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A Prospective Study to use and Misuse of Benzodiazepines to Different Examined Groups by Education in R. Macedonia

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Abstract

The purpose of this research is to depict the use of benzodiazepines in the Republic of Macedonia, according to different characteristics, combining alcohol and illegal toxic substances, the most common reasons for using them, symptoms arising from sudden cessation of use, modes of supply of the drug, increase of the dose alone, analyzed within groups of respondents divided according to gender, age and type of education (health professionals, non-medical persons). The research is conducted using a prospective survey in The Republic of Macedonia. In 2012 year, the third most commonly used benzodiazepine is diazepam (5.04%), whereas alprazolam is used with 2.64%. They are more used to group with non-medical education (81.5%), are bought without prescription 11.14%, mostly between the persons with non-medical education (81.08%). Sudden and unplanned cessation of the therapy with benzodiazepines is reported in 19.28% of the respondents, whereas 22.27% of them have had withdrawal symptoms or other symptoms. 11.90% increased the dosage of the therapy on their own, without consultations with a doctor. The use of benzodiazepines in the R. Macedonia has increased in the latest years, covering the youth population, and is indicating a larger use between the persons who are not medical educated, which suggests a lower degree of health awareness about consumption of these drugs.

Keywords: benzodiazepines; use; misuse; health; education

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1. Introduction

The long-term treatment with benzodiazepines is a subject of discussion in many scientific circles. The benzodiazepines are a drug group which are most commonly both used and misused, especially in countries where they can be easily purchased without a compulsory medical prescription. Benzodiazepines are considered as relatively safe drugs, which are usually safely consumed by the patients. However, they can also show negative and unwanted side-effects and/or interactions with other drugs and foods, as well as drug tolerance, which can be developed after long-lasting use of the drug. After a certain period of use, and especially after a sudden cessation of use of the drug, the consumers of benzodiazepines can feel symptoms of benzodiazepine withdrawal crisis.

Research of the negative side-effects of benzodiazepines has been conducted within a large number of scientific papers. In previous research [1]; the phenomenon of addiction to the benzodiazepines after their usage has been analyzed. There is a chance of developing a tolerance to the anxiolytic effects after a longer period of use of benzodiazepines [2]. The author in [3] confirms that there is an occurrence of physical dependence of patients with high-dose, long-term treatment with benzodiazepines. The author in [4] suggests that, the peoples who have previously misused alcohol or drugs have higher risk of developing a psychological dependence of benzodiazepines. These are mainly used for increasing the effects of other used medications, which complements the negative side-effects of other drugs. Benzodiazepines are usually administered and used for treating insomnia, anxiety, convulsions, pain and spasm of skeletal muscles, preoperational anxiety, epileptic seizures, weaning of alcohol etc [5]. In The Republic of Macedonia the most commonly used benzodiazepines are the drugs with the following names: alprazolam, bromazepam, diazepam, klonazepam, lorazepam.

1.1. Presence of benzodiazepines in Republic of Macedonia

For the presence of benzodiazepines in the Republic of Macedonia, speaks the data published by the Health Insurance Fund of Macedonia (future HIFM) for the medical prescriptions issued between the years of 2009-2012 year. In 2009 year, according to the data of HIFM, the most commonly sold drugs from the group of benzodiazepines were diazepam and alprazolam. According to the annual report for the “work of the HIFM and analysis of the economic-financial activities of the Fund and the public health institutions”, for 2010 year, the consumption of the benzodiazepine diazepam, was on the fourth place among the list of most commonly used drugs. [6] Most commonly used prescription drug in 2011 year was enalapril, and from the group of benzodiazepines, it was diazepam, which was on the third place [7]. In 2011 year, the most medical prescriptions for diazepam, were for the 5 mg. pills (461.317 or 31%), and the 2 mg. pills were on the second place of prescribed types of diazepam (308.669 or 20%) [8]. The consumption of benzodiazepines in 2012 year, are increased, compared to 2011 year. For the drug diazepam, are realized 882.013 prescriptions, an increase of 13.97% [9]. If one takes into consideration the fact that this drug is acquired without a medical prescription in a lot of pharmacy stores, it can be concluded that the real consumption of diazepam is even greater.

Additional information about cases of use and misuse of the benzodiazepines by citizens of The Republic of Macedonia can be found on certain web portals [10, 11, 12].

