Benzodiazepine consumption in three Balkan countries

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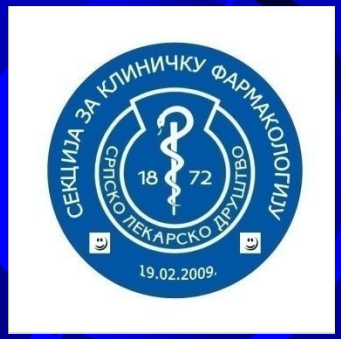


-Anxiety disorders are among the most common mental disorders
-They are characterized by inappropriate anxiety, panic and fear and related behaviors such as avoidant behavior.
-At least 25% of people meet the diagnostic criteria for some of their anxiety disorders during their lifetime
-Benzodiazepines belong to the group of anxiolytic sedatives and the most prescribed drugs in the world
-Over 300 benzodiazepines have been synthesized and over 40 are in clinical use in various parts of the world
- 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

The **aim** in ours 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.

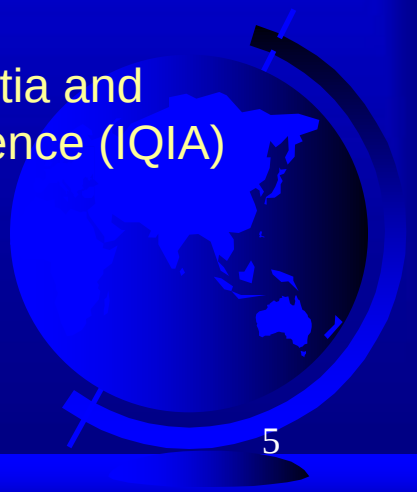
Methodology: a pharmacoepidemiological difference-in-difference time series analysis of population exposure to benzodiazepines between the three, geographically close Balkans countries with varying degrees of socioeconomic development has been carried out. Study was conducted as academic investigator 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.

- 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. 2004 became a member of the EU.
- 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%.
- **Serbia** has opened accession negotiations with the EU since 2013. In 2017, Serbia's GDP was $15,200 per capita with real growth rate of 3% and with unemployment rate of 16%

Data on benzodiazepines sold in each country (Serbia, Croatia and Slovenia) were obtained from the 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**:**

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

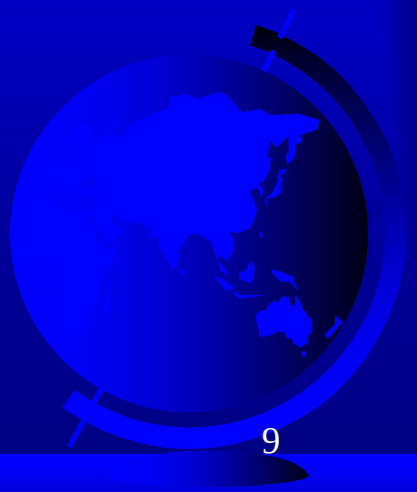
- Difference-in-difference analysis was conducted

RESULTS (Tab 1,2; Fig 1)

- 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
- 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
- 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 Serbia and Croatia
- 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 . Serbia consistently had approximately ten times the DID for bromazepam over Slovenia and Croatia throughout the study period
- No correlation was found with the difference in DIDs for alprazolam between countries.

- For lorazepam 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
- 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 . 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 DODs for oxazepam throughout the study period.

- 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



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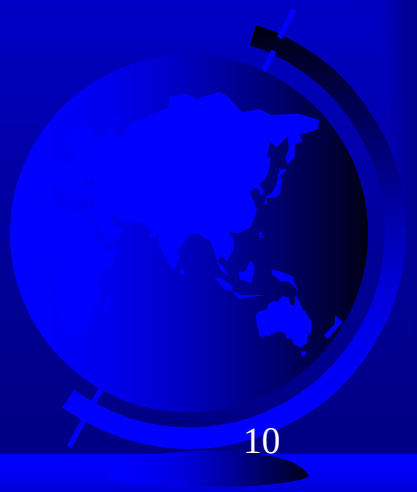
Differences in the policy of prescribing benzodiazepine anxiolytics between Croatia and Serbia comparing to Slovenia are observed precisely: a doctor in the primary care in Slovenia does not have the option of prescribing these medicines repeatedly, while in Croatia and Serbia such an option exists, 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; Offficial 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 Ccroatia 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).

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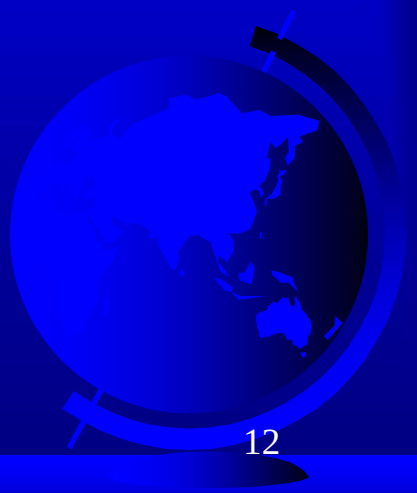
- Serbia and Croatia should provide resources as soon as possible in order to improve the structure of psychiatrists and psychotherapists in their healthcare facilities, both at primary and secondary level.

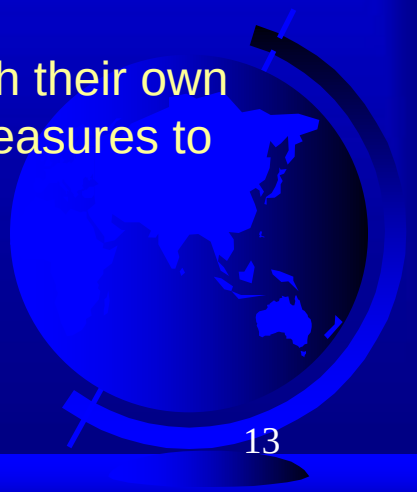
- The necessity of such an action can be seen from the population exposure to total benzodiazepines in these countries, which indicate that in 2018 one in ten resident of Serbia and one in twelve resident of Croatia was exposed daily to one DDD of benzodiazepines



Slovenia conducted quantitative Studies of prescribing benzodiazepines in primary care where the highest consumption comes from, studies aimed at informing the attitudes of family physicians about their own positive and negative experiences with benzodiazepine administration, 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.

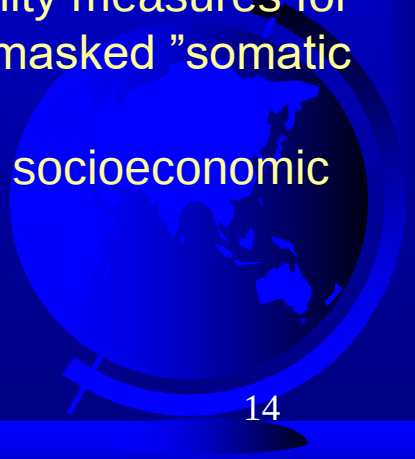
- the most prominent barrier was insufficient number of psychiatrists dealing with psychiatric disorders for which GPs prescribe benzodiazepines

- 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.



1. Koja, od navedene tri države sa Balkana, aktivno pravilno / uspešno usmerava potrošnju benzodiazepina?

Srbija

Hrvatska

→ Slovenija

2. Šta je efikasan metod za racionalnu upotrebu benzodiazepina?

edukacija, kliničke studije

obnavljanje infrastrukture zaposlenih psihijatara

zakonske korekcije

→ sve navedeno