

COMPARISON OF PSYCHOTROPIC DRUG PRESCRIBING QUALITY BETWEEN ZAGREB, CROATIA AND SARAJEVO, B&H

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SUMMARY

Background: The purpose of this paper was to compare outpatient consumption and quality of psychotropic drug prescribing between Croatia and Bosnia & Herzegovina 2006-2010.

Methods: Data on drug utilization from Zagreb Municipal Pharmacy and Sarajevo Public Pharmacy were used to calculate the number of defined daily doses (DDD) and DDD per 1000 inhabitants per day (DDD/TID) using the WHO Anatomical-Therapeutic-Chemical methodology.

Results: Total utilization of psychopharmaceuticals increased in both cities; however, it was higher in Zagreb than in Sarajevo throughout the study period. The utilization of psycholeptics increased in Zagreb by 2.4% (from 74.5 to 76.3 DDD/TID) and in Sarajevo by 3.8% (from 62.4 to 64.8 DDD/TID). The utilization of anxiolytics decreased in Zagreb by 2.1% and in Sarajevo by even 18.7%. The utilization of antidepressants increased in both cities with predominance of SSRI over TCA utilization, greater in Sarajevo (96.6%) than in Zagreb (10.2%). The anxiolytic/antidepressant ratio decreased by 11.1% in Zagreb (from 2.87 to 2.55) and by 58.7% in Sarajevo (from 5.66 to 2.34). Outpatient utilization of antipsychotics increased significantly in Sarajevo, predominated by typical ones, whereas in Zagreb the utilization of antipsychotics was stable, predominated by atypical ones.

Conclusions: In Croatia and Bosnia & Herzegovina, there was an obvious tendency to follow western trends in drug prescribing, as demonstrated by the increased use of antidepressants and reduced use of anxiolytics. Despite some improvement observed in the prescribing quality, high use of antipsychotics with dominance of typical antipsychotics in Sarajevo points to the need of prescribing guidelines for antipsychotics.

Key words: psychotropic drugs - prescribing quality - ATC/DDD methodology - Zagreb-Sarajevo

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INTRODUCTION

Mental disorders pose one of the priority public health problems worldwide. The burden of mental and neurological disorders has been seriously underestimated by traditional epidemiological methods that took into account only mortality, but not disability rate. The proportionate share of total global burden of disease due to neuropsychiatric disorders is projected to rise to 14.7% by 2020 (WHO 2006).

On the other hand, the burden posed by drug costs upon the otherwise inadequate health care resources and rational drug utilization are important segments of every national health policy. The Croatian government was concerned that Croatia appeared to spend more money on medicinal drugs than most other countries in the region (Harvey et al. 2004).

According to the Intercontinental Marketing Service (IMS) data, the leading groups of drugs utilized worldwide are cardiovascular drugs, immediately followed by central nervous system (CNS) drugs with a continuous annual rise of 11% (Intercontinental Marketing Service

2007). A similar pattern has been observed in Croatia, with a predominance of cardiovascular drugs followed by CNS drugs (Štimac et al. 2009, Erceg et al. 2005, Štimac et al. 2010).

We embarked upon this study to compare the quality of psychotropic drug prescribing between Zagreb, Croatia and Sarajevo, Bosnia and Herzegovina, as capitals of the two neighboring countries characterized by considerable differences as well as similarities such as common past (former Yugoslavia) and other features (war sufferings, transition countries).

Zagreb accounts for about 18% of the Croatian population and Sarajevo for approximately the same percentage of people inhabiting the Federation of Bosnia and Herzegovina. In addition, Zagreb accounts for 43% of the Croatian health resources and Sarajevo for 30%-40% of Bosnia and Herzegovina health resources (Štimac et al. 2009, Agency for Medicines and Medical Devices of Bosnia and Herzegovina 2011, Official Sarajevo City 2011). Both cities have the county status and represent the trends in their countries as a whole, which makes them highly comparable.

As drug prescribing behavior is known to be influenced by a number of individual factors such as sex, age, cultural background, patient needs and demands, pharmaceutical industry, etc., we were interested to identify the extent to which the Croatian and Bosnian prescribing habits follow modern principles of psychopharmacotherapy (Štimac et al. 2009).

