

# The benzodiazepine nation of Croatia: a retrospective, observational, comparative study of psychotropic drug utilization between Croatia and Sweden 2014-2015

---

Nham, Eric Guhyun

Master's thesis / Diplomski rad

2020

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Zagreb, School of Medicine / Sveučilište u Zagrebu, Medicinski fakultet**

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:105:016061>

Rights / Prava: [In copyright](#)/[Zaštićeno autorskim pravom.](#)

Download date / Datum preuzimanja: **2025-01-25**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine Digital Repository](#)



UNIVERSITY OF ZAGREB  
SCHOOL OF MEDICINE

**Eric Nham**

**Thesis title** – The benzodiazepine nation of Croatia: a retrospective, observational, comparative study of psychotropic drug utilization between Croatia and Sweden 2014-2015

**Graduate thesis**



Zagreb, 2020.

This graduate thesis was made at <sup>1</sup>University Hospital Centre Sisters of Charity, Vinogradska cesta 29, 10 000 Zagreb, Croatia <sup>2</sup>University of Zagreb School of Medicine, Šalata 3, 10 000 Zagreb, Croatia <sup>3</sup>University Hospital Centre Zagreb, Kišpatićeva cesta 12, 10 000 Zagreb, Croatia <sup>4</sup>Karolinska Institutet, Stockholm, Sweden <sup>5</sup>Public Healthcare Services Committee Stockholm County Council, Stockholm, Sweden, mentored by Prof. dr. sc Robert Likić and was published in Expert Review of Pharmacoeconomics & Outcomes Research.

## **List of abbreviations**

Agency for Medicinal Products and Medical Devices (HALMED)

Anatomical Therapeutic Chemical (ATC) classification system

Cross National Comparisons (CNC)

The Defined Daily Doses (DDD)

The Defined Daily Dose per 1000 Inhabitants Per Day (DDD/TID)

Drug Utilization Research (DUR)

European Union (EU)

The Gross Domestic Product (GDP)

International Monetary Fund (IMF)

Over The Counter (OTC)

Psychotropic Drug (PD)

The Purchasing Power Parity (PPP)

The World Health Organization (WHO)

## **Conflict of interest**

None declared.

## Summary

Ines Potočnjak, Robert Likić, Vesna Degoricija, Eric Nham & Björn Wettermark

**Background:** The consumption of psychotropic drugs (PD) is increasing worldwide with a significant variation between countries. Croatia and Sweden have similar health and pharmaceutical systems; however, Sweden is a high-income country with developed medical care, registries, and prescribing guidelines. We sought to compare the utilization of PD between Croatia and Sweden to identify areas for improvement in rational use of drugs.

**Methods:** This was a cross-sectional study using national databases to assess utilization of PD (ATC N05, N06) in Croatia and Sweden in 2014 and 2015.

**Results:** Prescribing of PD in Croatia increased from 127 DDD/TID (defined daily dose/1000 inhabitants) in 2014 to 131 DDD/TID in 2015. In Sweden, the total utilization was higher with an increase from 183 DDD/TID in 2014 to 188 DDD/TID in 2015. There were substantial differences. In Croatia, the utilization of benzodiazepine derivatives (N05BA) was 72.5 DDD/TID in 2014 and increased to 74.4 DDD/TID, in 2015. In Sweden, the utilization was only 11.2 DDD/TID for benzodiazepine derivatives in both years.

**Conclusions:** There were substantial differences in utilization of PD between Croatia and Sweden. Highlighting the problem of inappropriate benzodiazepine utilization in Croatia can help to introduce measures to change prescribing habits and improve prescribing quality.

## KEYWORDS

Benzodiazepines; drug safety; drug utilization; prescribing; psychotropic drugs

## Sažetak

Ines Potočnjak, Robert Likić, Vesna Degoricija, Eric Nham & Björn Wettermark

**Pozadina:** Potrošnja psihotropnih lijekova (PD) povećava se širom svijeta sa znatnim odstupanjima između zemalja. Hrvatska i Švedska imaju slične zdravstvene i farmaceutske sustave; međutim, Švedska je zemlja s visokim dohotkom s razvijenom medicinskom skrbi, registrima i propisivanjem smjernica. Pokušali smo usporediti uporabu PD-a između Hrvatske i Švedske kako bi se identificirala područja za poboljšanje racionalne uporabe droga.

**Metode:** Ovo je bila presječna studija koja je koristila nacionalne baze podataka za procjenu korištenja PD-a (ATC N05, N06) u Hrvatskoj i Švedskoj u 2014. i 2015. godini.

**Rezultati:** Propisivanje PD u Hrvatskoj povećalo se sa 127 DDD / TID (definirana dnevna doza / 1000 stanovnika) u 2014. na 131 DDD / TID u 2015. U Švedskoj je ukupna iskorištenost bila veća s porastom od 183 DDD / TID u 2014. na 188 DDD / TID u 2015. Bilo je značajnih razlika. U Hrvatskoj je upotreba derivata benzodiazepina (N05BA) u 2014. iznosila 72,5 DDD / TID i povećala se na 74,4 DDD / TID u 2015. U Švedskoj je upotreba bila samo 11,2 DDD / TID za benzodiazepinske derivate u obje godine.

