

IMPACT OF DIFFERENCES IN ECONOMIC DEVELOPMENT AND SOCIOECONOMIC STABILITY ON BENZODIAZEPINE EXPOSURE BETWEEN THE THREE BALKANS COUNTRIES

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SUMMARY

Introduction: Anxiety disorders are among the most common mental disorders. Benzodiazepines belong to the group of anxiolytic sedatives and the most prescribed drugs in the world. The aim in our study was to evaluate the differences in the exposure of the population to benzodiazepines (in period from 2014-2018) between Serbia, Slovenia and Croatia, the three countries of the Southwestern Balkans with varying degrees of socioeconomic development.

Study design: A academic investigator initiated, pharmacoepidemiological difference-in-difference time series analysis of population exposure to benzodiazepines between the three, geographically close Balkans countries (Slovenia, Serbia, Croatia) with varying degrees of socioeconomic development has been carried out. Study was conducted as academic investigator initiated, in a retrospective manner on monthly basis international data set from January 2014 to December 2018.

Results: At the annual level, during the study period from January 2014 to December 2018, compared to Slovenia, Serbia and Croatia had higher DIDs, from 5 fold (Croatia) to 6 fold (Serbia), for all benzodiazepines in total. By analyzing the differences-in-difference, we have shown that influence of both time (month) and country on DIDs is significant as well as their mutual interaction (the country × month) for all benzodiazepines in total.

Conclusion: Serbia and Croatia must implement explicit measures of reducing benzodiazepine prescription in health primary care based on evidence-based recommendations in the indications where general medicine practitioners/family doctors most commonly prescribe these medicines. Without providing a realistic supplement/alternative to benzodiazepines such as increasing the availability of psychotherapy and improving the structure of psychiatric professionals in healthcare settings, implicit measures are not recommended for reducing prescription, implementing accountability measures for prolonged prescription of benzodiazepines, and in particular for "masked" somatic diseases. All this comes to the fore by raising economic development and socioeconomic stability.

Key words: benzodiazepines – anxiety - socioeconomic stability - psychiatrists

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INTRODUCTION

Anxiety disorders are among the most common mental disorders. They are characterized by inappropriate anxiety, panic and fear and related behaviors such as avoidant behavior. At least 25% of people meet the diagnostic criteria for some of their anxiety disorders during their lifetime. The incidence of anxiety disorders is higher than the incidence of mood disorders. Anxiety disorders are differentiated by the type of situations and objects that cause anxiety, fear, panic or avoidant behavior and associated way of thinking. However, patients often exhibit criteria for two or more anxiety disorders

at the same time, so mutual comorbidity of anxiety disorders is a relatively common phenomenon (Jakovljević 2015, Goldstein-Piekarski et al. 2016). Also, anxiety conditions exhibit frequent comorbidity with other mental disorders such as affective disorders (Wu et al. 2013), psychosomatic disorders (Bekhuis et al. 2015), addiction illness (Alegria et al. 2010), and psychosis (Kiran & Chaudhury 2016, Dernovsek & Sprah 2009).

Benzodiazepines belong to the group of anxiolytic sedatives and the most prescribed drugs in the world (Guina & Merrill 2018).

When Sterbach synthesized the first benzodiazepine chlordiazepoxide in 1955, it was thought to be an inert

