, movies or series, showing benzodiazepines as easily accessible pleasure-inducing drugs.

The result, stating that lorazepam is the most common BZD, is specific to the Lithuanian population, since similar studies in other countries show other benzodiazepines being the most popular [21]. Before 1st of July 1, 2021, lorazepam used to be included in the B list of reimbursable medicines in Lithuania, meaning that particular diagnoses allow reimbursement of the drug. This situation could possibly encourage irrational use of the pharmaceutical. Following the example of the Netherlands, exclusion of lorazepam from the list, would help to reduce its misuse [22].

Longer BZD use was related to the need for longer hospitalization and more non-BZD medicines prescribed for outpatient treatment after detoxification. This might indicate that longer BZD use might aggravate the process of detoxification for the patient causing worse withdrawal symptoms that last for a longer time, therefore, discontinuation of BZD is more difficult to achieve. Hospitalization and detoxification treatment was also longer in females than in males which is a common result in many studies: men are more likely to leave the hospital against medical advice [23–25].

Earlier studies have found that mental disorders, especially anxiety and mood disorders, increase the risk of any BZD use in the general population [11,14]. Also, heavy alcohol consumption in BZD users is thought to be lower than in the general population allegedly due to physicians and pharmacists' warnings [26]. More than half (58.3%) of the patients in this study had been diagnosed with some psychiatric disorder (other than F13.2) and the most common ones were alcohol dependence, as well as depression spectrum disorders. This might be due to the fact that alcohol withdrawals are typically treated using BZDs and some of the patients, suffering from substance abuse disorder, are prone to replace one substance with other. In addition, alcohol users had been hospitalized for longer period than non-users. The importance of mental disorders in BZD misuse is undeniable, however, alcohol misuse appears to have a more complex role in the pathogenesis of BZD addiction. Therefore, more detailed studies are needed to analyse the relationship between mental disorders, alcohol abuse, and BZD addiction.

Certain limitations of this study should be noted. First, quite a small sample does not reflect the population and the results concerning BZD use disorder in Lithuania can be inadequate. Second, the retrospective study offers scarce details about BZD use and earlier detoxification treatments, therefore, prospective studies with additional questioning of the patients and larger samples should be conducted.

5. Conclusions

Among long-term BZD users, males have been using higher BZD doses than females, also, higher doses have been the characteristic of younger patients. The patients, who had used higher BZD doses before the detoxification treatment, have been discharged with higher BZD doses and more non-BZD medicines prescribed for outpatient treatment. It is important to note that lorazepam remains the most common BZD among people with BZD addiction in Lithuania. Longer BZD use was related to a longer period of detoxification. Females have been hospitalized longer than males, and alcohol users have been hospitalized for a shorter time than non-users. Nevertheless, prospective studies with larger samples are needed to verify the strength of these results.

References

1. Airagnes G, Pelissolo A, Lavallée M, Flament M, Limosin F. Benzodiazepine Misuse in the Elderly: Risk Factors, Consequences, and Management. *Current Psychiatry Reports*. 2016 Oct;18(10):89. <https://doi.org/10.1007/s11920-016-0727-9>.
2. Kang M, Ghassemzadeh S. Benzodiazepine Toxicity. StatPearls Publishing. 2021.
3. Lugoboni F, Gerra G, Tamburin S. Treatment

of Benzodiazepine Dependence. *The New England Journal of Medicine*. 2017 Jun 15;376(24):2397–400.

<https://doi.org/10.1056/NEJMc1705239>.

4. Brett J, Murnion B. Management of benzodiazepine misuse and dependence. *Australian Prescriber*. 2015 Oct 1;38(5):152–5. <https://doi.org/10.18773/austprescr.2015.055>.

5. Votaw VR, Geyer R, Rieselbach MM, McHugh RK. The epidemiology of benzodiazepine misuse: A systematic review. *Drug and Alcohol Dependence*. 2019. <https://doi.org/10.1016/j.drugalcdep.2019.02.003>.

6. Harro J, Aadamsoo K, Rootslane L, Laius O, O'Leary A, Adomaitiene V, et al. Comparison of psychotropic medication use in the Baltic countries. *Nordic Journal of Psychiatry*. 2020 May 1;74(4):301–6. <https://doi.org/10.1080/08039488.2019.1707283>.

7. Rickels K, Moeller HJ. Benzodiazepines in anxiety disorders: Reassessment of usefulness and safety. *The World Journal of Biological Psychiatry*. 2019 Aug 9;20(7):514–8. <https://doi.org/10.1080/15622975.2018.1500031>.