**Zaključci:** Postoje značajne razlike u korištenju PD-a između Hrvatske i Švedske. Isticanje problema neprimjerene upotrebe benzodiazepina u Hrvatskoj može pomoći uvođenju mjera za promjenu navika propisivanja i poboljšanje kvalitete propisivanja.

## KLJUČNE RIJEČI

benzodiazepini; sigurnost lijekova; korištenje droga; propisivanje; psihotropni lijekovi

## 1.Introduction

The term psychotropic drugs (PD) was introduced in 1975. According to The World Health Organization, PD is equivalent to the term psychoactive substance, which when taken in or administered into the body, affects mental processes thus influencing psychological functions. PD are among the most commonly used medicines in the population, also accounting for substantial expenditure [1]. However there are two major problems: nonadherence and addiction [2]. These drugs also have many drug–drug interactions and side effects [3]. They are often prescribed off-label and increase in PD polypharmacy has been reported worldwide [2]. However, there are both issues of over- and underprescribing. There are also different challenges for the different PD classes. Many patients have a chronic use of benzodiazepines despite that these should only be used for short time periods of up to 4 or 6 weeks. However, efforts to regulate their use seem to be failing and large differences exist between health-care systems around the world [2]. It is likely that there is an underuse of antidepressants instead. Many patients with depression are not prescribed antidepressants for an appropriate time period and it has been suggested that the increased use of antidepressants could contribute to a decrease in suicide rate [4].

The high consumption of PD is not surprising, given the burden of mental health problems. In Croatia, an increase of hospital morbidity due to depressive disorders with a significant increase in number and rate of hospitalizations was recorded between 1995 and 2010 [5]. The total hospitalization rate in 1995 was 54.6/100,000 which more than doubled to 122.4/100,000 in 2010 [5]. In Sweden, the 5-year prevalence of depression has been estimated to 8.7% in women and 4.4% in men, and for anxiety disorders/phobia to 6.3% in women and 3.4% in men [6]. Medicines used for nervous system disorders are also commonly used. In 2014, in Croatia the total expenditure was 107.13 million euros, and the consumption 158.8 DDD/TID (defined daily dose/1000 inhabitants), placing it on the second place among all medicines of consumption by volume [7]. According to the Agency for Medicinal Products and Medical Devices (HALMED), the rate of consumption showed a slow and constant growth between 2010 and 2014 [7]. The growth was approximately 3% per year in DDD/TID, while financial expenditure remained stable with, on average, a minimum increase in price of 0.3% per year [7]. In accordance to an increasing consumption, drug abuse remains a great undetected and underreported problem in Croatia [8].

According to the Report on people treated for psychoactive drugs abuse in Croatia, there were only 85 patients treated for abuse of benzodiazepines and 21 for abuse of hypnotics and

sedatives [8]. Data obtained from HALMED state that in the period from 2005 to 2017, only 15 benzodiazepines and Z-drugs and 8 antidepressants and antipsychotics-related adverse drug reactions of abuse, misuse, and addiction were reported. Cross-national comparisons (CNC) of drug utilization are valuable tools to learn and find areas for improvement [9]. Comparative drug utilization studies aim to promote an efficient, effective, and safe use of medicines, even though data collection is one of the major barriers to performing CNC. Today, national registers on drug consumption allow us to perform comparative studies between European countries [10].

### **1.1 Objectives**

The aim of this study was to compare PD utilization between Croatia and Sweden in 2014 and 2015 and to identify the problematic areas and stimulate discussion to improve the quality of prescribing, dispensing, and consumption of medicines.

Croatia is placed between Central Europe, Southeast Europe, and the Mediterranean, and has been listed since 2008 among high-income economies. Sweden, which is a Scandinavian country, has been a high-income economy according to the World Bank since 1987 [11]. This study was performed as a geographical comparison of drug utilization [10]. The authors assumed that Sweden, as a high-income, developed country with developed medical care, registries, and prescribing guidelines, represents a good model country to be compared with

## **2. Methods**

### **2.1. Setting**

This study was conducted with data for Croatia and Sweden, two European countries with publicly funded national health systems. GDP for Sweden was according to the International Monetary Fund (2016) (based on estimates of projected data) 49,678, and for Croatia, it was 22,415. According to the last Census of Population in 2011, the population of Croatia was 4.3 million [12]. The population of Sweden in 2014 was 9.6 million and it increased to 9.7 million in 2015. In Croatia, Croatian Kuna (HRK) were used and in Sweden, Swedish Krona (SEK), with a conversion rate of 1 SEK = 0.76 HRK on 9



June 2017. The conversion rate for euro (EUR) is 1 EUR = 7.42 HRK on 9 June 2017. The pharmaceutical systems in the two countries are similar with external price referencing and reference price systems being applied in Croatia, but valuable based pricing in Sweden [13,14].

## **2.2. Study type**

This observational, retrospective, cross-sectional study was conducted in accordance with the current Good Clinical Practice and local regulations. The ATC system was used as a tool for the purposes of drug utilization comparisons. In this study, we compared the utilization of PD between Croatia and Sweden in a period between 2014 and 2015.