The aims of the study were: 1) to determine the outpatient utilization of psychiatric drugs in Zagreb and Sarajevo; 2) to compare the outpatient utilization of psychiatric drugs between the two cities; and 3) to assess the quality of psychopharmaceutical prescribing using the World Health Organization Anatomical-Therapeutic-Chemical classification system (ATC)/Defined Daily Doses (DDD) methodology (ATC/DDD methodology) and Eurostat ratio indicators (WHO 2009).

METHODS

Data on the outpatient utilization of psycholeptics and psychoanaleptics (ATC groups N05 and N06) in both cities were received from pharmacies and collected during 2006, 2007, 2008, 2009 and 2010. Data are expressed as defined daily doses *per* thousand inhabitants *per* day (DDD/TID). Using the ATC/DDD methodology, the data obtained can be compared with other settings and between different time periods (WHO 2009).

On DDD/TID calculation, data from the 2001 census were used, according to which the population of Zagreb was 770 058 (Croatian Bureau of Statistics 2011). As for Sarajevo, we used the latest data published by the Federation of Bosnia and Herzegovina Federal Office of Statistics, according to which the population of Sarajevo County was 423 645 (FBiH Federal Office of Statistics 2011). Total outpatient utilization of ATC N05 and N06 prescription drugs, utilization distribution of these groups of drugs at

secondary, tertiary and quarterly level, and consumption of individual drugs were analyzed.

The Drug Utilization 90% (DU90%) method and Eurostat ratio indicators were used on prescribing quality evaluation (EURO-MED-STAT Group 2003).

RESULTS

The utilization of psycholeptics increased in Zagreb by 2.4% (from 74.5 to 76.3 DDD/TID) and in Sarajevo by 3.8% (from 62.4 to 64.8 DDD/TID) (Table 1). The utilization of antidepressants was on an increase in both cities. It increased by 10.2% (from 18.6 DDD/TID in 2006 to 20.5 DDD/TID in 2010) in Zagreb and by far more (96.6%) in Sarajevo (from 8.9 DDD/TID in 2006 to 17.5 DDD/TID in 2010). Analysis of trends in Zagreb revealed continuous rise in the utilization of antidepressants until 2008, followed by a 6.8% decline in 2010. In Sarajevo, the rising trend was continuously recorded, being more pronounced in 2007 compared to 2006 and in 2009 compared to 2008.

The utilization of anxiolytics was on a decrease in both cities. It decreased by 2.1% in Zagreb and significantly more, by 18.7%, in Sarajevo. Analysis of trends in Zagreb revealed a rising trend until 2008, followed by a decline. Although a greater decline in the utilization of anxiolytics was recorded in Sarajevo, the decreasing trend was not continuous.

In total antidepressant and anxiolytic utilization during the 2006-2010 period, the utilization of anxiolytics exceeded the utilization of antidepressants both in Zagreb and in Sarajevo. Antipsychotic drugs are divided into two subgroups for this overall analysis. Outpatient utilization of atypical antipsychotics including clozapine, olanzapine, quetiapine, sulpiride, ziprasidone, zuclopentixole and risperidone increased in both cities. The utilization of typical antipsychotics showed a declining tendency in Zagreb, whereas in Sarajevo a significant increase was recorded (Table 1).

Table 1. Utilization of psychiatric drugs in Zagreb and Sarajevo during the 2006-2010 period expressed as DDD/TID

	Year	DDD/TID				Antidepressants N06A
		Psycholeptics N05	Antipsychotics Typical	N05A Atypical	Anxiolytics N05B	
Zagreb	2006	74.5	2.8	5.5	53.4	18.6
	2007	77.5	2.9	5.9	54.4	20.2
	2008	82.0	2.8	6.1	57.4	22.0
	2009	76.1	2.7	5.9	52.2	20.8
	2010	76.3	2.5	5.9	52.3	20.5
Sarajevo	2006	62.4	3.4	3.5	50.4	8.9
	2007	57.2	2.8	2.4	45.8	11.8
	2008	69	5.1	5.4	51.9	11.3
	2009	61.6	5.9	6.4	39.5	16.9
	2010	64.8	6.4	7.7	41.0	17.5

Table 2. Psycholeptics and psychoanaleptics within Drug Utilization 90% (DU90%) segment expressed as DDD/TID in Zagreb in 2010