substance. Two years later, during the routine preparation of the laboratory, several hundred milligrams of this substance were taken for testing and an unexpected sedative and muscle relaxant effect was detected. Since then, over 300 benzodiazepines have been synthesized and over 40 are in clinical use in various parts of the world (Sternabch 1979). Discovery was followed by the rapid development of other benzodiazepines, where these drugs initially replaced the hypnotics/sedatives used at that time and then became 'small tranquilizers' in the 1970s, replacing other commonly used drugs at that time, especially drugs such as barbiturates and meprobamate. Compared to barbiturates, benzodiazepines have been shown to have a ten-fold larger range between therapeutic and toxic doses, less frequently adverse effects, and less frequent occurrence of overdose and abuse (Wesson et al. 2008, Ashton 2005). For these reasons, many prescribers considered that benzodiazepines did not carry significant risk and that they did not cause addiction, so they were prescribed without any time limit in various situations: for the treatment of anxiety and/or insomnia, in cases of discontinuation of other drugs, for the treatment of neuroses, epilepsy, psychosis, depression, in anesthesia, but also for the treatment of cardiac arrhythmias and myocardial infarction (Guina & Merril 2018, Wesson et al. 2008, Rickels 1978, Barker et al. 2004, Micheline et al. 1996). However, it was not until 1980 that the first reports from controlled randomized studies indicated that long-term benzodiazepines could create dependence addiction (Ashton 2005), along with an increase in the number of such reports, followed by the popularization of cognitive-behavioral therapy and the demonstration of strong anxiolytic action of drugs by similar selective serotonin uptake inhibitors. Thus, 1970 benzodiazepines were the most prescribed drugs in the world and their prescribing would decline slightly in the mid-1980s, mainly due to a decrease in their use for insomnia (Pary & Lewis 2008). Despite explicit recommendations that benzodiazepines should be administered for a shorter period (2–4 weeks) due to the possibility of addiction, the increase in benzodiazepine administration from 2009–2014 is mainly due to continued benzodiazepine prescribing to patients for a longer period of time, which could be measured for months, even for years (Kaufmann et al. 2018). In some developed countries, it has been reported that over 90% of patients with post-traumatic stress syndrome received benzodiazepine supplies within one month of use, while about 30% received quarterly supplies of these drugs (Lund et al. 2012, Lund et al. 2013). Recent evidence-based recommendations, indicate that psychotherapy involving a variety of behavioral techniques, alone or in combination with selective or non-selective serotonin reuptake inhibitors, is the first line of therapy for anxiety disorders. However, only in individual cases, when a treatment revision was made, the question was raised

whether these recommendations were indeed a realistic alternative to benzodiazepines, which is only recommended when the first-line therapy failed. This issue is essential, given the insufficient availability and with the open question of satisfactory effectiveness of psychotherapy treatment for patients with both anxiety and other mental disorders (Guina & Merrill 2018). Worldwide research on prescribing, published back in 1974, demonstrated that 5 to 15% of the population of developed countries had used benzodiazepines in one period during the year (Butler et al. 1974). In order to provide physicians and the professional community with accurate information about the cost/ benefit of using benzodiazepine, the World Health Organization launched multicenter studies, placing physicians' views first (Kastratović 1994). Researchers objectified results through the use of modern statistical methods in pharmacotherapy (Marković et al. 2019), physicians are exchanging and improving their work through academic networks in Europe (Marković et al. 2015), which is the tangible reality of evidence-based medicine.

From the global geopolitical and economic point of view, the period from 2009 to the present is characterized by: consequences of the global economic crisis 2008, consequences of previous or current war and devastation in individual countries, process of globalization, population migration, turbulent geopolitical and economic events around the world, inability to implement a good clinical guidelines in particular health systems due to the lack of specific profiles of clinical specialists and/or equipment in healthcare institutions and ad hoc forced to give preference to certain administrations to economic restrictions over economic reforms with consequent disregard for the quality of health care, both by healthcare providers and themselves health professionals (Jakovljević et al. 2016, Vuković & Jakovljević 2015). All those together have contributed more to generating new ones than to solving old problems in healthcare systems. The possibility of long-term planning and undertaking meaningful activities by health insurance providers to improve the treatment of mental and/or physical disorders, including the treatment of anxiety disorders, is commensurate with the economic and political power of countries, but also with their cultural adaptability to cope with and overcome their growing contextual or global barriers to enhancing healthcare. The latter, of course, involves prioritizing the analysis, consideration and strategic planning of benzodiazepine (otherwise cheap medicines) prescribing policies, especially in countries that have been experiencing complex social, political and economic hardships or recessions for long time. Specifically, countries in recession due to the accumulation of social and other problems are at risk of increasing the incidence of anxiety disorders in the population, especially employees (Avcin et al. 2011, Sargent et al. 2011, Evans-Lacko et al. 2013).

In view of the foregoing, the Aim in our study was to evaluate the differences in the exposure of the population to benzodiazepines (in period from 2014–2018) between Serbia, Slovenia and Croatia, the three countries of the Southwestern Balkans with varying degrees of socioeconomic development.

METHODS

Study design

A pharmacoepidemiological difference-in-difference time series analysis of population exposure to benzodiazepines between the three, geographically close Balkans countries with varying degrees of socioeconomic development has been carried out. Study was conducted as academic investigator initiated, in a retrospective manner on monthly basis international data set from January 2014 to December 2018.

Characteristics of countries

Data for population exposure to benzodiazepines were collected and processed for Slovenia, Croatia and Serbia. These three countries are now separate Balkans states. Until the breakup of Yugoslavia in 1991, they coexisted together with three other federal units (Macedonia, Montenegro and Bosnia and Herzegovina), within Yugoslav federation.