## **2.3. Data sources**

Wholesale data on all drugs distributed in Croatia and Sweden were collected. For Croatia sales, data are submitted to HALMED by all legal and physical persons in the sector of retail sale of medicines. HALMED received the data for 97.97% (2015) and 97.5% (2014) of all entities engaged in the trade of remedies on Croatian territory [15,16]. Since the collected data represent 97.97% of the possible total, the method of extrapolation was used and an increase of 2.03% (2015) and 2.5% (2014) was applied, thus yielding a presumed overall value of drug consumption in 2014 and 2015, respectively.

The extrapolated results have previously been validated showing a credible result [15,16]. Vogler et al. describe reimbursement policies in Croatia [13]. For Croatia, we decided to retrieve data on drug consumption from HALMED instead of the Croatian Health Insurance Fund's electronic database of drug prescribing which contains data on all reimbursed drugs that were prescribed in the country, since that approach better reflects overall drug utilization and covers reimbursed as well as over the counter drugs. The Swedish data were obtained from the Swedish eHealth Agency [17]. Swedish Agency gathers and supplies statistics about pharmaceutical sales from all pharmacies, retailers, and wholesalers. Anyone selling pharmaceuticals in Sweden is bound by law to provide regular reports of their sales to the eHealth Agency so 100% of data is collected [17].

## **2.4. Outcomes measures**

In this study, the DDD methodology was used. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults [18]. To enable comparison of exposure between the

two countries' DDDs was adjusted for population size and time using the measure DDD/1000 inhabitants and day (DDD/TID), a commonly used measure in drug utilization studies [19]. Comparisons were made each year for all drugs within the following ATC-groups: N05 Psycholeptics and N06 Psychoanaleptics (second level, therapeutic subgroup). Those are drugs acting on the nervous system and are used in the treatment of depression, panic, anxiety, agitation, sleep disorders and wakefulness, alcoholism, eating disorders (anorexia, bulimia), and others [7]. The group categorization and data are presented in Tables 1 and 2 [15,16].

### **3. Results**

Prescribing of PD in Croatia increased from 127 DDD/TID in 2014 to 131 DDD/TID in 2015. In Sweden the total utilization was higher and increased further from 183 DDD/TID in 2014 to 188 DDD/TID in 2015. There were substantial differences between the countries in utilization of the different drug classes. In Croatia, the utilization of anxiolytics (N05B) and benzodiazepine derivatives (N05BA) were 72.5 DDD/TID for both groups in 2014 and they slightly increased to 74.5 and 74.4 DDD/TID, respectively in 2015. In Sweden, the utilization was only 15 DDD/TID for anxiolytics and 11.2 DDD/TID for benzodiazepine derivatives in both years. Furthermore, use of anxiolytics was 4.8 times higher, and use of benzodiazepine derivatives was 6.7 times higher in Croatia. Nearly the entire consumption of anxiolytics per DDD/TID in 2014 in Croatia belongs to the benzodiazepine derivatives, among which diazepam (34.4 DDD/TID, at the fourth place in drug consumption in 2014) and alprazolam (25.5 DDD/TID, at the seventh place of drug consumption in 2014) [7] were most frequently used. In Croatia, DDD/TID for diazepam was 34.4 in 2014 and 35.8 in 2015, followed by alprazolam 25.5 in 2014 and 26.2 in 2015 (Table 1 and Figure 1). In Sweden, DDD/TID for diazepam was 4.3 and for alprazolam it was 3.2 both in 2014 and 2015.

Table 1. Utilization of psycholeptics (ATC N05) in Croatia and Sweden ranked by DDD per 1000 inhabitants per day (TID).