1.2. Goals

- To analyze the use/misuse of the benzodiazepines in The Republic of Macedonia, according to the following profiling parameters: gender, age and kind of education of the subjects:
 - **Health professionals:** persons, which are currently pursuing or have previously obtained a degree in one of these three faculties: Faculty of Medicine, Faculty of Pharmacy, Faculty of Dentistry, and who are finished High and Higher medical schools;
 - **Non-medical persons:** persons which do not pursue or possess a degree of health education (medicine, pharmacy, dentistry, high and higher medical schools);
- To determine the situation of consumption of benzodiazepines in The Republic of Macedonia and the awareness for these drugs of the population, according to specific modalities consisted in the questionnaire;
- To confirm or reject the statistically relevant correlation between the use of benzodiazepines by certain profiles and the reasons for the use;
- To obtain information about the frequency of use of benzodiazepines in times of pregnancy and breastfeeding, as well as combining it with alcohol and drugs;

- To analyze the most common reasons for use, the means of procurement, the awareness of the citizens about the psychological and physical dependence, with the use of statistical tests and methods;
- To discuss and compare the results of this research with similar research on the topic from other authors;
- To draw conclusions and list recommendations for the health security for the times before and after the use of benzodiazepines.

2. Materials and methods

The used methods for this research include the epidemiological method with prospective cohort survey and the health-statistical methods with use of statistical tests and methods. The questionnaire consists of 22 questions, and the data is gathered, both using electronic and hard-copy surveys.

2.2 *Place, timeframe and target group of the research:* The research is conducted on the territory of The Republic of Macedonia in 12 municipalities: Bitola, Resen, Ohrid, Skopje, Prilep, Demir Hisar, Stip, Gevgelija, Bogdanci, Kicevo, Vinica, Kumanovo, between January and July, 2013, by students from the Higher Medical School in Bitola and the Faculty of Pharmacy in Skopje. The target group of the research included the student population (from the Higher medical school in Bitola, the Faculty of Law in Bitola and the Faculty of Pharmacy in Skopje and the general population.

2.3 *Means of research:* The research subjects are chosen on the basis of random choice: on the street, in the classroom, in the cafeterias, in the homes of the citizens, in organizations, in health institutions, through phone and internet).

2.4 *Research subject profile:* The research includes 1328 subjects (564 male and 764 female), which are categorized into two main profiles: health professionals (410 subjects) and non-medical persons (918 subjects). The respondents are at the age of <20 to the age of >61 years.

2.5 *Statistical analysis:* The following statistical and mathematical tests and methods are used: relative numbers, comparative analysis, proportions, correlation coefficient (r), X²-test and contingency coefficient (C). The gathered data is statistically and mathematically processed with Microsoft Excel, and depicted in tables and figures.

3. Results

In order to determine the magnitude of the problem with the use and misuse of benzodiazepines in The Republic of Macedonia, the results of the prospective survey will be shown through data analysis of the answers of some of the questions consisted within the questionnaire. From the total 1328 examined persons, a larger number of the respondents are from the female gender (764 or 57.53%), whereas according to the type of education, with greater representation in this research are the non-medical persons (918 or 69.12%). The most commonly present respondents are profiles according to age, at the health professionals, are persons to age of under 20 years (203 or 49.51%), and at the non-medical persons are the age groups between 21 and 30 years (325 or 35.40%).

Table 1: Consumption of benzodiazepines between subjects divided according to type of education (health professionals and non-medical persons)

Consumption of benzodiazepines	Health professionals		Non-medical persons		Total	
	Number	(%)	Number	(%)	Number	(%)
Have consumed	104	18.47	459	81.53	563	100.0
Have never consumed	306	40.00	459	60.00	765	100.0
Total	410	30.87	918	69.13	1328	100.0

From the analysis of the data, presented in Table 1, one could notice that out of the total of 563 respondents which consume benzodiazepines, in a larger percentage are non-medical persons (459 or 81.53%). To the health

professionals, more frequent are those who do not consume benzodiazepines (74.63% compared to the total amount of respondents in the group of health professionals). There is a correlation between the consumption of benzodiazepines and the type of education, $X^2=70.425$, $C=0.22$, $p<0.05$. Out of the total number of examined persons, who use benzodiazepine, according to gender and age (results gathered with proportion), more are females (392 subjects or 58.16%). The most frequent age at females is of 31-40 years (40.1%) and at males is of 21-30 years, or 28.7%.