Number	Drug name	DDD/TID	Share (%)
1	Diazepam	24.55	25.35
2	Alprazolam	14.93	15.42
3	Zolpidem	12.58	12.99
4	Oxazepam	7.13	7.36
5	Lorazepam	5.20	5.37
6	Sertraline	5.17	5.34
7	Paroxetine	3.82	3.95
8	Olanzapine	2.78	2.87
9	Escitalopram	2.34	2.42
10	Nitrazepam	2.20	2.27
11	Citalopram	2.05	2.11
12	Fluvoxamine	1.87	1.93
13	Fluoxetine	1.76	1.82
14	Promazine	0.99	1.02
DU90% 1-14		87.36	90.21
Others 15-49		9.48	9.79
Total		96.84	100.00

Table 3. Psycholeptics and psychoanaleptics within Drug Utilization 90% (DU90%) segment expressed as DDD/TID in Sarajevo in 2010

Number	Drug name	DDD/TID	Share (%)
1	Diazepam	22.96	27.87
2	Bromazepam	13.12	15.93
3	Paroxetine	5.78	7.02
4	Fluoxetine	4.9	5.95
5	Zolpidem	4.66	5.66
6	Sertraline	4.06	4.93
7	Nitrazepam	4	4.86
8	Lorazepam	2.66	3.23
9	Olanzapine	1.96	2.38
10	Clozapine	1.7	2.06
11	Haloperidol	1.62	1.97
12	Sulpiride	1.58	1.92
13	Amitriptyline	1.38	1.68
14	Risperidone	1.28	1.55
15	Promazine	1.24	1.51
16	Ziprasidone	1.18	1.43
DU90% 1-16		74.08	89.92
Others 17-31		8.3	10.08
Total		82.38	100.00

Outpatient drug utilization within and beyond DU90% segment in 2010 was compared between Zagreb (Table 2) and Sarajevo (Table 3). Fourteen and 16 drugs fell under DU90% segment in Zagreb and Sarajevo, respectively. In Zagreb, four benzodiazepines and two hypnotics, six antidepressants, one third-generation antipsychotic (olanzapine) and one first generation antipsychotic (promazine) were pre-

sent within DU90% segment. The most used benzodiazepines were diazepam and alprazolam. The most used antidepressants were sertraline and paroxetine, both SSRIs.

In Sarajevo DU90% profile comprised of 16 drugs – three benzodiazepines and two hypnotics, four antidepressants, and seven antipsychotics.

Haloperidol among typical, and olanzapine among atypical, were the most used antipsychotic drugs in Sarajevo (Table 2, Table 3).

DISCUSSION

In this retrospective study we compared the utilization of CNS drugs. Study results pointed to differences in the psychopharmaceutical utilization pattern in primary health care between Zagreb County and Sarajevo Canton. The differences were partly attributable to different socioeconomic and health policy factors in the two settings.

DU90% is a simple and rapid but rough method for assessing drug prescribing in routine healthcare settings. It enabled us to highlight the drugs most used in each year and to determine the effect of the list update: almost immediately after the update, the newly introduced drugs fell into the DU90% profile. The number of drugs in the DU90% profile can also provide valuable information on the prescribing habits in the growing drug market (Štimac 2009, EURO-MED-STAT Group 2003, Marković-Peković et al. 2010, Bergman et al. 1998).

Analysis of DU90% segment in Zagreb in 2010 revealed utilization of even 5 benzodiazepines including 4 anxiolytics and one hypnotic (nitrazepam). Zolpidem belongs to a new generation of benzodiazepine related hypnotics, which is currently recommended as therapy for insomnia; in Zagreb, the utilization of zolpidem was on an increase from 2003 (from 8.1 to 12.99 DDD/TID) (Andersen & Frydenberg 2011). A similar trend was recorded in Sarajevo, however, the overall share of benzodiazepines within DU90% segment was lower than that found in Zagreb. Along to the high utilization of zolpidem, a high utilization of nitrazepam was also recorded in Sarajevo.