Fifth level, chemical substance (ATC code) N05B ANXIOLYTICS; N05BA Benzodiazepine derivatives	Croatia		Sweden	
	2014	2015	2014	2015
	<b>N NERVOUS SYSTEM</b>	<b>158.8</b>	<b>165.1</b>	<b>278.0</b>
<b>N05 PSYCHOLEPTICS</b>	<b>98.9</b>	<b>102.1</b>	<b>78.5</b>	<b>77.8</b>
N05A ANTIPSYCHOTICS	13.2	14.0	10.4	10.6
N05AA Phenothiazines with aliphatic side-chain	1.8	1.7	0.2	0.2
N05AA02 Levomepromazine	0.2	0.2	0.2	0.2
N05AA03 Promazine	1.5	1.5		
N05AB Phenothiazines with piperazine structure	1.0	1.3	0.4	0.4
N05AB02 Fluphenazine	1.0	1.3	0.0	0.0
N05AD Butyrophenone derivatives	1.6	1.7	0.6	0.6
N05AD01 Haloperidol	1.6	1.7	0.6	0.5
N05AE Indole derivatives	0.2	0.2	0.1	0.1
N05AE03 Sertindole	0.0	0.0	0.0	0.0
N05AE04 Ziprasidone	0.2	0.2	0.1	0.1
N05AF Thioxanthene derivatives	0.1	0.1	0.8	0.8
N05AF05 Zuclophentixol	0.1	0.1	0.6	0.6
N05AH Diazepines, oxazepines, thiazepines and oxepines	6.1	6.2	4.7	4.8
N05AH02 Clozapine	1.0	0.9	0.6	0.6
N05AH03 Olanzapine	3.3	3.1	2.7	2.8
N05AH04 Quetiapine	1.9	2.1	1.3	1.4
N05AL Benzamides	0.6	0.6		
N05AL01 Sulpiride	0.5	0.5	-	-
N05AL05 Amisulpride	0.1	0.1	-	-
N05AN Lithium	0.0	0.0	1.6	1.6
N05AN01 Lithium	0.0	0.0	1.6	1.6
N05AX Other antipsychotics	1.9	2.1	2.1	2.2
N05AX08 Risperidone	1.4	1.4	0.9	0.9
N05AX12 Aripiprazole	0.1	0.3	0.9	1.0
N05AX13 Paliperidone	0.3	0.5	0.2	0.3
<b>N05B ANXIOLYTICS</b>	<b>72.5</b>	<b>74.5</b>	<b>15.0</b>	<b>14.5</b>
N05BA Benzodiazepine derivatives	72.5	74.4	11.2	10.6
Diazepam (N05BA01)	34.4	35.8	4.3	4.1
Oxazepam (N05BA04)	5.6	5.5	3.5	3.3
Lorazepam (N05BA06)	5.1	5.1	0.2	0.2
Bromazepam (N05BA08)	1.2	1.9	-	-
Klobazam (N05BA09)	0.0	0.0	0.0	0.0
Alprazolam (N05BA12)	25.5	26.2	3.2	3.0
N05BB Diphenylmethane derivatives			0.0	3.5
N05BB01 Hydroxyzine			0.0	3.5
N05BE Azaspirodecanedione derivatives			0.1	0.3
N05BE01 Buspirone			0.1	0.3
<b>N05C HYPNOTICS AND SEDATIVES</b>	<b>13.2</b>	<b>13.7</b>	<b>53.2</b>	<b>52.6</b>
N05CD Benzodiazepine derivatives	4.5	5.3	2.7	2.4
N05CD01 Flurazepam	0.4	0.4		
N05CD02 Nitrazepam	3.7	4.4	1.2	1.1
N05CD03 Flunitrazepam			1.2	1.1
N05CD08 Midazolam	0.4	0.5	0.1	0.1
<b>N05CF Benzodiazepine-related drugs</b>	<b>8.7</b>	<b>8.4</b>	<b>36.0</b>	<b>35.4</b>
<b>N05CF01 Zopiclone</b>			<b>23.6</b>	<b>23.5</b>
<b>N05CF02 Zolpidem</b>	<b>8.6</b>	<b>8.4</b>	<b>12.3</b>	<b>11.8</b>
N05CF03 Zaleplon	0.1	0.1	0.1	0.1
N05CH Melatonin receptor agonists	0.0	0.0	1.4	1.8
N05CH01 Melatonin	0.0	0.0	1.4	1.8
<b>N05CM Other hypnotics and sedatives</b>	<b>0.0</b>	<b>0.0</b>	<b>13.1</b>	<b>13.0</b>
<b>N05CM06 Propiomazine</b>			<b>12.8</b>	<b>12.8</b>

Grey color represents that the drugs are not available in the country.

Table 2. Utilization of psychoanalectics (ATC N06) in Croatia and Sweden ranked by DDD per 1000 inhabitants per day (TID).

Fifth level, chemical substance (ATC code) N06 PSYCHOANALEPTICS; N06A ANTIDEPRESSANTS	Croatia		Sweden	
	2014	2015	2014	2015
	<b>N NERVOUS SYSTEM</b>	<b>158.8</b>	<b>165.1</b>	<b>278.0</b>
<b>N06 PSYCHOANALEPTICS</b>	<b>28.4</b>	<b>29.1</b>	<b>103.6</b>	<b>109.6</b>
<b>N06A ANTIDEPRESSANTS</b>	<b>27.3</b>	<b>27.9</b>	<b>87.8</b>	<b>92.5</b>
N06AA Nonselective monoamine reuptake inhibitors	1.0	1.0	3.3	3.4
N06AA04 Clomipramine	0.0	0.0	1.0	0.9
N06AA09 Amitriptyline	0.5	0.5	2.2	2.3
N06AA21 Maprotiline	0.5	0.5	0.0	0.0
N06AB Selective serotonin reuptake inhibitors	19.7	19.6	59.8	62.5
N06AB03 Fluoxetine	1.1	1.0	5.3	5.6
N06AB04 Citalopram	1.0	0.9	20.5	19.6
N06AB05 Paroxetine	3.7	3.6	3.0	2.9
N06AB06 Sertraline	7.1	6.8	24.0	26.1
N06AB08 Fluvoxamine	2.0	1.9	0.0	0.0
N06AB10 Escitalopram	4.9	5.6	7.0	8.3
N06AG Monoamine oxidase A inhibitors	0.0	0.0	0.1	0.1
N06AG02 Modobemide	0.0	0.0	0.1	0.1
N06AX Other antidepressants	6.6	7.3	24.7	26.6
N06AX11 Mirtazapine	2.6	2.8	10.3	10.9
N06AX12 Bupropion	0.1	0.1	1.2	1.4
N06AX14 Tianeptin	0.6	0.8	-	-
N06AX16 Venlafaxine	2.4	2.4	9.0	9.6
N06AX18 Reboxetine	0.0	0.0	0.1	0.1
N06AX21 Duloxetine	0.8	0.8	3.2	3.3
N06AX22 Agomelatine	0.1	0.1	0.5	0.5
N06AX26 Vortioxetine			0.1	0.3
<b>N06B PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS</b>	0.1	0.1		
N06BA Centrally acting sympathomimetics	0.0	0.0		
N06BA04 Methylphenidate	0.0	0.0		
N06BX Other psychostimulants and nootropics	0.1	0.1		
N06BX03 Piracetam	0.1	0.1		
<b>N06D ANTI-DEMENTIA DRUGS</b>	2.0	1.1		
N06DA Anticholinesterases	0.1	0.2		
N06DA02 donepezil	0.1	0.2		
N06DX Other anti-dementia drugs	0.9	0.9		
N06DX01 Memantine	0.2	0.3		
N06DX02 Ginkgo folium	0.6	0.6		