In 2017, Slovenia had one of the highest per capita GDPs (\$34,100) in Central Europe with real GDP growth rate of 4%, and with unemployment rate of 6.8%, despite having suffered a protracted recession in the 2008-09 in the wake of the global financial crisis. Since 1991, Slovenia has been an independent state that left Yugoslavia without significant conflicts and in 2004 became a member of the European Union. Slovenia is characterized as one of the most stable political transitions in Central and Southeast Europe. (IndexMundi Slovenia, The Worldfact book Slovenia)

Though still one of the wealthiest of the former Yugoslav republics, Croatia's economy suffered badly during the 1991-95 war. The country's output during that time collapsed and Croatia missed the early waves of investment in Central and East Europe that followed the fall of the Berlin Wall. Between 2000 and 2007, Croatia's economy began to improve. Croatia experienced an abrupt slowdown in the economy in 2008 and has been slowly recovering ever since. In 2013 Croatia joined the EU, following a decade-long application process. In 2017, Croatia's GDP was \$24,100 per capita with real growth rate of 2.9% and with unemployment rate of 13.9% (IndexMundi Croatia, The World Factbook Croatia).

In Serbia, the period from 1991 to 2000 is characterized by mismanagement of the economy, an extended period of international economic sanctions, civil war,

and the damage to Serbia's infrastructure and industry during the NATO airstrikes in 1999, leaving the economy worse off than it was in 1990. In the period from 2001 to 2008, high unemployment and stagnant household incomes are ongoing political and economic problems, so that in the next five years and due to the onset of the global economic crisis, Serbia is threatened with bankruptcy. Serbia has been slowly implementing structural economic reforms to ensure the country's long-term prosperity. Serbia has opened accession negotiations with the European Union since 2013. In 2017, Serbia's GDP was \$15,200 per capita with real growth rate of 3% and with unemployment rate of 16% (IndexMundi Serbia, The World Factbook Serbia).

Data

Data on benzodiazepines sold in each country (Serbia, Croatia and Slovenia) were obtained from the IQIA Institute for Human Data Science (IQIA). On a monthly basis, in mentioned data were included: the type of active ingredient, the amount of active ingredient, unit (packs-bottles) and the number of pharmaceutical forms per pack unit. All calculations carried out to measure exposure to benzodiazepines were performed on the basis of the recommended defined daily doses (DDD) according to the ATC/DDD methodology of the WHO Collaborating Center for Drug Statistics Methodology (ATC code: N05BA) (WHO).

Consumption of all medicines by their generic ingredients is transposed as a defined daily dose per 1000 inhabitants per day (DID) according to the following formula:

$$DID = \frac{U \times PF \times Q \times 1000}{DDD \times \text{inhabitants} \times \text{number of days in each month}}$$

where are

U – units (packs/bottles),

PF – number of pharmaceutical forms per unit,

Q – amount of active ingredient in each pharmaceutical form,

DID is used to measure the daily exposure of the population to a particular drug.

Data on the number of inhabitants for Serbia and Slovenia are taken as publicly available from the sites of their domicile statistical offices (Statistical office of the Republic of Serbia, Statistical office of the Republic of Slovenia), while these data for Croatia is taken as EUROSTAT resource (European Commission, Eurostat Database).

Data analysis

A difference-in-difference analysis was conducted where the dependent variables were considered as DIDs for each benzodiazepines anxiolytic, the same as DIDs for all benzodiazepines in total. A difference-in-

difference analysis was based on multiple linear regression analyses with a constant, in order to test the significance of dependent variables correlation with time (month), then with the country factor, as well as the country × month interaction. The data on annually basis are described by the arithmetic mean and standard deviation. The accepted level of significance was set at 0.05. The statistical analysis was conducted using IBM SPSS 20 (NY).

RESULTS

At the annual level, during the study period from January 2014 to December 2018, compared to Slovenia, Serbia and Croatia had higher DIDs, from 5 fold (Croatia) to 6 fold (Serbia), for all benzodiazepines in

total (Table 1). By analyzing the differences-in-difference, we have shown that influence of both time (month) and country on DIDs is significant as well as their mutual interaction (the country × month) for all benzodiazepines in total (Table 2 and Figure 1).

