Analysis of the Benzodiazepine Prescribing Patterns in the Primary Healthcare of the Republic of Srpska

Žana Maksimović1,2, Mladen Stajić1,2, Dragana Lončar-Stojiljković3

ABSTRACT

Background: Benzodiazepines (BZDs) are very often inappropriately prescribed drugs. The aim of this study is to analyse physicians’ prescribing patterns for BZD in the Republic of Srpska, and to assess to what extent primary diagnosis determine the dose and the length of use of BZDs.

Methods: A retrospective analysis of the physicians’ prescription habits based on the database of Family Medicine Information Systems of Republic of Srpska, as well as on data from patient’s medical record were performed. Patients’ socio-demographic and clinical characteristics, including the data on the type and dose of BZDs prescribed, were recorded and evaluated.

Results: BZDs were mostly prescribed for anxiety disorders (30.05%), for depressive disorders (17.54%), and for anxiety-depressive disorders (10.86%). A significant amount of BZDs was prescribed for non-psychiatric diagnoses (23.81%). Patients suffering from psychotic disorders were taking the highest dose of BZD and for the longest periods of time (p<0.001). Longer use of BZDs was in women (r=0.04, p<0.001), elderly (r=0.178, p<0.001), single people (r=0.12, p<0.001), those who live in urban areas (r=0.45, p<0.001) and those who were prescribed higher doses (r=0.213, p<0.001).

Conclusion: A significant percentage of patients were using the BZDs for longer period of time than recommended. Strongest positive correlation was found between the dose and the length of use, which implies the addictive potential of BZDs. Since it has been noticed that prolonged use, or abuse is present regardless of the diagnosis, precaution is advised when prescribing BZDs even for acute diseases.

Key words: benzodiazepines, primary healthcare, analysis of medicine use, rational pharmacotherapy.

INTRODUCTION

Benzodiazepines (BZDs) are agonists of the BZD receptors at the γ-amino-butyric acid A (GABA-A) receptor complex. The effect of stimulation of GABA receptors provides its anxiolytic, sedative, hypnotic, anticonvulsant and myorelaxant effect.1 BZDs are used in treatment of insomnia, anxiety disorders and along with antidepressant.2 They are also used in the treatment of terminally ill cancer patients.3 According to current guidelines the use of BZD should be limited to shorter use (up to 4 weeks) to minimize the risk of adverse reactions (e.g. dependence or withdrawal symptoms).4,5 However, it is estimated that 3% of the general population use BZD for the period longer than 6 months in continuity.6 The long term use of these drugs is potentially inappropriate and can cause a range of adverse side effects including cognitive and psychomotor impairment, particularly in older patients.
Most authors agree that use of BZDs for longer than 6 months suggests addiction. Abuse of opiates and BZDs is often coinciding. Longer use of BZDs, especially in the elderly, is correlated with frequent falls, moderate risk of all causes of death and dementia. Despite lack of recommendations, BZDs are often used for treatment of pain and somatic disorders. Furthermore, there are even relative contraindications for use of BZDs in patients suffering from schizophrenia, and in patients with psychotic disorders BZDs should only be used for very short sedation and calming down of acutely agitated patients.

The aim of this study is to evaluate physicians’ habits in prescribing of BZD in the primary health care settings of Republic of Srpska, and to assess to what extent the primary diagnosis determines the dose and the length of use of BZDs.

METHODS

Retrospective cross-sectional study was conducted. Doctors prescribing practice data in primary healthcare were collected from the Family Medicine Information Systems (WebMedic) of Republic of Srpska. Anonymity of patients was preserved. Personal medical record of each patient was coded, without data related to patients’ name, initials or personal identification number. Only data of patients age and sex were available.

I. Prescription analysis
All patients that had been using BZDs from February 2011 to February 2018 were included in this study. Basic socio-demographic and clinical data such as: gender (male/female), age (years), smoking status (smoking/not smoking), place of residence (urban environment: municipality population ≥ 20,000 inhabitants / rural environment: municipality population <20,000 inhabitants), marital status (married/single), prescribing diagnosis for BZDs, existence and type of comorbidity were analysed.