Grey color represent that the drugs are not available in the country.

\*Table 1. Table 2. From Ines Potočnjak, Robert Likić, Vesna Degoricija, Eric Nham & Björn Wettermark (2018) The benzodiazepine nation of Croatia: an observational, comparative study of psychotropic drug utilization between Croatia and Sweden 2014–2015, Expert Review of Pharmacoeconomics & Outcomes Research, 18:6, 641-646, DOI: 10.1080/14737167.2018.1507820

Prescribing of anxiolytics increased by 2.56% in Croatia from 2014 to 2015. In Sweden, the utilization remained unchanged, 15 DDD/TID, which obviously was substantially lower than in Croatia. In contrast, utilization of antidepressants (N06A), selective serotonin reuptake inhibitors (SSRIs; N06AB), and other

antidepressants (N06AX) were three times higher in Sweden (Table 2 and Figure 2) than in Croatia. In Croatia, the volumes of antidepressants (N06A) were only 27.3 DDD/ TID in 2014 and 27.9 DDD/TID in 2015, in contrast to 87.8 DDD/TID in 2014 and 92.5 DDD/TID in 2015 in Sweden. There was a greater utilization of SSRI in Sweden than in Croatia (59.8 and 62.5 vs. 19.7 and 19.6). Especially for citalopram, which was 20 times more utilized in Sweden than in Croatia. In Sweden the consumption was 20.5 DDD/TID in 2014 and 2015, and in Croatia 1 and 0.9 DDD/TID in the same time period. However, there was a greater utilization of benzodiazepine-related hypnotics in Sweden than in Croatia (36 and 35.4, vs. 8.7 and 8.4 for 2014 and 2015, respectively, Table 2).

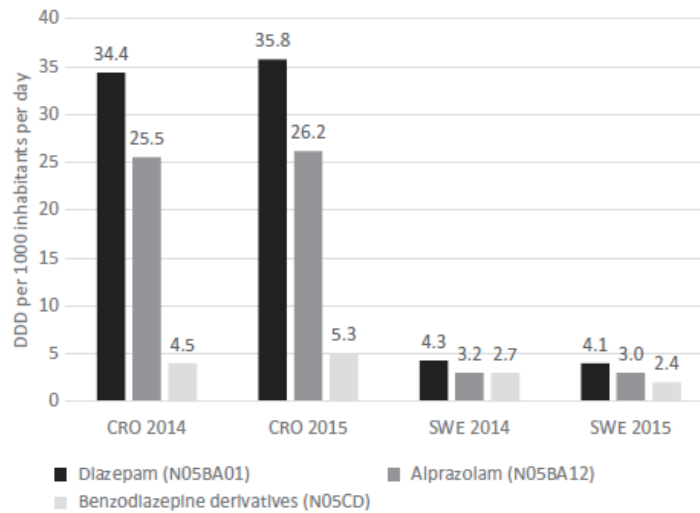


Figure 1. The use of anxiolytics in the treatment (ATC code N05B); N05BA benzodiazepine derivatives (ATC code N05BA and N05CD) in Croatia (CRO) and Sweden (SWE) ranked by DDD per 1000 inhabitants per day (TID). Diazepam (N05BA01), alprazolam (N05BA12).

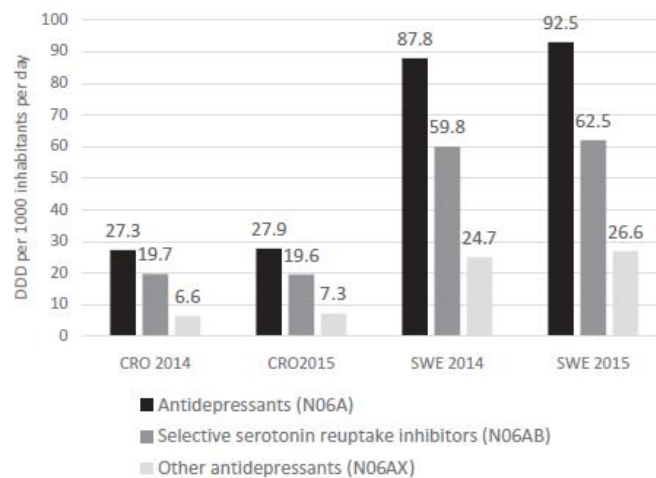


Figure 2. The use of antidepressants in the treatment (ATC code N06A); N06AB selective serotonin reuptake inhibitors and other antidepressants (ATC code N06AX) in Croatia (CRO) and Sweden (SWE) ranked by DDD per 1000 inhabitants per day (TID). N06A ANTIDEPRESSANTS, N06AB selective serotonin reuptake inhibitors, N06AX other antidepressants.