Table 2: Number of respondents according to ways of procurement of the drugs

If you use (or have used) benzodiazepines, you procured them...						
Answers	Health professionals		Non-medical persons		Total	
	Number	%	Number	%	Number	%
With a medical prescription	79	19.27	344	37.47	423	31.86
Without a medical prescription	28	6.83	120	13.07	148	11.14
I have never used benzodiazepines	303	73.90	454	49.46	757	57.00
Total	410	100.00	918	100.00	1328	100.00

Most of the respondents (table 2) have reported to obtain the benzodiazepines with a medical prescription (423 or 31.86%). But, the number of the respondents, that have reported to obtain these drugs on their own, without a medical prescription is not so low (148, or 11.14%). The most of them are non-medical persons (120 or 81.08%).

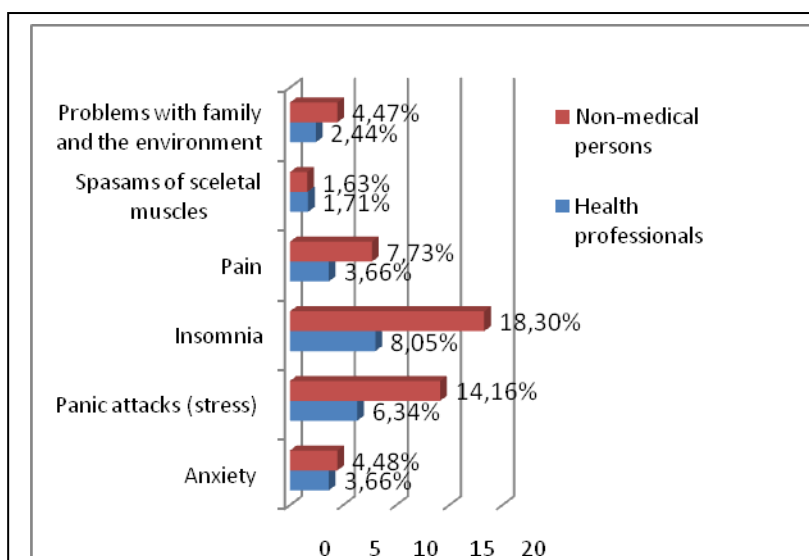


Fig. 1 Percentage of respondents which have listed the most common reasons for use of benzodiazepines

The most reasons for the use of benzodiazepines (figure 1), is insomnia at both groups (health professionals and non-medical persons), with total presence of 15.14%, with a higher prevalence in non-medical persons (18.30%) . Second factor which is listed is the stress, with total presence of 11.75% of the reasons, again with a higher prevalence in non-medical persons (14.16%), whereas the problems in the family and environment are total present for only 3.83%. On the question “Do you drive a motor vehicle after the use of benzodiazepines”, positive is, that the most of the respondents are answered with “no” (481 subject or 36.22%). However, 9.26% are used a vehicle, because they believe that the use of benzodiazepines does not present an obstacle for controlling a motor vehicle. A very small percent (only 1.81%) of the respondents use benzodiazepines in combination with alcohol, for amplifying the effects of it. We could to guess that this is due to the sufficient level of information about the undesired effects of this combination to the persons. In this research, only 28 examined persons, or 2.11%, have reported to use illegal

drugs. However, only 8 respondents, or 0.60% have combined illegal drugs with benzodiazepines, (28.57%) out of the total number (28) of illegal drug users.

On the question “Have you suddenly stopped the therapy with benzodiazepines”, 256 respondents or 19.28% are answered with “yes”. Those who positively answered of this question (57 persons or 22.26%) have reported, for symptoms of crisis because of abstaining. The result which is very interesting is, that out of the total of 1328 respondents, 158 or 11.90% have taken a decision for increasing the benzodiazepine therapy dose on their own, without consultation with a doctor, which counts for $\frac{1}{3}$ (28.6%) of the total number of examined persons, which are users of benzodiazepines (563).

The results from the study regarding the opinion as to whether benzodiazepines can causing psychological and physical dependence, and the different types of education, show that there is a statistically significant $X^2=75.926$, $C=0.23$, ($p<0.05$). A larger number of the non-medical persons (78.18%) have responded that benzodiazepines cannot cause dependency, 62.06% of the non-medical persons have also answered that the use of benzodiazepines is not harmful during pregnancy and breastfeeding, whereas 79.10% are reported that are not informed about it. To some extent, there is a statistically correlation between the opinion about the usage of benzodiazepines during pregnancy and breastfeeding, and the different type of education (health professionals and non-medical persons) $X^2=49.523$, $C=0.2$, ($p<0.05$).