For easier comparison, all diagnoses for which BZDs were prescribed are grouped as follows: (1) mixed anxiety-depressive disorder; (2) anxiety disorders; (3) depressive disorders; (4) psychotic disorders; (5) other psychiatric disorders (psychiatric diagnoses that do not fit into the first four groups); (6) non-psychiatric disorders. To compare different doses of BZDs, a table of equivalence was used. Equivalent dose (ED) matches the clinical equivalence when a patient is ‘switched’ from one BZD to another, and ED = 1 matches 10 mg diazepam and equivalent doses of other BZDs. Furthermore, for easier comparison, based on their elimination half-lives, BZDs were grouped as: short-acting BZDs (half-life <12 h), intermediate-acting BZDs (half-life 12-24 h) and long-acting BZDs (half-life > 24 h) (Table 1). For significant number of patients, the combination of two different BZDs, from the same or different BZD subgroups, had been prescribed and these patients were put in a separate, fourth category.

Table 1: Duration of action and equivalent doses of BZD

<table>
<thead>
<tr>
<th>Duration of BZD action</th>
<th>INN</th>
<th>ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting (t/2 &lt;12 h)</td>
<td>alprazolam</td>
<td>0.5 mg</td>
</tr>
<tr>
<td></td>
<td>brotizolam</td>
<td>0.25 mg</td>
</tr>
<tr>
<td></td>
<td>midazolam</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>oxazepam</td>
<td>20 mg</td>
</tr>
<tr>
<td>Intermediate-acting (t/2=12-24 h)</td>
<td>bromazepam</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>lorazepam</td>
<td>1 mg</td>
</tr>
<tr>
<td></td>
<td>nitrazepam</td>
<td>10 mg</td>
</tr>
<tr>
<td>Long-acting (t/2 &gt; 24 h)</td>
<td>diazepam</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>clorazepate</td>
<td>15 mg</td>
</tr>
<tr>
<td></td>
<td>flurazepam</td>
<td>20 mg</td>
</tr>
<tr>
<td></td>
<td>clonazepam</td>
<td>20 mg</td>
</tr>
<tr>
<td></td>
<td>medazepam</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>prazepam</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

BZD-benzodiazepine; t/2-half-life; INN-international nonproprietary name; ED-equivalent dose

RESULTS

Total number of prescriptions of all drugs for all years amounted 37,741,591. Number of patients in the database was 1,422,931. Number of prescriptions of BZDs for all years amounted 1,125,632 (2.98% of all prescriptions). That number of prescriptions was prescribed to 151,204 different patients (10.63% of all patients). Socio-demographical differences are shown in Table 2. Two thirds of the patients to whom BZDs had been prescribed were women. Average age of patients was 60, with only 1/10 of patients being younger than 40, and half of the patients aging 41-65. Two thirds of patients were single. Again, two thirds of patients lived in urban areas. Of the sample of 515 patients,
3/4 were non-smokers, while 139 were smokers (26.99%). (Table 2).

Table 2: Socio-demographic characteristics of benzodiazepine users

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52254</td>
<td>52254</td>
</tr>
<tr>
<td>Female</td>
<td>98950</td>
<td>98950</td>
</tr>
<tr>
<td>Age (Mean (SD): 60.46 (15.00))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 40 years</td>
<td>16782</td>
<td>11.10</td>
</tr>
<tr>
<td>41 - 65 years</td>
<td>74731</td>
<td>49.42</td>
</tr>
<tr>
<td>&gt;= 66 years</td>
<td>59691</td>
<td>39.48</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>59781</td>
<td>39.54</td>
</tr>
<tr>
<td>Single</td>
<td>91423</td>
<td>60.46</td>
</tr>
<tr>
<td>Place of residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban areas</td>
<td>105365</td>
<td>69.68</td>
</tr>
<tr>
<td>Rural areas</td>
<td>45839</td>
<td>30.32</td>
</tr>
<tr>
<td>TOTAL</td>
<td>151204</td>
<td>100.00</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>476</td>
<td>73.01</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>139</td>
<td>26.99</td>
</tr>
<tr>
<td>TOTAL</td>
<td>515</td>
<td>100.00</td>
</tr>
</tbody>
</table>

N = number of patients; SD = standard deviation

Half of the patients used BZDs for the recommended 3 months. The other half used them longer; 30% even longer than 10 months, averaging in total 5.5 months. Spearman’s correlation showed that longer use of BZDs occurred in women (r=0.04, p<0.001), elderly (r=0.178, p<0.001), single patients (r=0.12, p<0.001), those who live in urban areas (r=0.45, p<0.001) and those who use higher doses of BZDs (r=0.213, p<0.001). There was no significance in the smoking status of patients (r=0.60, p=0.171).