In the differences-in-difference analysis, a significant association was found with the difference in diazepam exposure between months, as well as with the difference between countries, but no correlation with the trend differences between countries was found (Table 2 and Figure 1). Croatia had the highest population exposure to diazepam during the study period with upward trend, followed by Serbia with slightly lower values and with upward trend also while Slovenia had a low level of DIDs for diazepam with downward trend compared to the previous two countries.

Table 1. Comparative presentation of descriptive statistics on annual basis for benzodiazepines defined daily doses per 1000 inhabitants per day between Serbia, Croatia and Slovenia

		Serbia Mean ± SD	Croatia Mean ± SD	Slovenia Mean ± SD
DIDs for diazepam	2014	19.12±2.34	35.94±5.59	3.63±0.25
	2015	22.05±4.06	36.07±7.79	3.40±0.23
	2016	23.13±4.70	37.83±6.98	3.18±0.19
	2017	31.25±15.91	38.80±6.41	3.01±0.18
	2018	24.82±5.82	38.60±5.16	2.71±0.15
DIDs for bromazepam	2014	30.83±2.66	3.03±0.25	3.28±0.20
	2015	32.11±5.49	2.96±0.42	3.11±0.19
	2016	31.93±6.42	2.88±0.31	2.85±0.24
	2017	33.77±3.90	2.84±0.26	2.65±0.22
	2018	33.31±3.81	2.85±0.28	2.49±0.09
DIDs for prazepam	2014	0.72±0.16	/	6.46±0.52
	2015	0.65±0.09	/	6.21±0.38
	2016	0.65±0.13	/	5.85±0.36
	2017	0.42±0.43	/	5.41±0.60
	2018	0.43±0.06	/	5.04±0.23
DIDs for alprazolam	2014	9.98±1.84	26.43±2.94	1.01±0.15
	2015	12.72±2.04	25.99±3.96	1.11±0.09
	2016	14.20±3.55	26.72±4.17	1.17±0.11
	2017	20.83±7.59	27.16±2.28	3.16±1.29
	2018	22.11±6.55	27.47±2.82	4.03±0.13
DIDs for lorazepam	2014	21.55±2.13	5.24±0.80	0.26±0.01
	2015	23.14±3.42	5.18±1.70	0.27±0.02
	2016	23.17±3.97	5.10±0.56	0.27±0.01
	2017	25.42±3.36	5.16±0.57	0.28±0.02
	2018	25.77±2.95	5.24±0.64	0.28±0.04
DIDs for oxazepam	2014	/	5.98±1.48	0.07±0.01
	2015	/	5.61±2.35	0.02±0.01
	2016	/	5.22±0.68	0.06±0.01
	2017	/	5.41±0.59	0.05±0.01
	2018	0.002±0.002	5.28±0.59	0.04±0.01
DIDs for all benzodiazepines	2014	82.27±6.74	76.64±8.29	14.87±1.00
	2015	90.71±10.12	75.83±13.88	14.31±0.87
	2016	93.10±16.01	77.77±10.59	13.52±0.84
	2017	111.71±28.61	79.40±6.95	14.70±1.39
	2018	106.45±15.29	79.45±5.51	14.72±0.50

SD – standard deviation; DIDs – defined daily doses per 1000 inhabitants per day

Table 2. Regression parameters in prediction of benzodiazepines defined daily doses per 1000 inhabitants per day between Serbia, Croatia and Slovenia in difference-in-difference analyses