In Zagreb, even 6 of 6 antidepressants within DU90% segment were from the SSRI group. The utilization of escitalopram (although on the Supplementary List of the Croatian Institute of Health Insurance, CIHI) exceeded the utilization of citalopram (CIHI Main List), along the lines of the latest research suggesting that escitalopram is more efficient than citalopram and other SSRIs or SNRIs according to health and economic indicators. Escitalopram has been associated with lower cost and lower health care utilization, primarily owing to less common and shorter hospitalizations relative to citalopram. In addition, patients administered escitalopram have to switch to other antidepressants less frequently than those taking citalopram (Wu et al. 2012,

CIHI 2006). In Sarajevo, 3 of the 4 antidepressants were from the SSRI subgroup (paroxetine, fluoxetine and sertraline), along with one tricyclic amitriptyline, which is according to current knowledge, responsible for more side effects than SSRI (Štimac et al. 2009, Marković-Peković et al. 2010, Sauer et al. 2003).

In Zagreb, olanzapine was the antipsychotic falling within DU90% segment; it is the third generation antipsychotic which is included in the CIHI Main List but can only be prescribed if recommended by a psychiatrist. Total antipsychotic utilization was stable throughout the study period (8.3 DDD/TID in 2006 vs. 8.4 DDD/TID in 2010), with a predominance of atypical antipsychotics. Newer atypical antipsychotics have a number of advantages over old typical antipsychotics, such as better tolerability and a significantly lower incidence of extrapyramidal side effects (Jakovljević 2001, Štimac et al. 2009). The third generation antipsychotics have become the standard of antipsychotic pharmacotherapy and the first line treatment for schizophrenia (Jakovljević 2009, Thibaut 2014), although the results of some pragmatic clinical trials have delivered controversial messages about comparative efficacy and effectiveness of the new generation antipsychotics. Personalized medicine in psychiatry is not possible without the availability of enough number of different modern antipsychotics (Jakovljević 2009).

In Sarajevo, even 7 antipsychotics including 2 typical antipsychotics were within DU90% segment, which was quite surprising for outpatient drug utilization at the primary health care level. During the 5-year period, the outpatient utilization of antipsychotics increased by 104% (from 6.9 DDD/TID in 2006 to 14.1 DDD/TID in 2010). The utilization of typical antipsychotics was still too high, although their rise during the study period was lower compared to the rise in the utilization of atypical antipsychotics (88% vs. 120%), similar to Slovenia, Serbia and Montenegro; however, in these countries, the increase in the utilization of typical antipsychotics was considerably lower or almost stopped (Medicines and Medical Devices Agency of Serbia 2007, Montenegro Health Insurance Fund 2008, Divac et al. 2006, Furst & Kocmur 2003).

The recent inclusion of a number of antipsychotics on the List of Drugs approved by the Sarajevo Canton Institute of Health Insurance must have been the main reason for the increased utilization of antipsychotics in Sarajevo, as it enabled wide use of these drugs (Sarajevo Canton Institute of Health Insurance 2009). In addition, a project of mental health improvement, with special reference to posttraumatic stress disorder (PTSD) patients, was launched at the time; along with socioeconomic status (a high rate of unemployment), PTSD could also add to the increased utilization of antipsychotics (Sarajevo Canton Institute of Health Insurance 2007). The citizens of Sarajevo were long exposed to war actions, which certainly contributed to the high prevalence of mental disorders in comparison

with Zagreb citizens. Numerous studies have confirmed the association of exposure to war actions and prevalence of mental disorders, PTSD and major depression in particular; the more so, a study conducted in five Balkans countries showed the prevalence of these disorders in Bosnia and Herzegovina to exceed the prevalence recorded in other countries involved (Priebe et al. 2010).