Average dose per patient amounted 0.88 ED. Two thirds used less than 1 ED, but 5.39% used 2-3 EDs, and 3.37% used a dose higher than 4 EDs. Spearman’s correlation showed that higher dose was associated with men (r=0.81, p<0.001), married patients (r=0.20, p<0.001), younger patients (r=0.55, p<0.001), smokers (r=0.16, p<0.001) and those who live in rural areas (r=0.22, p<0.001).

BZDs were mostly prescribed for anxiety disorders. A significant amount of BZDs was prescribed for non-psychiatric diagnoses. Data related to the diagnosis, dosage and length of use of BZDs are shown in Table 3. Patients suffering from psychotic disorders received highest doses (Kruskal-Wallis test: χ²=7504.63, p<0.001), followed by patients suffering from depressive disorders. Lowest doses were used by patients suffering from non-psychiatric disorders. Patients suffering from psychotic disorders have been taking BZDs for longest periods of time (Kruskal-Wallis test χ²=755.02, p<0.001), followed by patients suffering from depressive disorders. Patients suffering from anxiety disorders have been taking BZD for the shortest periods of time, followed by patients with non-psychiatric disorders. (Table 3).

Table 3: Average dose and length of use of benzodiazepines depending on diagnosis

<table>
<thead>
<tr>
<th>Diagnosis (group)</th>
<th>N</th>
<th>%</th>
<th>ED</th>
<th>Length of use (in months)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anxiety-depressive disorder</td>
<td>1622</td>
<td>10.86</td>
<td>1.25 (1.21)</td>
<td>5.38 (4.32)</td>
</tr>
<tr>
<td>2. Anxiety disorders</td>
<td>45432</td>
<td>30.05</td>
<td>0.97 (0.96)</td>
<td>5.09 (4.33)</td>
</tr>
<tr>
<td>3. Depressive disorders</td>
<td>26516</td>
<td>17.54</td>
<td>1.48 (1.43)</td>
<td>5.93 (4.46)</td>
</tr>
<tr>
<td>4. Psychotic disorders</td>
<td>7925</td>
<td>5.24</td>
<td>1.87 (1.56)</td>
<td>6.86 (4.56)</td>
</tr>
<tr>
<td>5. Other psychiatric disorders</td>
<td>18904</td>
<td>12.50</td>
<td>1.21 (1.21)</td>
<td>5.50 (4.42)</td>
</tr>
<tr>
<td>6. Non-psychiatric disorders</td>
<td>36005</td>
<td>23.81</td>
<td>0.77 (0.73)</td>
<td>5.27 (4.36)</td>
</tr>
</tbody>
</table>

TOTAL: 151204 100.00 1.13 (1.19) 5.46 (4.40)

*Mean (SD); N: number of patients; **ED: approximately equivalent dosage between benzodiazepines, which 1 correspond with 10 mg of diazepam.

Diagnosis had statistical impact on choice of BZDs (χ²=13747.23, p<0.001). Short-acting BZDs were most commonly prescribed for depressive and mixed anxiety-depressive disorders, and least for psychotic and non-psychiatric disorders (Figure 1). Intermediate-acting BZDs were most commonly prescribed for non-psychiatric and anxiety disorders, and least for psychotic disorders. Patients suffering from psychotic disorders, used long-acting BZDs (even more than intermediate-acting), and this was the only group in any category, that did not prefer intermediate-acting BZD. Patients that suffer from depressive and mixed anxiety-depressive disorders more often than other patients used different BZDs. (Figure 1 near here).