Dependent Variable: DIDs for all benzodiazepines								
Model 1	B	SE	Beta	t	p	95.0% Confidence Interval for B		R ²
						Lower Bound	Upper Bound	
Constant	119.223	6.117		19.491	0.000	107.152	131.295	0.836
Month	0.860	0.174	0.398	4.932	0.000	0.516	1.204	
Country	-31.712	2.832	-0.693	-11.200	0.000	-37.300	-26.124	
Month × Country	-0.311	0.081	-0.374	-3.858	0.000	-0.471	-0.152	
Dependent Variable: DIDs for diazepam								
Model 2	B	SE	Beta	t	p	95.0% Confidence Interval for B		R ²
						Lower Bound	Upper Bound	
Constant	33.405	5.121		6.524	0.000	23.299	43.511	0.324
Month	0.297	0.146	0.333	2.033	0.044	0.009	0.585	
Country	-7.166	2.370	-0.379	-3.023	0.003	-11.844	-2.488	
Month × Country	-0.107	0.068	-0.313	-1.590	0.114	-0.241	0.026	
Dependent Variable: DIDs for bromazepam								
Model 3	B	SE	Beta	t	p	95.0% Confidence Interval for B		R ²
						Lower Bound	Upper Bound	
Constant	39.688	2.993		13.258	0.000	33.780	45.595	0.726
Month	0.084	0.085	0.102	0.981	0.328	-0.085	0.252	
Country	-13.659	1.386	-0.788	-9.857	0.000	-16.394	-10.924	
Month × Country	-0.036	0.040	-0.114	-0.910	0.364	-0.114	0.042	
Dependent Variable: DIDs for alprazolam								
Model 4	B	SE	Beta	t	p	95.0% Confidence Interval for B		R ²
						Lower Bound	Upper Bound	
Constant	13.904	3.301		4.213	0.000	7.390	20.418	0.271
Month	0.408	0.094	0.738	4.336	0.000	0.222	0.594	
Country	-0.304	1.528	-0.026	-0.199	0.843	-3.319	2.712	
Month × Country	-0.157	0.044	-0.736	-3.600	0.000	-0.243	-0.071	
Dependent Variable: DIDs for lorazepam								
Model 5	B	SE	Beta	t	p	95.0% Confidence Interval for B		R ²
						Lower Bound	Upper Bound	
Constant	29.515	1.684		17.530	0.000	26.193	32.838	0.821
Month	0.084	0.048	0.148	1.754	0.081	-0.011	0.179	
Country	-10.414	0.779	-0.864	-13.362	0.000	-11.952	-8.876	
Month × Country	-0.015	0.022	-0.066	-0.654	0.514	-0.058	0.029	
Dependent Variable: DIDs for oxazepam								
Model	B	SE	Beta	t	p	95.0% Confidence Interval for B		R ²
						Lower Bound	Upper Bound	
Constant	1.841	1.080		1.704	0.090	-0.291	3.974	0.030
Month	-0.003	0.031	-0.018	-0.090	0.928	-0.064	0.058	
Country	0.072	0.500	0.022	0.145	0.885	-0.915	1.059	
Month × Country	0.000	0.014	-0.007	-0.031	0.976	-0.029	0.028	

