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ADVERSE EFFECTS OF BENZODIAZEPINES IN PSYCHIATRIC OUTPATIENTS

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SUMMARY

Background: *Benzodiazepines are among the most frequently prescribed drugs. Of all their side effects, hip fractures and possibility of developing dependence are usually studied.*

Objective: *The aim of this study was to determine how often do psychiatric outpatients suffer from adverse effects of benzodiazepines, and which adverse effects do they notice.*

Subjects and method: *109 patients on two consecutive days were asked to fill in the questionnaire. Among them were 29 women and 80 men. Ten women (1/3) and 20 men (1/4) refused to participate in the study.*

Results: *68% of women and 93% of men used benzodiazepines at least once in a lifetime; 40% of women used benzodiazepines in the last seven days, and 93% of men (32% of women and 44% of men used benzodiazepines every day for the last seven days). Unfortunately, 8% of men used more then one benzodiazepine daily.*

All of the women who used benzodiazepines had at least one adverse effect; and 91% of men had adverse effects. One third of women and one quarter of men stopped taking benzodiazepines due to adverse effects.

The mean number of adverse effects was 4.8 both in men and women. Those who stopped taking benzodiazepines didn't have more adverse effects in comparison to those who continued to use them.

More than half of the participants suffered from sleepiness, slowness and fatigue. One third of the participants said they noticed the change in sexual drive. More then 30% of women noticed dizziness and only 6% of men. None of the participants said to have jaundice after using benzodiazepines. The same adverse effects were present in those who stopped taking the drugs and in those who continued to use them.

Conclusion: *The prevalence of benzodiazepine use is very high in psychiatric patients. Many of them notice adverse effects, but mainly continue to use the drug.*

Key words: *benzodiazepines - adverse effects - prevalence of use*

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INTRODUCTION

Although benzodiazepines were developed during 1930s and set into use in 1950s, research on prevalence of adverse effects of these drugs is scarce (Lader 2008). Mainly, there are case reports on special or unusual adverse effects or research on prevalence of adverse effects of special populations (such as older people, because of the possibility of resulting in falls and hip fractures) (Kirby et al. 1999, Johnell & Fastbom 2009, Taylor et al. 1998).

The most common adverse effects are: drowsiness, sedation, dizziness and ataxia (Kaplan & Sadock 1994).

The efficacy of benzodiazepines have been re-analyzed in light of the fact that there is a possibility of developing dependence in long term use (3-6 months or longer) (Schweizer & Rickels 1998). But, despite knowledge to such possibilities, and despite limited evidence to their efficacy (especially in light of newer pharmacotherapeutic possibilities of treating anxiety disorders), benzodiazepines continue to be among the most

commonly prescribed drugs (Struzik et al. 2004, Stahl 2002).

The aim of this study was to determine how often and which adverse effects do experience psychiatric outpatients.

SUBJECTS AND METHOD

The sample included all the patients on two consecutive days that attended outpatient unit at the General hospital Karlovac. There were 109 patients.

Patients were offered to fill in the questionnaire on adverse effects of benzodiazepines. Patients were told that the questionnaire was anonymous and that they were free to choose whether to participate or not in the study. 30 patients refused to participate in the study.

The questionnaire consisted of three parts. In the first part general sociodemographic date were collected: age, gender, marital status, and educational level. In the second part patients were asked to answer weather they used benzodiazepines in the last seven days, last month and ever in their life. All the benzodiazepines (anxiolytics-sedatives) registered in Croatia were offered, using their trade names. Also, patients were asked who proposed them to use the drug (a doctor, a pharmacist, newspapers, radio or TV, a neighbour, a friend, a nurse or they, themselves). They were asked if the drug was useful to them, and they answered on a Likert scale: my problems/troubles resolved fully; it helped me very much; it helped me; it did not help me; my problems/troubles worsened.

In the third part of the questionnaire patients were offered to choose among 27 side effects if they experienced them during benzodiazepine usage (Kaplan & Sadock 1994). Also, they were asked whether they stopped taking the drug due to these side-effects.

RESULTS

Of 109 patients, who were asked to participate in the study, there were 29 women (26.6%) and 80 men (73.4%). Gender and age characteristics of patients willing to participate and those who didn't want to participate are presented in Table 1. There are no gender differences in these two groups (chi2=0.959; p=0.327). Also, there are no statistical differences in age (women: t=1.03, p=0.31; men: t=1.10; p=0.27).