Since it was noticed that BZD had been prescribed to a significant percentage of patients based on non-psychiatric diagnosis, further analysis was conducted. Within the non-psych-
The results of this study showed that BZDs were mainly prescribed to women as well as to older patients. Women have been taking BZDs almost twice as often as men, and studies from other countries showed similar results.\(^{18-26}\) BZDs were used mainly by older patients and also for longer time compared to younger patients, which corresponds to studies from abroad that classified BZDs, specifically long-acting BZDs, as top 5 most inappropriately prescribed drugs in the...
elderly.\textsuperscript{18,20,21,25-30} In terms of correlations, there
was a statistically significant negative correlation between the dose of BZD and the age pa-
tients - the older the age, the smaller the daily
dose. This finding is in accordance with global
findings, which also state that older patients use
smaller doses of BZDs, which is logical, based
on the narrow therapeutic width of BZDs in
the elderly population, due to lower creatinine
clearance values, reduced liver functionality,
polypharmacy and interaction with other drugs
and reduced body weight.\textsuperscript{21,25,29,30} When it comes
to marital status, nearly 60% of patients were
single. That coincides with results of published
studies.\textsuperscript{29,31} Our results show that patients from
urban areas tend to use BZDs more often than
those living in rural areas (70\%:30\%). Other
studies comparing incidence of depressive and
anxiety disorders showed that mood disorders
occur more often in patients from urban ar-
as compared to the rural ones.\textsuperscript{32} Also, citizens
of urban areas take BZDs for longer periods of
time.\textsuperscript{33-35} This is somewhat logical taking in con-
sideration faster life style, noise, traffic, air pol-
lution and other factors that citizens of urban
areas are more exposed to.

The percentage of smokers in the examined
sample matched the estimated percentage of
smokers in Republic of Srpska. Data show that
smokers use significantly larger doses of BZDs,
which corresponds the data from the literature.\textsuperscript{25}
Furthermore, this study showed that there were
more smokers among the users of long-act-
ing BZDs. This is probably due to the fact that
smokers are being generally more anxious, with
weaker impulse control, so they need a stronger
and longer-lasting anxiolytic effect.\textsuperscript{36,37}

Based on the diagnosis, use of BZDs is expected-
ly high in patients with anxiety and depressive
diseases, but unusually high (23.8\%) in pa-
tients with non-psychiatric disorders. Some re-
gional studies show a high trend of prescribing
BZDs to hypertensive patients, but it is known
from primary care practice that the trend exists
in other non-psychiatric disorders (low back
pain, diabetes, myalgia, headache), as was con-
firmed by our findings.\textsuperscript{38,39} One of the reasons
for such a high percentage of prescribed BZDs
for non-psychiatric disorders could also be the
lack of care by family medicine physicians when
it comes to making a diagnosis. Doctors may
have thought that anxiety of the patient makes
the primary disease worse, but they did not find
it necessary to introduce officially into patient’s
record the diagnosis of anxiety or mixed mood
disorder. Prescription of BZDs in mentioned
indications is justified, but length of their use
in these indications is troubling. For example,
BZDs have been used for such a long time for low
back pain and for anxiety-depressive disorders.
Evidently, prolonged usage, or abuse, of BZDs is
equally present regardless of the diagnosis.

Short-acting BZDs were most often prescribed
to patients suffering from depressive and mixed
anxio-depressive disorders, which is logical
when taking in consideration that they have the
fastest onset of therapeutic effect, and patients
take them to control acute anxiety attacks. It
would be logical that they are prescribed most
frequently in patients with anxiety disorders
as well, however intermediate-acting BZDs are
most frequently prescribed in these disorders.
Long-acting BZDs are most often prescribed in
patients with psychotic disorders. Reason for
this is probably that the agitated psychotic pa-
tient needs to be sedated for the longest period
possible.