\*Figure 1 and figure 2 from Ines Potočnjak, Robert Likić, Vesna Degoricija, Eric Nham & Björn Wettermark (2018) The benzodiazepine nation of Croatia: an observational, comparative study of psychotropic drug utilization between Croatia and Sweden 2014–2015, *Expert Review of Pharmacoeconomics & Outcomes Research*, 18:6, 641-646, DOI: 10.1080/14737167.2018.1507820

In Sweden, the utilization of zopiclone was 23.6 DDD/TID, while this drug was not prescribed at all in Croatia. The consumption of zolpidem was 11.8 DDD/TID in Sweden in 2014 and 2015 and 8.6 and 8.4 DDD/TID for Croatia. The utilization of propiomazine was 12.8 DDD/TID for Sweden (this drug is not used in Croatia).

#### **4. Discussion**

Drug utilization studies are useful tools to identify areas for improvement that may subsequently be used to change prescribing habits. In this study, we found that there were substantial differences between Croatia and Sweden in utilization of the different PD. In Croatia, the utilization of anxiolytics and benzodiazepine derivatives was 4.8 and 6.5 times larger than in Sweden. However, the use of antidepressants was 3.3 times higher in Sweden, especially for SSRI. The substantial difference between the countries in utilization of anxiolytics may have several explanations. Higher socioeconomic status of the population in Sweden might have influenced the prescribing patterns of anxiolytic drugs in Sweden. Better knowledge or superior continuous medical education of the Swedish general practitioners regarding depression treatment could also have played a role in the difference in benzodiazepine/anxiolytics prescribing practices between the two countries. General prescribing trends of psychotropic medicines in Croatia and Sweden could also differ due to different economic conditions of the countries, organization of the health-care systems, or differences in pharmaceutical regulation and reimbursement. The use of benzodiazepine derivatives is slowly increasing in Croatia possibly because of their low price, ease of access, and outdated prescribing practices. In Croatia, benzodiazepines are prescription only drugs, which are prescribed by general practitioners/family doctors and psychiatrists. Misuse, 'medicalization' of non-pathological or social problems, and self-medication could be a generator of high prescription and drug use. The problem of benzodiazepine prescription was already observed by authors Vlastelica, Arbanas, and Uzun referring to prescribing tradition and difficulties associated with benzodiazepine withdrawal [20–22]. A literature search performed by Uzun revealed different side effects associated with treatment with benzodiazepines [23].

Benzodiazepines are, as previously reported, considered potentially inappropriate drugs in the elderly [24]. A study performed by de las Cuevas concluded that there is a necessity for education on benzodiazepine use aiming at developing new attitudes in health-care professionals and general population [25]. Good control of drug prescribing would strongly improve the quality of pharmacotherapy in Croatia. General practitioners in Croatia prescribe benzodiazepines instead of antidepressants for treatment of depression as these drugs are cheaper than antidepressants and not on a restricted release drug list. Consequently, antidepressants, which are also more expensive, are less prescribed in Croatia than they are in Sweden. Benzodiazepines cause dependence after more than 6 weeks of use, especially the potent ones such as alprazolam, creating a new and long-lasting problem. Several previous studies dealt with the prescribing practices of psychotropic medicines in Croatia. Štimac, Vlahović-Palčevski, and Živković recommended additional rationalization in the prescribing quality [26–28]. Kiivet recommended rational drug use and use of medicines with proven clinical therapeutic value [29]. Jordanova suggested that prescribing patterns should be improved by an introduction of clear national guidelines and routine prescribing audits [30]. Importantly, in Sweden and some other countries, benzodiazepines are placed on the ‘restricted release’ drug list. Moreover, benzodiazepines are regarded as potentially inappropriate medicines according to the Swedish National Board of Health and Welfare [31]. In a study by Järbrink et al., differences in physicians’ propensity to prescribe benzodiazepines were based on medical training, as psychiatrists were found to be less likely to prescribe benzodiazepines than family physicians or private practitioners [32]. Patients who are benzodiazepine dependent or at risk of misuse should be identified and appropriately evaluated in order to determine their risk of harm. Depending on their characteristics, benzodiazepines can be withdrawn, or the patient stabilized on a maintenance program [26]. Finally, differences in PD prescribing practices between the two countries cannot be explained by different prevalences of depressive or anxiety disorders, since in Croatia in 2015 the estimated prevalence rates were 5.1% for depressive disorders and 3.8% for anxiety disorders, while the estimated prevalence rates in Sweden were 4.9% for depressive disorders and 4.8% for anxiety disorders [33]. We believe, that substantial differences that were observed can be explained by the outdated and noncritical benzodiazepines prescribing practices, poor psychotherapy management, lower socioeconomic status, and lower benzodiazepine prices in Croatia.