Table 1. Gender and age characteristics of the sample

Characteristic	Did not participate	Participated
Gender	10 women, 20 men	19 women, 60 men
Age /years/	Women 50.90 ± 10.22 Men 49.10 ± 6.99	Women 45.22 ± 15.66 Men 45.25 ± 8.72

Among the people who participated in the study, 68% of women and 93% of men used benzodiazepines at least once in their lifetime! 40% of women and 93% of men used benzodiazepines in the last seven days! Also, 32% of women and 44% of men used benzodiazepines every day for the last seven days.

More then 40% of the patients who used benzodiazepines used alprazolam, and 20% used diazepam (Figures 1 and 2).

Unfortunately 8% of men used more then one benzodiazepine daily, and none of the women.

In the vast majority of patients they used benzodiazepines prescribed by their physicians (94%). In one case, the drug was advised by a neighbour, a friend, TV or the patient himself.

Adverse effects were prevalent in the sample: all the women had at least one adverse effect; and 91% of men experienced at least one adverse effect. The mean number of adverse effects in both men and women were 4.8.

The most prevalent adverse effects in men were: slowness (59%), sleepiness (55%), fatigue (55%), change in sexual drive (33%), nervousness

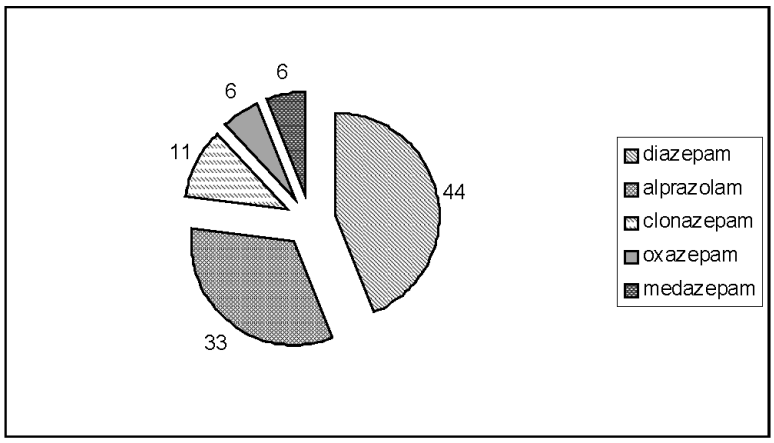

Figure 1. Benzodiazepines used in women

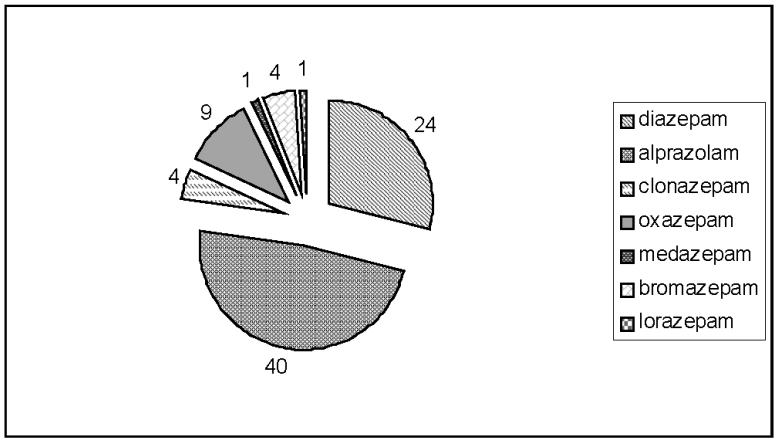

Figure 2. Benzodiazepines used in men

(29%), forgetfulness (27%), headache (25%), irritability (24%), weakness in muscles (24%), fear (22%), and confusion (20%).

In women the most prevalent adverse effects were: sleepiness (69%), slowness (69%), fatigue (54%), change in sexual drive (38%), dizziness (31%), irritability (23%), aggressiveness (23%), forgetfulness (23%), amnesia (23%) and changes in body weight (23%). None of the participants reported jaundice as an adverse effect.

The most evident difference was the high prevalence of dizziness in women (31%) and low in men (6%).