When comparing the dose and the length of use
with diagnosis, it was apparent that patients with
anxiety and psychotic disorders are prescribed
with both highest doses and for the longest peri-
od of time, whereas patients with non-psychiat-
ric disorders receive the smallest doses. Prescrip-
tion of BZDs to patients with psychotic disorders
is not in accordance with guidelines, especially
during longer period of time. However, prescrip-
tion of BZDs to patients suffering from schizo-
phrenia is only justified for acute treatment of
agitated patients. Same patients use BZDs for
the longest periods of time, and use long-acting
BZDs the most often. Patients suffering from
psychotic disorders fit the only group that takes
long-acting BZD more often compared to inter-
mediate-acting ones. Length of use of BZDs in
patients with psychotic disorders is totally op-
posite from the guidelines. Possible reasons are
fear and prejudice of doctors towards these pa-
tients, and the need to calm these patients down,
even though the stabilisation of mood in these
patients is not achieved with use of BZDs. Larg-
er doses in patients with depressive disorders
would be justified if the length of use was short-
er. In all new depressive episodes, along with an
antidepressant an anxiolytic is also introduced,
but it is recommended that the dose should start
to decrease after three weeks until complete dis-
continuation of its use. Taken in consideration
that this was not the case in these results, this
is an example of poor prescribing practice. Both
shortest length of use and smallest dose of BZDs
were prescribed to patients with non-psychiat-
ric disorders, which is logical given that these
are usually temporary conditions. High blood
pressure episode in acute stress reaction (which
should be treated with anxiolytics) is often mis-
categorised as hypertension, rather than a psy-
chiatric disorder. Worldwide studies showed
that patients with sleeping disorders, dementia
and depression use BZDs for longest time peri-
dods.\textsuperscript{39,40}

Existence and type of comorbidity had no effect
on length of use of BZDs, which is somewhat log-
cal, considering that primary diagnosis should
be a reason for shorter or longer length of use, not
a comorbidity. Patients without comorbidities
tested those with comorbidities used higher doses, which is justified.\textsuperscript{39} However, fur-
ther analysis showed that lower dose was pre-
scribed only to patients that suffer from cardio-
vascular diseases, including hypertension, and
other diseases were not taken into consideration.
Lack of reduction of the BZD dose, especially in
patients who had more than three chronic dis-

cases and used more than five different drugs
every day is highly alarming. Unfortunately, this
is also an example of poor prescribing practice,
considering that interactions among drugs in
polypharmacy is very often. Family doctor, as a
physician able to see the entire medical history
of a patient, must take a responsibility, if neces-
sary, for reduction of dose if psychiatrist, or
other specialist, overlooked polypharmacy.\textsuperscript{41,42}

In conclusion, a significant percentage of pa-
tients were using the BZDs for a longer time pe-
riod than recommended. Strongest positive cor-
relation was found between dose and longer use,
which implies addictive potential of BZDs. Since
it has been noticed that prolonged use, or abuse
is present regarding the diagnosis, precaution is
advised when prescribing BZDs even for acute
diseases.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

None.

REFERENCES

1. Roy-Byrne PP. The GABA-benzodiazepine receptor
complex: structure, function, and role in anxiety. J
2. Winkler A, Auer C, Doering BK, Rief W. Drug treat-
ment of primary insomnia: a meta-analysis of polyso-

mographic randomized controlled trials. CNS Drugs
2014 Sep;28(9):799-816.
3. Lindqvist O, Lundquist G, Dickman A, Bükki J, Lunder
U, Hagelin CL, et al. Four essential drugs need-
ed for quality care of the dying: a Delphi-study based
international expert consensus opinion. J Palliat Med
4. Benzodiazepine Committee. Benzodiazepines: good
practice guidelines for clinicians [Internet]. Dublin:
Department of Health and Children; 2002 [cited 2015
.ie/5349/
5. The Royal Australian College of General Practitioners.
Prescribing drugs of dependence in general practice,
Part B – benzodiazepines [Internet]. Victoria (AU):
The Royal Australian College of General Practitioners;
drugsandalcohol.ie/24380/
6. Kurko TA, Saastamoinen LH, Tahkapaa S, Tuulio-Hen-
use of benzodiazepines: definitions, prevalence and
usage patterns – a systematic review of register-based
7. Lader M. Benzodiazepine harm: how can it be re-
8. Jones JD, Mogali S, Comer SD. Polydrug abuse: a re-
view of opioid and benzodiazepine combination use.
Sturkenboom MC, et al. Inappropriate benzodiazepine
use in older adults and the risk of fracture. Br J Clin
Medications associated with falls in older people: sys-
tematic review of publications from a recent 5-year pe-
11. Palmaro A, Dupouy J, Lapeyre-Mestre M. Benzodiaz-
epines and risk of death: Results from two large cohort
studies in France and UK. Eur Neuropsychopharmacol
12. Zhong G, Wang Y, Zhang Y, Zhao Y. Association be-
tween benzodiazepine use and dementia: a meta-anal-
S. Benzodiazepines for schizophrenia. Cochrane Data-