SE – standard error; DIDs – defined daily doses per 1000 inhabitants per day

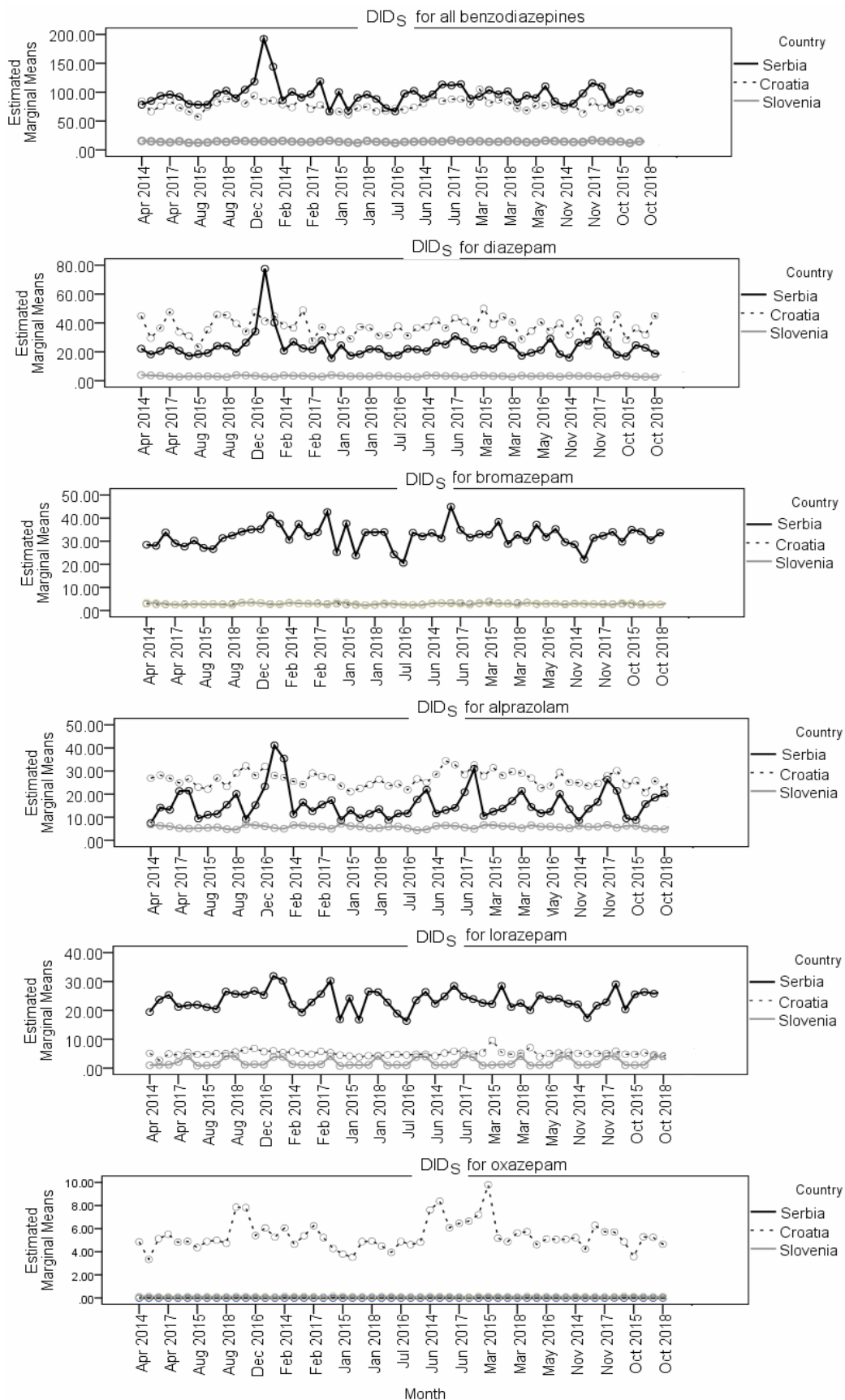


Figure 1. Times series for benzodiazepines defined daily doses per 1000 inhabitants per day between Serbia, Croatia and Slovenia (January 2014 - December 2018)

With respect to DIDs for bromazepam, no association was found with the difference in months or with the difference in trend between countries, but an association with the difference in population exposure of bromazepam between countries was found (Table 2 and Figure 1). Serbia consistently had approximately ten times the DID for bromazepam over Slovenia and Croatia throughout the study period (Table 1, Table 2 and Figure 1).

In the differences-in-difference analysis of DIDs for alprazolam, the influence of the difference in trend between countries as well as the difference between months was shown, but no correlation was found with the difference in DIDs for alprazolam between countries. Although Croatia consistently had steady highest DIDs for alprazolam, Serbia showed a high upward trend in population exposure to alprazolam, while these values were low in case of Slovenia, but with a significant upward trend in 2017 and 2018 (Table 1, Table 2 and Figure 1).

By analyzing the differences-in-difference we have shown that there are no significant correlation with time (month) and interaction (the country \times month) on DIDs for lorazepam (Table 2 and Figure 1), but the significant impact of differences between countries has been shown. Serbia had permanently about five times the value of DIDs compared to Croatia, while Slovenia had minor values ?? of DIDs for lorazepam throughout the study period (Figure 1 and Table 1).

No association of DIDs was found for oxazepam in the differences-in-difference analysis, and it was also shown that the obtained regression model was not linear since the constant was not significant in the model (Table 2). Unlike Croatia and Slovenia, Serbia did not have population exposure to oxazepam at all in the first four years of the study period, unlike Croatia and Slovenia, which had low DIDs for oxazepam throughout the study period (Table 1 and Figure 2).

DISCUSSION

By the difference-in-difference analysis, we showed a significant negative correlation of population exposure to benzodiazepine anxiolytics with increasing level of socioeconomic development and country stability, which is reflected in the negative regression coefficients for the country predictor in the explained dependent variable DIDs for all benzodiazepines (Model 1 in Table 2), so that Serbia has the highest DIDs values was an economically underdeveloped country with high economic instability, followed by Croatia with medium economic development and economic instability, while Slovenia has the least DIDs values was an economically well developed country with a high degree of economic stability. There are also differences in the monthly trend of DIDs between countries for all benzodiazepines