One third or women (36.4%) and one quarter of men (26.9%) stopped using benzodiazepines. Interestingly, the number of side effects did not differ in those who stopped to use the drugs, and in those who continued the usage. Also, there was the same profile of adverse effects in those who stopped, and in those who continued to take the drug.

DISCUSSION

The aim of this study was to evaluate the prevalence of adverse effects of benzodiazepines. Although benzodiazepines are widely used drugs, the researches on the prevalence of adverse effects in patients attending outpatient clinics are scarce (North et al. 1992).

72.5% of patients consented to participate in the study. Gender and age characteristics of the non-participating and participating patients were the same, so we think we can generalize the results to all the outpatients who were contacted. The gender profile (more then 70% of men) is due to the fact that there are many people with PTSD in Croatia who attend mental health system, and who are mainly men.

There is a very high prevalence of use of benzodiazepines in these patients, higher then in other researches: 40% of women and 93% of men used these drugs in the last seven days (Bartels et

al. 1997; Valenstein et al. 2004; Johnson et al. 2007). This gender profile is probably due to the diagnostic differences (many of the male patients suffer from PTSD, while majority of women suffered from depression). If we look at the results keeping in mind this diagnostic difference, than the results are more in concordance with other studies, showing that 30-40% of depressed patients use benzodiazepines (like women in our sample), and that patients who suffer from more then one disorder (especially PTSD or other anxious disorder) have higher percentages of benzodiazepine use (like men in our sample) (Olfson et al. 2002, Benitez et al. 2008).

Among the women almost half (44.4%) used diazepam, and one third (33.3%) used alprazolam, one tenth clonazepam (11.1%). Among the men, half of them used alprazolam (48.2%), and one third diazepam (28.9%), then follows oxazepam (10.8%) and clonazepam (4.8%). So, it seems that vast majority of patients used only two different benzodiazepines (in Croatia there are seven different benzodiazepines registered). It was due to the physician (general practitioner and/or psychiatrist) choice, because 94% of the patients said that they were prescribed the drug, and only individual patients decided themselves (or were advised by a neighbour or a friend). We can only speculate why these two drugs were the most often prescribed, but one of the possible reasons is that diazepam, clonazepam and alprazolam are the benzodiazepines that can be given in Croatia, with no financial participation of the patient. So, other benzodiazepines that require patient financial participation were less often prescribed. But, this does not answer the question why was clonazepam used much less then diazepam and alprazolam.

All the women and 91% of men who used benzodiazepines experienced at least one adverse effect. This is almost unbelievable percentage. It is possible that patients linked these adverse effects with benzodiazepines, while taking some other drugs at the same time. But, on the other hand, the most usually reported side effects were sleepiness, slowness and fatigue, which were the most expected side effects. These three adverse effects happened (each of them) in more then half of the patients who suffered from side effects.

The interesting gender difference was that 30% of women and only 6% of men experienced dizziness. We can not explain why there is such a difference.

We compared patients taking benzodiazepines who stopped taking the drugs and those who continued to use them. There were no difference in terms of age, gender, educational level, marital status, benzodiazepine used, number of adverse effects, type of side effects, or satisfaction with the effect of benzodiazepine. So, we could not differentiate among the patients who will discontinue and those who will continue to take the drug.

Thus, patients suffer often and with many adverse effects, but still use benzodiazepines. The question is why. Possible answers are that these drugs are highly effective, achieve their effect quickly, can be used when needed and because physicians prescribe them (Bendtsen et al. 1999; Hylan T. et al 1999; Valenstein M. et al. 2004). Why do physicians prescribe these drugs so often, despite that guidelines on the treatment of mental disorders do not consider benzodiazepines any more (in case of depression, anxiety disorders and PTSD) as the first line drugs (American Psychiatric Association 2000, Baldwin et al. 2005).

The major shortcoming of this study is that we do not know what disorders the participants suffer from. They were asked to fill in the questionnaire anonymously, and in the questionnaire they were asked which disorder do they suffer from, but their perception is not always the same as the diagnosis of their psychiatrist.

Also, the study relies solely on participants' self-report of the type of medications used and adverse effects experienced, and did not include any of the additional sources, such as medical or pharmacy records or family members.