#### **4.1. Strengths and limitations**

This was a retrospective, observational study using aggregated data; therefore, the findings should be interpreted accordingly. According to available age and gender world data, Croatia and Sweden have similar demographic structure. Median age for Croatia is 42.7 years, for Sweden 41.2, with no great difference between median male 40.8 and 40.2 years, and median female 44.8 and 42.2 years, which might be one of the strengths of this study [34]. There were no discrepancies in the data collection methods between Croatia and Sweden. In order to perform a CNC, it was important to ensure validity of reliable data. Analysis of our data allows us to highlight the problem of inappropriately high benzodiazepine derivatives utilization, determine potential support measures to change prescribing habits, and improve the quality of pharmacotherapy in Croatia. However, there is limited evidence about benzodiazepine prescribing practice in Croatia. Due to addictive characteristics of these drugs, part of the increased consumption is likely to be due to overdosing and self-medication. Still, we were not able to determine how much of consumption they represent.

## **5. Conclusion**

This study revealed large differences in prescribing practice with high rates of benzodiazepine prescribing in Croatia, while antidepressants were used in Sweden to a higher degree. Benzodiazepines are regarded as a highly addictive drug class and cause psychological and physical dependence. In Sweden, benzodiazepines are on a 'restricted release' drug list and are considered to be potentially inappropriate medicines, especially in the elderly. The follow-up of drug consumption requires the collaboration of a multidisciplinary team of clinicians, prescribers, clinical pharmacologists, pharmacists, and epidemiologists. Rational prescribing of benzodiazepines is crucial. Analyses of data on drug consumption allow us to highlight problems in utilization of medicines and address them. In the case of benzodiazepines, regulations should be put in place in Croatia to limit the autonomy of clinicians regarding prescribing of these drugs, as is the case in Sweden. The rational use of PD is of major public importance.

## **Acknowledgments**

Authors would like to thank Maria Juhasz-Haverinen and Helena

Ramström for obtaining data for Sweden.

## Author contributions

IP, RL, VD, EN, BW were involved in the conception and design, analysis and interpretation of the data; IP, RL, VD, EN, BW were involved in drafting of the paper or revising it critically for intellectual content; and all the authors gave the final approval of the version to be published; and that all authors agree to be accountable for all aspects of the work.

## References

1. Kleinrock M. The use of medicines in the United States: review of 2010 report by the IMS Institute for Healthcare Informatics. 2011;1–36.
2. Zoëga H, Smith A, Barozzi N. Drug utilization research in the area of analgesics and psychotropics. Chapter 28. In: M. Elseviers, B. Wettermark, A. Birna Almarsdóttir et al., editor. Drug utilization research: methods and applications. 1st ed. Vol. 2016. Chichester, West Sussex : Hoboken, NJ: John Wiley & Sons, Ltd.; 2016. p. 294–301.
3. Potočnjak I, Degoricija V, Vukičević BD, et al. Cardiovascular side effects of psychopharmacologic therapy. *Int J Cardiol.* 2016;219:367–372.
4. Isacsson G. Suicide prevention - a medical breakthrough? *Acta Psychiatr Scand.* 2000;102:113–117.
5. Kralj V, Silobrčić Radić M Mentalne poremećaji u Republici Hrvatskoj [Mental diseases in the Republic of Croatia]. Hrvatski Zavod za Javno Zdravstvo, Ministarstvo Zdravlja Republine Hrvatske. Uvez, d.o.o; 2011.
6. Carlsson AC, Wändell P, Ösby U, et al. High prevalence of diagnosis of diabetes, depression, anxiety, hypertension, asthma and COPD in the total population of Stockholm, Sweden - a challenge for public health. *BMC Public Health.* 2013;13(1):670.