The ratio of anxiolytics to antidepressants has also been used as an indicator of psychopharmaceutical prescribing quality in a particular setting, whereby antidepressants as etiological therapy should prevail (EURO-MED-STAT Group 2003, Štimac et al. 2009). In Zagreb, the anxiolytic/antidepressant ratio decreased from 2.87 in 2006 to 2.55 in 2010. The decrease in the utilization of anxiolytics with symptomatic action and the increased utilization of antidepressants with etiological action points to improved psychopharmaceutical prescribing quality. Although this ratio decreased by 11.1% during the study period, and by even 65.1% from 2001, it still remained unfavorable in comparison with Scandinavian countries, where it ranges from 0.7 in Finland, through 0.4 in Norway and Denmark, to 0.3 in Sweden, and also with Slovenia (0.5), while being better in comparison with the Republic of Srpska, Bosnia and Herzegovina (8.8) and Serbia (10.7) (Divac et al. 2004, Divac et al. 2006, Norwegian Institute for Public Health 2011, Svab et al. 2011, Štimac et al. 2009). In Sarajevo, the anxiolytic/antidepressant ratio decreased by 58.7% during the study period (from 5.66 in 2006 to 2.34 in 2010). This great and abrupt reduction in the utilization of anxiolytics must have resulted from the efforts invested by the Bosnia and Herzegovina Agency for Drugs and Medicinal Products and strict inspection in public pharmacies because the principle of prescription drug issuing used to be obviated quite frequently, so that these relatively inexpensive drugs could be bought as over-the-counter medicines. In private sector, this practice then persisted for some time, however, showing a declining tendency. It was one of the private sector measures to attract these patients; when they could not buy the drug without prescription in public pharmacy, they used to go to private pharmacy to get the drug (Agency for Drugs and Medicinal Products of Bosnia and Herzegovina 2008). The psychopharmaceutical prescribing quality has been influenced by the specific socioeconomic features in these countries.

The fact that the outpatient drug utilization data were systematically collected in Croatia, whereas in Bosnia and Herzegovina the issue is not regulated by law, could be perceived as one of the study limitations (By-Law on the Type of Data and Reporting on Drug Utilization 2005). This may be one of the obstacles in conducting studies like this, which can help improve the prescribing habits.

Until 2001, only economic indicators of drug consumption were monitored in Zagreb and Croatia; therefore the problem of benzodiazepine overutilization

because of their low price could not be identified. Upon switching to the new methodology of monitoring drug utilization and introducing the WHO ATC/DDD method, the problem has emerged and an array of public health and regulatory measures have been launched, i.e. education of primary health care physicians on the rational use of benzodiazepines and inclusion of SSRI on the Main List of Drugs (By-Law on the Type of Data and Reporting on Drug Utilization 2005). These interventions have resulted in a reduced utilization of benzodiazepines and improved prescribing quality in Zagreb.

Another limitation of this study was the limitation of the DDD methodology itself, as the defined daily dose does not necessarily reflect the recommended or prescribed daily dose. This methodology provides only a rough estimate of consumption and not an exact picture of actual use (Bergman et al. 1998, EURO-MED-STAT Group 2003, Štimac et al. 2009).

CONCLUSION

Comparison of psychopharmaceutical utilization in Zagreb County and Sarajevo Canton during the study period (2006-2010) revealed some similarities as well as some significant differences. Although the utilization of anxiolytics was found to have decreased in both cities, it was still too high and irrational due to the high utilization of benzodiazepines. The utilization of antidepressants increased in both cities, whereby the utilization of TCA was lower in Zagreb as compared with Sarajevo. The utilization of SSRI was higher in Zagreb, pointing to better quality of antidepressant prescribing in this city.

Updating the list of drugs with SSRI antidepressants is a rational and unavoidable decision, paving the way for implementation of clinical guidelines for the treatment of mental disorders. It also influenced the anxiolytic/antidepressant ratio, which was found to have improved considerably in both cities in 2010 as compared with previous years, as an indicator of more favorable prescribing habits in the treatment of anxiety and depression as the two most common mental disorders managed by general practitioners.

The utilization of psycholeptics increased in Sarajevo during the 5-year study period; while the utilization of anxiolytics was significantly reduced, the utilization of antipsychotics showed a rising tendency.

The outpatient utilization of antipsychotics was too high and irrational considering the high share of typical antipsychotics within DU90% segment and the fact that these drugs can only be prescribed to the general population if recommended by a psychiatrist. The high utilization of antipsychotics in Sarajevo was probably related to the high prevalence of PTSD.

In Croatia and Bosnia and Herzegovina, there is an obvious tendency to follow western trends in drug prescribing, as demonstrated by the increased utilization of antidepressants and reduced use of anxiolytics.

Despite some improvement observed in the prescribing quality, high use of antipsychotics with dominance of typical antipsychotics in Sarajevo points to the need of prescribing guidelines for antipsychotics in Bosnia & Herzegovina. However, greater efforts need to be invested to additionally improve the prescribing quality in both countries.

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