The second problem is that male and female participants in this sample are not comparable, but this is the reflection of the naturalistic sample in our outpatient unit. In all the Croatia there are many men diagnosed with PTSD, after the war trauma, and they make a high percentage of psychiatric patients, biasing the sample.

Future studies should focus on prevalence of benzodiazepine use and their side effects in specific diagnostic groups.

CONCLUSION

Outpatients use benzodiazepines (too) often. Although more then 90% of them experience adverse effects, they continue to use them. The mean number of adverse effects experienced is 4.8 in moth men and women.

REFERENCES

1. *American Psychiatric Association: Practice Guideline for the treatment of patients with major depressive disorder (revision). Am J Psychiatry, 2000; 157 (suppl).*
2. *Baldwin DS, Anderson IM, Nutt DJ, Bandelow B, Bond A, Davidson JR, den Boer JA, Fineberg NA, Knapp M, Scott J, Wittchen HU: Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J Psychopharmacol, 2005; 19: 567-596.*
3. *Bartels SJ, Horn S, Sharkey P, Levine K: Treatment of depression in older primary care patients in health maintenance organizations. Int J Psychiatry Med, 1997; 27: 215-231.*
4. *Bendtsen P, Hensing G, McKenzie L, Stridsman, AK: Prescribing benzodiazepines - a critical incident study of a physician dilemma. Soc Sci Med, 1994; 49: 459-467.*
5. *Benitez CIP, Smith K, Vasile RG, Rende R, Edelen MO, Keller MB: Use of benzodiazepines and selective serotonin reuptake inhibitors in middle-aged and older adults with anxiety disorders. Am J Geriatr Psychiatry, 2008; 16: 5-13.*
6. *Hylan T, Cworn WH, Meneades L, Heiligenstein JH, Melfi CA, Croghan TWBuesching DP: SSRI antidepressant drug use patterns in the naturalistic setting: a multivariate analysis. Med Care, 1999; 37: AS36-AS44.*
7. *Johnell K, Fastbom J: The use of benzodiazepines and related drugs amongst older people in Sweden: Associated factors and concomitant use of other psychotropics. Int J Geriatr Psychiatry, 2009 /ahead of print/.*
8. *Johnson C, Baxter B, Brough R, Buchanan J: Benzodiazepine prescribing: lessons from interprofessional dialogue. Australian Fam Pract, 2007; 36: 245-246.*
9. *Kaplan HI, Sadock BJ: Benzodiazepine receptor agonists and antagonists, in Synopsis of psychiatry behavioral sciences/clinical psychiatry, 989-999. 8th ed. Baltimore: Lippincott Williams & Wilkins, 1994.*
10. *Kirby M, Denihan A, Bruce I, Radic A, Coakley D, Lawlor BA: Benzodiazepine use among the eldery in the community. Int J Geriatr Psychiatry, 1999; 14: 280-284.*
11. *Lader M: Effectiveness of benzodiazepines: do they work or not? Expert Rev Neurother, 2008; 8: 1189-1191.*
12. *North DA, McAvoy BR, Powell AM: Benzodiazepine use in general practice - is it a problem? N Z Med J, 1991; 105: 287-289.*
13. *Olafson M, Marcus SC, Druss B, Elinson L, Tainelian T, Pincus HA: National trends in the outpatient treatment of depression. JAMA, 2002; 287: 203-209.*
14. *Schweizer E, Rickels K: Benzodiazpeine dependence and withdrawal: a review of the syndrome and its clinical management. Acta Psychiatr Scand Suppl, 1998; 393: 95-101.*
15. *Stahl SM: Don't ask, don't tell, but benzodiazepines are still the leading treatments for anxiety disorder. J Clin Psychiatry, 2002; 63: 756-757.*
16. *Struzik L, Vermani M, Coonerty-Fermiano A, Katzman MA: Treatments for generalized anxiety disorder. Expert Rev Neurother, 2004; 4: 285-294.*
17. *Taylor S, McCracken CF, Wilson KC, Copeland JR: Extend and appropriateness of benzodiazepine use. Results from an elderly urban community. Br J Psychiatry, 1998; 173: 433-438.*
18. *Valenstein M, Taylor KK, Austin K, Kales HC, McCarthy JF, Blow FC: Benzodiazepime use among depressed patients treated in mental health settings. Am J Psychiatry, 2004; 161: 654-661.*

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