(Model 1 in Table 2), which also correlates negatively with the level of socioeconomic development and stability of the country, where Serbia has the steepest upward trend of DIDs for all benzodiazepines, Croatia has a slightly lower trend while Slovenia practically does not change DIDs for all benzodiazepines from month to month throughout the study period (Figure 1). These results can be explained from the point of view of already proven positive correlations of anxiety disorder incidence with socioeconomic instability and recession (Avcin et al. 2011, Sargent et al. 2011, Evans-Lacko et al. 2013), but also from the point of view of differences in benzodiazepine and /or other prescribing policies, which may also be related to differences in economic stability between observed countries. As the aforementioned points of view may seem to be independent of one another or as two different options in explaining the results obtained, we will expose the following scenarios: (1) recession or prolonged economic instability, which is primarily reflected in the unemployment rate of the country's population (Serbia and Croatia), is increasingly producing anxiety of the working age population (among employees because of the possibility of losing his job and among unemployed because of socioeconomic endangerment) leads to an increase in the incidence of anxiety disorders in the population with consequently greater prescribing of benzodiazepine anxiolytics (Karanikolos et al. 2013); (2) in conditions of recession or economic instability (Serbia and Croatia) the prescribing policy of benzodiazepines is based on implicit economic impacts (resource allocation decisions come from the microeconomic level due to the forced "ad hoc" reaction of healthcare insurance provider to direct the decision to allocate resources to a prescriber who, due to lack of resources, chooses the most affordable ("cheapest") therapeutic alternative without considering the consequences of such a decision on all potential therapeutic outcomes (Strech et al. 2009) and (3) under conditions of economic development and stability (Slovenia) the prescribing policy of benzodiazepine anxiolytics is based on explicit economic impacts (the healthcare provider allocates resources, which is projected from a macroeconomic or mesoeconomic level over a long time period (10-12 years), systematically providing all necessary resources to the prescriber select the therapeutic alternative that is evidence-based producing the most favorable outcomes (Eccles & Mason 2001).

It is well known that primary health care is responsible for majority inadequately prescribed benzodiazepines, where benzodiazepines are prescribed for a long time in the treatment of chronic insomnia, as well as in elderly people who use a large number of medications, which are administered for long periods without prior recommendation of a psychiatrist, that is. without a psychiatric diagnosis (Guina & Merrill 2018). In such cases, when patients with long-term administration of

benzodiazepine are finally referred to a psychiatrist, they are expected to assume responsibility for the previously prescribed primary care physician therapy. Differences in the policy of prescribing benzodiazepine anxiolytics between Croatia and Serbia comparing to Slovenia are observed precisely at the level of primary health care, in terms of the regulation defining the possibility of re-prescribing benzodiazepines by the chosen doctor. Namely, a doctor in the primary care in Slovenia does not have the option of prescribing these medicines repeatedly, while in Croatia and Serbia such an option exists, while providing the patient with a stockpile for up to 30 days per prescription (Official Gazette of Republic of Serbia 2018 & 2019; Official Gazette of Republic of Croatia 2013, 2014, 2015, 2016; Official Gazette of the Republic of Slovenia 2008, 2010, 2012). It is clearly observed that already at the level of primary protection, prescribing regulations in Serbia and Croatia allow the use of benzodiazepines for a longer period than recommended (no longer than 2-4 weeks). On the other hand, the health insurance provider in Slovenia does not leave the option for the primary care physician to repeat the prescription of the benzodiazepine anxiolytic for the same patient without the consent of a psychiatrist. The above facts support our view that, in addition to the potential increase in the incidence of anxiety conditions in Serbia and Croatia due to their socioeconomic instability, large population exposure to all benzodiazepines together is the result of inadequate prescribing policies. Prescribing policies in Serbia and Croatia allow the long-term administration of these drugs with the consequent creation of benzodiazepine dependence. Abrupt discontinuation of these sedatives / hypnotics, which can be created even after one week of administration, leads to a relapse and exacerbation of previous symptoms and the potential development of recurrent anxiety. This may be just another cause of an increase in the incidence of anxiety conditions in Serbia and Croatia, especially in individuals who are prescribed a benzodiazepine anxiolytic without a psychiatric diagnosis (non-psychiatric prescription).

Long-term administration of benzodiazepines also carries other risks depending on their pharmacokinetic profile and half-elimination time, that is, their liposolubility and generation of active metabolites. Thus, benzodiazepines with short elimination half-lives and shorter duration of action (alprazolam, lorazepam, and oxazepam) are less likely to result in adverse effects due to drug retention than long-acting benzodiazepines, while longer-acting benzodiazepines (diazepam, bromazepam). Symptoms characteristic of the absence of action (similar to the abrupt discontinuation of benzodiazepines) (Uzun et al. 2010). In our study, regarding the consideration of potential risks of side effects in the elderly due to the retention of benzodiazepines, we

found that in Serbia there is a reason for concern about high DID values for bromazepam and diazepam, whereas Croatia in this regard should share concern with Serbia about very high DID values for diazepam. Medical practice and prescribing lessons on benzodiazepines are always insufficient, although they have been implemented for decades. (Lader 2011)

Attempt to resolve the situation by applying the Guidelines in Denmark, one of the most developed and stable countries, has proved ineffective (Bjerrum et al. 2002).