The results from this study suggest that the respondents - health professionals, have knowledge of the harmful effects from the use of benzodiazepines while driving, in contrast to non-medical persons (42.66%:57.34%). There is a strong statistically significant correlation in terms of this opinion, $X^2=90.771$, $C=0.25$, ($p<0.05$). The number of persons that consume benzodiazepines, shows a tendency of increase with the increase of age. According to the value of the correlation coefficient, one could conclude that with the age increase, the tendency of females to become benzodiazepine consumers is greater than at males ($r=0.1616>0.0321$).

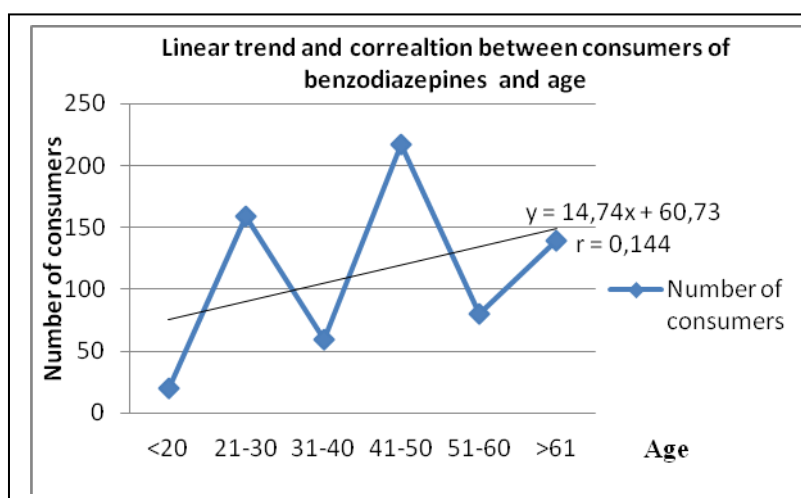


Fig. 2 Correlation between the age of respondents and consumers of The benzodiazepines

The figure 2 shows, that the linear trend is increase, at the same time with the age. According to the results of the coefficient of correlation ($r = 0.144$), we can conclude that, between the age and the likelihood the people to begin of consummation of benzodiazepines, there is weak correlation.

4. Discussion

From the gathered results from this study regarding the use/misuse of benzodiazepines, it could be concluded that this problem is present in The Republic of Macedonia, with a tendency of an increase in the consumption of this class of drugs in the last several years. This condition represents an important social and public health problem, as the great consumption of these drugs with medical prescriptions, and also the funds spending for those prescriptions, which can be seen in the past years. However, if we take into consideration the procurement of these drugs in

pharmacy stores and other locations without medical prescriptions, where there is no information and evidence from it, then one could easily assess that this problem is becoming more serious.

According to the information of the Health Insurance Fund of Macedonia, the most commonly sold benzodiazepines between 2009-2012 year, are diazepam and alprazolam, with an increase in consumption from one year to next one. The consumption of benzodiazepines in 2012 year has increased, compared to the one in 2011 year, and the drug diazepam is increased in procurement for 13.97%.

A similar is the situation with the patients observed (Stanetić K., Savić S. 2010), in the Health Center "Banja Luka" (R. Bosnia and Hercegovina), where out of 583 patients, 66.39% are diazepam users.

From the analysis of the prospective research in Republic of Macedonia, it could be observed that there is a large percentage of benzodiazepine users, with a same presence at the both groups respondents (50.00%). At the group of Health professionals, a larger number of respondents (74.63%) belong to the group of persons, who do not consume benzodiazepines. According to this data, it could be concluded that the health education provides greater information about the role of benzodiazepines and the expected effects in the treatment of particular diseases. In the following research [13], out of 583 patients, followed in the Health Center of Banja Luka (R. Bosnia and Hercegovina), 20.41% are benzodiazepine users.

In The Republic of Macedonia, greater consumers of benzodiazepines are females (58.16%), and according to age, more prevalent is the age group of 31-40 years (40.1%). For determining the causes of the greater consumption of benzodiazepines in females, it is necessary to in the future, somebody to conduct new research.