8. Valstybinė vaistų kontrolės tarnyba. Ataskaita apie 2020 metais suvartotus vaistus.

9. Greller H, Gupta A. Benzodiazepine poisoning and withdrawal. UpToDate. 2020 October 20.

10. ATLAS of Substance Use Disorders Resources for the Prevention and Treatment of Substance Use Disorders Country Profile: Lithuania demography. 2006.

11. Aranauskas, R., Vaičiulienė L. Šeimos gydytojo pacientų, vartojančių benzodiazepinus, priklausomybės išsivystymo tendencijos. *Sveikatos Mokslai/Health Sciences*

in Eastern Europe. 2018;(2):95.
<https://doi.org/10.5200/sm-hs.2018.027>.

12. V-2771 Dėl Lietuvos Respublikos sveikatos apsaugos ministro 2002 m. kovo 8 d. įsakymo Nr. 112 „Dėl Receptų rašymo ir vaistinių preparatų, medicinos priemonių (medicinos prietaisų) ir kompensuojamųjų medicinos pagalbos priemonių išdavimo (pardavimo) vaistinėse gyventojams ir popierinių receptų saugojimo, išdavus (pardavus) vaistinius preparatus, medicinos priemones (medicinos prietaisus) ir kompensuojamąsias medicinos pagalbos priemones vaistinėje, taisyklių patvirtinimo“ pakeitimo.

13. Esterlis I, Ph D, Mckee SA, Ph D, Kirk K, Lee D, et al. Sex-specific differences in GABAA -benzodiazepine receptor availability: Relationship with sensitivity to pain and tobacco smoking craving. 2014;18(2):370–8.

14. Lagnaoui R, Depont F, Fourrier A, Abouelfath A, Bégaud B, Verdoux H, et al. Patterns and correlates of benzodiazepine use in the French general population. *European Journal of Clinical Pharmacology*. 2004 Sep;60(7):523–9.

<https://doi.org/10.1007/s00228-004-0808-2>.

15. Neutel CI. The epidemiology of long-term benzodiazepine use. *International Review of Psychiatry*. 2005 Jun;17(3):189–97.
<https://doi.org/10.1080/09540260500071863>.

16. Griffin CE, Kaye AM, Rivera Bueno F, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. *Ochsner J*. 2013;13(2):214–23.

17. Shi S, Klotz U. Age-related changes in pharmacokinetics. *Current Drug Metabolism*. 2011 Sep;12(7):601–10.
<https://doi.org/10.2174/138920011796504527>.

18. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and

pharmacodynamics: Basic principles and practical applications. *British Journal of Clinical Pharmacology*. 2004;57(1):6–14.
<https://doi.org/10.1046/j.1365-2125.2003.02007.x>.

19. Kurtz SP, Surratt HL, Levi-Minzi MA, Mooss A. Benzodiazepine dependence among multidrug users in the club scene. *Drug Alcohol Depend*. 2011 Dec;119(1–2):99–105.
<https://doi.org/10.1016/j.drugalcdep.2011.05.036>.

20. Murphy KD, Lambert S, McCarthy S, Sahn LJ, Byrne S. “You Don’t Feel”: The Experience of Youth Benzodiazepine Misuse in Ireland. *Journal of Psychoactive Drugs*. 2018;50(2):121–8.
<https://doi.org/10.1080/02791072.2017.1371365>.

21. Szymański M, Korzeniowska K, Jabłeczka A. Addiction to benzodiazepines - analysis of patients of Independent Public Hospital for Mental Diseases Patients in Międzyrzecz. *Przegl Lek*. 2016;73(10):737–40.

22. Eteris E, Gerasimavičiūtė V. Benzodiazepinai: Kompleksinių priemonių rinkinys. In: Enrikas Eteris Dr Vaiva Gerasimavičiūtė „Kurk Lietuvai“ programa. 2019.

23. Manuel JI, Lee J. Gender differences in discharge dispositions of emergency department visits involving drug misuse and abuse—2004-2011. *Subst Abuse Treat Prev Policy*. 2017;12(1):28.
<https://doi.org/10.1186/s13011-017-0114-5>.

24. Alfandre DJ. “I’m going home”: Discharges against medical advice. *Mayo Clinic Proceedings*. 2009;84(3):255–60.

25. Youssef A. Factors associated with discharge against medical advice in a Saudi teaching hospital. *Journal of Taibah University*

Medical Sciences. 2012;7(1):13–8.

<https://doi.org/10.1016/j.jtumed.2012.07.006>.

26. Veldhuizen S, Wade TJ, Cairney J. Alcohol consumption among Canadians taking benzodiazepines and related drugs. *Pharmacoepidemiology and Drug Safety*. 2009 Mar;18(3):203.

<https://doi.org/10.1002/pds.1702>.