However, as part of an "anti-benzodiazepine campaign" in France, attempts have been made to curb the prescribing of benzodiazepines in primary care in order to shift the prescription of long-acting benzodiazepines to the elderly who have undergone long-term benzodiazepine therapy, for a prescription of short-acting benzodiazepines (Rat et al. 2014). Unfortunately, over the following few years, there has been no decrease in overall benzodiazepine prescription, rather an increase in the number of prescriptions for short-acting benzodiazepines, their long-term use has increased, although long-term benzodiazepine prescription has been significantly reduced. Interestingly, huge funds were invested in a campaign to carry out a range of activities that included the distribution of appropriate guidelines with evidence-based recommendations on the use of benzodiazepines to primary care physicians. The French "pay-to-performance" project has even provided significant cash benefits to primary care physicians in order to reduce their overall benzodiazepine prescription. Bearing in mind the French experience, it must be noted that the measures taken in the "anti-benzodiazepine campaign" were ad hoc and had an implicit impact. Although an economically developed country, France did not strategically plan its resources by redistributing them over the long term, thus creating a realistic alternative to benzodiazepines, increasing the availability of psychiatric examinations to patients with anxiety to adequately manage their mental state with psychotherapy support. Therefore, we cannot propose to Serbia and Croatia similar, ad hoc planned, implicit-impact interventions, such as the "anti-benzodiazepine campaign" in France, in order to solve their problems related to the prescription of benzodiazepine anxiolytics. On the contrary, Serbia and Croatia should provide resources as soon as possible in order to improve the structure of psychiatrists and psychotherapists in their healthcare facilities, both at primary and secondary level. The necessity of such an action can be seen from the population exposure to total benzodiazepines in these countries, which indicate that in 2018 one in ten resident of Serbia and one in twelve resident of Croatia was exposed daily to one DDD of benzodiazepines. On the other hand, treating benzodiazepine addiction is an extremely complex and time-consuming job even for

psychiatrists specialists in the field of addiction therapy (Mugunthan et al. 2011, Denis et al. 2006). As a result of the comparison of benzodiazepine consumption, the authors suggest that Serbia and Croatia should just follow the strategic management of benzodiazepine consumption in Slovenia (Subelj 2010). First, Slovenia conducted quantitative studies of prescribing benzodiazepines in primary care where the highest consumption comes from, and then conducted studies aimed at informing the attitudes of family physicians about their own positive and negative experiences with benzodiazepine administration. Slovenia also measured the level of compliance, but also identified barriers to implementation of evidence-based recommendations for therapeutic procedures in psychiatric disorders, where benzodiazepines were most commonly prescribed by family physicians / GPs in the past. Specifically, the most prominent barrier was insufficient number of psychiatrists dealing with psychiatric disorders for which GPs prescribe benzodiazepines, in addition to often pronounced resistance to change of therapy in patients on long-term benzodiazepine therapy. The premise in the successful management of benzodiazepine administration should be the fact that sustained anxiety can be a symptom of serious psychiatric illnesses as well as serious somatic illnesses in the undiagnosed stage (CVD, malignancy). Only after gaining experience from similar studies and in line with their own resources, Serbia and Croatia should take appropriate explicit measures to gradually reduce population exposure to benzodiazepines.

CONCLUSION

In terms of curbing benzodiazepine prescription due to extremely high population exposure to benzodiazepines in 2014-2018, Serbia and Croatia should do what Slovenia did in this regard over the past decade, which resulted in low population exposure to benzodiazepines in 2014 - 2018. Serbia and Croatia must implement explicit measures of reducing benzodiazepine prescription in primary care based on evidence-based recommendations in the indications where general medicine practitioners / family doctors most commonly prescribe these medicines. Without providing a realistic supplement/alternative to benzodiazepines such as increasing the availability of psychotherapy and improving the structure of psychiatric professionals in healthcare settings, implicit measures are not recommended for reducing prescription, implementing accountability measures for prolonged prescription of benzodiazepines, and in particular for "masked" somatic diseases. All these come to the fore by raising economic development and socioeconomic stability.

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Contribution of individual authors:

Srdjan Z. Marković: idea for research, designed of the study, analyzing the results, literature analyses, drafting the paper.

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Mira H. Vuković: statistical analyses, interpretation of data, drafting the paper.

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