The authors in [14] concluded that benzodiazepines have identified in the urine in 33% of the patients, more between females (48%). A significant percent of the subjects in The Republic of Macedonia procure the benzodiazepines on their own, without a consultation with a medical expert (11.14%), and mostly in groups non-medical persons (120 or 81.08%). 1/3 of the respondents, are pointed at the existence of easy ways of procurement of benzodiazepines, without a medical prescription (32.08%). This method of procurement of drugs more are practiced by the non-medical persons (69.24%), most probably due to the low level of health awareness and culture regarding the consequences. A large is the number of respondents, which are not informed regarding this problem (46.31%).

The lack of awareness regarding the proper use of benzodiazepines, makes this problem more complicated. A certain number of citizens (9.26%) use vehicles while taking benzodiazepines, probably due to the lack of information, about the recommendations for the use of benzodiazepines. Optimistic is the data, that only a small number of respondents use benzodiazepines in combination with alcohol, for increasing the effects of the benzodiazepines, most probably due to the better awareness of the citizens for the negative impact of this habit to health. Although in the research, very few respondents, who have reported to consume drugs, a large number, of around 1/3 of drug users (28.57%), combine benzodiazepines with drugs, most commonly for increasing the effects of the drug. According to the data analysis, a sudden cessation therapy with benzodiazepines was the case in 19.28% of respondents, whereas a small percent of them (4.29%) who are showed symptoms of crisis due to withdrawal or some other symptom. That situation, go supports the thesis, that benzodiazepines can create dependence to some users after long time use.

One third of subjects (28.06%) who are consumers of benzodiazepines, alone are determining the quantity and the dosage of medicines, without professional consultations with doctors. Non-medical persons are also not informed enough, about the harmful effects of using benzodiazepines during pregnancy and breastfeeding. In [3] the researchers found that; mothers who used benzodiazepines during pregnancy, are answered that: have increased risk of early birth and low birth weight to their newborn child. (3)

There is an increase of relatively large birth malformations, at infants, from mothers which used benzodiazepines at the beginning of their pregnancy [15]. On the other hand, another author (McElhatton PR., London, 1994) claims the opposite. In a period of 4 years, he is observed 550 children, from mothers who used benzodiazepines during pregnancy. The author did not confirm any increase the rate of malformations and he also claimed that this condition does not result with changes in IQ of the children [16].

Large number of the non-medical persons (88.78%) did not know, if there is any adverse reaction from consuming benzodiazepines, while they are managed by a vehicle. From the analysis of the gathered data of the study, we can concluded that with the increase of age, the tendency to start with use benzodiazepines is higher at women than at men ($r = 0.1616 > 0.0321$).

The results of the study point out to the conclusion that there is a significant consumption of benzodiazepines between the Macedonian citizens, including the young generation. On the other hand, they are not enough aware of the health effects, especially in the group of non-medical persons. From the data analysis, as well as from other research and references, regarding use benzodiazepines, conducted in R. Macedonia or outside from its borders, it can be concluded that the results of those studies are very similar.

4.1 Recommendations of health safety, before and after use of benzodiazepines

For the purposes of avoiding the health risks of the frequent use or misuse of benzodiazepines, it is essential that preventive measures to contain within the National strategy of the country. The recommendations of this strategy should be disseminated as widely, as possible between the population. For minimizing the risks of the benzodiazepine therapy at women, who are pregnant or are breastfeeding, a consultation with specialist is compulsory, who should recommend use of benzodiazepines for the shortest possible period. Other recommendations for this group of potential consumers are: avoiding use of benzodiazepines in the first trimester of the pregnancy, avoiding taking more medications at the same time and if it is necessary to use benzodiazepines, to use low-dose.

A continuous health education of the wider public and the young population through media is necessary. This health education should answer all questions regarding the use/misuse of benzodiazepines, for which the citizens are not informed enough.

In order to decrease the procurement of benzodiazepines without medical prescription, a stronger control from the respective authorities is necessary, both at the specialists, who prescribe this medications, and the pharmacy stores, which trade them.

Finally, it also was necessary health care professionals to help to older peoples in the implementation of preventive measures and measures avoiding abuse with benzodiazepines. A special control for the use of benzodiazepines is necessary for consumers of alcohol and narcotic substances, with a special focus, to put on those who use benzodiazepines for withdrawing from their addiction or increasing the effect of the alcohol or drugs.

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