7. Draganić P, Žeželić S, Oštarčević S, et al. Potrošnja lijekova u Hrvatskoj 2010–2014 (eng. Consumption of medicines in Croatia 2010–2014). Agencija za lijekove i medicinske proizvode –HALMED; 2016.
8. Katalinić D, Huskić A Izvješće o osobama liječenim zbog zlouporabe psihoaktivnih droga u Hrvatskoj u 2015. godini [Report on persons treated for drug abuse in Croatia in 2015]. Hrvatski zavod za javno zdravstvo; 2015. Available from: <http://www.hzjz.hr/sluzbe/sluzbaza-epidemiologiju/odjel-za-nadzor-i-istrazivanje-ne-zaraznihbolesti/odsjek-za-pracenje-ovisnosti-s-registrom-osoba-lijecenihzbog-zlouporabe-psihoaktivnih-droga/>
9. Gillström A, Wettermark B Literature review cross-national comparison of DU activities. For the Scientific Committee of the ISPE/ EuroDurg meeting in Antwerp 2011\*. EuroDURG/ISPE Meet;2011.
10. Vlahović-Palčevski V, Wettermark B, Ibáñez L, et al. Comparison of drug utilization across different geographical areas Chapter 14. In: M. Elseviers, B. Wettermark, A. Birna Almarsdóttir et al., editor. Drug utilization research: methods and applications. 1st ed.
11. World Bank Data. 2006. Available from: <https://datahelpdesk.worldbank.org/knowledgebase/articles/378834-how-does-the-worldbank-classify-countries>. [cited 2017 Aug].
12. Ostroški L. Census of population, households and dwellings 2011, population by sex and age. Croatian Bureau of Statistics. 2013. [cited 2017 Aug]. Available from: <http://www.dzs.hr/>.
13. Vogler S, Habl C, Bogut M, et al. Comparing pharmaceutical pricing and reimbursement policies in Croatia to the European Union Member States. *Croat Med J.* 2011;52:183–197.
14. Godman B, Wettermark B, Hoffmann M, et al. Multifaceted national and regional drug reforms and initiatives in ambulatory care in Sweden: global relevance. *Expert Rev Pharmacoecon Outcomes Res.* 2009;9(1):65–83.
15. HALMED. Ukupna potrošnja lijekova u 2014. Godini. 2014. [cited 2017Aug]. Available from: <http://www.halmed.hr/Promet-proizvodnja-i-inspekcija/Promet/Potrosnja-lijekova/Izvjesca-o-prometu-lijekova/>

16. HALMED. Ukupna potrošnja lijekova u 2015. Godini. 2015. [cited 2017Aug]. Available from: <http://www.halmed.hr/Promet-proizvodnja-i-inspekcija/Promet/Potrosnja-lijekova/Izvjesca-o-prometu-lijekova/>
17. Swedish eHealth agency. [cited 2017 Aug]. Available from: <https://www.ehalsomyndigheten.se/other-languages/english/>
18. WHO Collaborating Centre for Drug Statistics Methodology. Definition and general considerations. [cited 2018 Jun 30]. Available from: [https://www.whocc.no/ddd/definition\\_and\\_general\\_considera/](https://www.whocc.no/ddd/definition_and_general_considera/)
19. Salvesen Blix H. Measurement units of drug utilization. Chapter. In M. Elseviers, B. Wettermark, A. Birna Almarsdóttir et al., editors. Drug utilization research – methods and applications.
20. Vlastelica M, Jelaska M. Zašto su benzodiazepine još uvijek u širokoj primjeni? Acta med Croat. 2012;66:137–140.
21. Arbanas G, Arbanas D, Dujam K. Adverse effects of benzodiazepines in psychiatric outpatients. Psychiatr Danub. 2009;21(1):103–107.
22. Uzun S, Kozumplik O. Reinforcement of irritability during therapy with benzodiazepines. Psychiatr Danub. 2011;23(1):129–130.
23. Uzun S, Kozumplik O, Jakovljević M, et al. Side effects of treatment with benzodiazepines. Psychiatr Danub. 2010;22(1):90–93.
24. Ćurković M, Dodig-Ćurković K, Petek Erić A, et al. Psychotropic medications in older adults: a review. Psychiatr Danub. 2016;28(1):13–24.
25. De Las Cuevas C, Sanz EJ. Controversial issues associated with the prescription of benzodiazepines by general practitioners and psychiatrists. Med Sci Monit. 2004;10(7):CR288–CR293.
26. Štimac D, Čulig J. Outpatient utilization of psychopharmaceuticals in the city of Zagreb 2001–2006. Psychiatr Danub. 2009;21(1):56–64.

27. Vlahović-Palčevski V, Bergman U. Quality of prescribing for the elderly in Croatia - computerized pharmacy data can be used to screen for potentially inappropriate prescribing. *Eur J Clin Pharmacol.* 2004;60:217–220.
28. Živković K, Zelić-Kerep A, Štimac D, et al. A study on the quality of outpatient prescription of psychopharmaceuticals in the City of Zagreb 2006–2009. *Coll Antropol.* 2014;38(2):717–724.
29. Kiivet RA, Bergman U, Rootslane L, et al. Drug use in Estonia in 1994–1995: a follow-up from 1989 and comparison with two Nordic countries. *Eur J Clin Pharmacol.* 1998;54(2):119–124.
30. Jordanova V, Maric NP, Alikaj V, et al. Prescribing practices in psychiatric hospitals in Eastern Europe. *Eur Psychiatry.* 2011;26 (7):414–418.
31. Lenander C, Bondesson Å, Viberg N, et al. Effects of an intervention (SÄKLÄK) on prescription of potentially inappropriate medication in elderly patients. *Family Practice.* 2016;1–6. DOI:10.1093/fampra/cmw121
32. Järbrink K, Carlsten A, Frederiksen SO. Swedish physicians' inclination to prescribe benzodiazepines: differences between regions and characteristics of the prescriber. *Scand J Public Health.* 1999;1:22–29.
33. World Health Organization. Depression and other common mental disorders: global health estimates. Rep. CC BY-NC-SA 3.0 IGO. Geneva: World Health Organization; 2017.
34. World Population Review. Countries by median age. 2018. [cited 2018 Jun 28]. Available from: <http://worldpopulationreview.com/countries/median-age/> Accessed.