Psychiatria Danubina, 2009; Vol. 21, No. 1, pp 56–64 *Original paper*

OUTPATIENT UTILIZATION OF PSYCHOPHARMACEUTICALS IN THE CITY OF ZAGREB 2001-2006

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SUMMARY

Background: *A comprehensive insight into drug utilization as an economic and primarily a public health issue can only be acquired in the context of overall health state of the respective population. The objectives of the study were: 1) to determine the real outpatient utilization of psychopharmaceuticals in Zagreb, 2) to determine the psychopharmaceutical prescribing quality during the study period; and 3) to propose appropriate interventions in Zagreb on the basis of the results obtained.*

Subjects and methods: *Data on drug utilization were obtained from all Zagreb pharmacies. The number of defined daily doses (DDD) and number of DDD* per *1000 inhabitants* per *day (DDD/1000/day) were calculated from the number of particular drug packages. The Drug Utilization 90% (DU90%) method was used as a criterion of prescribing quality.*

Results: *Outpatient utilization of psychopharmaceuticals showed a declining pattern from 115.40 DDD/1000/day in 2001 to 93.15 DDD/1000/day in 2006. Anxiolytics accounted for the majority of this drug group utilization in the City of Zagreb, although the anxiolytic/antidepressant ratio decreased from 7.19 in 2001 to 3.86 in 2006. The utilization of selective serotonin reuptake inhibitors showed a 2.5-fold increase and accounted for 90% of overall antidepressant utilization. A 2.5-fold decrease was recorded in the utilization of antipsychotics, while the atypical/typical antipsychotic ratio changed from 1:2 in 2001 to 1.1:1 in 2006.*

Conclusion: *Despite some improvement observed in the prescribing quality, the predominance of benzodiazepines in the utilization of psychopharmaceuticals points to the need of additional rationalization in the field.*

Key words: *psychotropic – drugs – utilization – Zagreb - ATC/DDD methodology*

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INTRODUCTION

Drug utilization is in the very focus of discussion from the economic, political and health care viewpoints. A comprehensive insight into drug utilization as an economic and primarily a public health issue can only be acquired in the context of overall health state of the respective population.

The pharmaceutical system reform is part of the overall health care reform that has been under way in the Republic of Croatia. These changes should also include establishment of a national drug policy to cover, among other elements, uniform prescription guidelines for psychiatric drugs, and measures for their implementation and evaluation. According to 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). The aging of the population, the emergence of new drugs on the market, and the impact of pharmaceutical industry marketing are only some of the reasons for the continuous rise of drug utilization (Vukušić el al.2005, Smith 2003). A similar pattern has been observed in Croatia, with a predominance of cardiovascular drugs followed by CNS drugs (Lukovnjak et al. 2006, Štimac et al. 2007). There have been no studies assessing the justifiability of such a high utilization of these drugs. These data stimulated us to undertake the present study.

The objectives of the study were: 1) to determine the real outpatient utilization of psychopharmaceuticals in Zagreb, the capital of Croatia, using the Anatomical-Therapeutic-Chemical drug classification (ATC) and defined daily doses (DDD), i.e. ATC/DDD methodology as a standard method of drug utilization monitoring (Wertheimer 1986, Natsch et al. 1998, Ronning et al. 2000); 2) to determine the psychopharmaceutical prescribing quality during the study period; and 3) to propose appropriate interventions in Zagreb on the basis of the results obtained. Zagreb accounts for about 18% of the Croatian population and 43% of the Croatian health resources, thus quite reliably representing the trends in Croatia as a whole, where the prescribing quality is likely to be equal or lower (Croatian Statistic Institute 2007, Institute of Zagreb City Development and Enviroment 2007).

SUBJECTS AND METHODS

Data on the outpatient utilization of psycholeptics and psychoanaleptics (ATC groups N05 and N06) in the City of Zagreb were collected during the 2001-2006 period. Data were received from pharmacies, and were based on individual prescriptions. Data on the size and number of packages, and financial data based on wholesale price were obtained from all Zagreb pharmacies for each individual drug. All drugs were classified according to ATC system. Based on the data obtained, the number of DDD and DDD *per* 1000 inhabitants *per* day (DDD/1000/day) were calculated for all N05 and N06 drugs using ATC indexes with DDDs for 2001, 2002, 2003, 2004, 2005 and 2006 (Word Health Organization Collaborating Centre for Drug Statistic Methodology 2001, 2002, 2003, 2004, 2005, 2006). On DDD/1000/day calculation, data from the latest 2001 census were used, according to which the population of the City of Zagreb was 770,588. Total outpatient utilization of ATC N05 and N06 prescription drugs, utilization distribution of these groups of drugs at secondary, tertiary and quaternary level, and consumption of individual drugs were analyzed. The Drug Utilization 90% (DU90%) method was used as a criterion of prescribing quality (Bergman et al. 1998, Wettermark et al. 2003). In order to compare drug costs with other national reports, additional indicators of rational drug utilization were also determined, e.g., cost *per* DDD within DU90% segment (cost/DDD); cost/DDD for drugs beyond DU90% segment; and cost/DDD for all psychopharmaceuticals analyzed.

RESULTS

According to ATC classification, psychopharmaceuticals are divided into two main anatomical groups: psycholeptics (N05) including antipsychotics (N05A), anxiolytics (N05B) and hypnotics (N05C); and psychoanaleptics (N06) including antidepressants (N06A), psychostimulants, drugs for attention-deficit/hyperactivity disorder (ADHD), nootropics (N06B) and antidementia drugs (N06D). Total utilization of psycholeptics and psychoanaleptics (N05 and N06) is presented in Table 1.

During the 2001-2006 period, total utilization of psychopharmaceuticals showed a declining tendency, with a decrease recorded in the utilization of psycholeptics and an increase in the utilization of psychoanaleptics. Benzodiazepines, anxiolytics in particular, accounted for the majority of psycholeptic utilization. The pattern of outpatient utilization of the most frequently prescribed benzodiazepines and the hypnotic zolpidem from the group of benzodiazepine related drugs is presented in Figure 1.

Antidepressants (N06A) accounted for nearly entire utilization of psychoanaleptics. During the study period, outpatient utilization of antidepressants increased by 41.93%, mostly due to the more than twofold increase in the utilization of selective serotonin reuptake inhibitors (SSRI). At the same time, the utilization of nonselective monoamine reuptake inhibitors decreased by 53.32%, while the use of other antidepressants was rather low (Fig 2).

Tables 2 and 3 depict those drugs that accounted for the majority of utilization, and illustrate the psychopharmaceutical prescribing quality in 2001 and 2006, respectively.

Table 1. Utilization of psycholeptics (N05) and psychoanaleptics (N06) in Zagreb 2001-2006 expressed as number of DDD/TID

ATC Code	2001	2002	2003	2004	2005	2006
N05A	15.52	11.56	9.04	10.66	8.27	8.26
N05B	77.84	70.22	74.13	67.97	58.37	53.44
N05C	8.55	9.40	11.11	13.28	11.96	12.82
N05	101.91	91.18	94.28	91.91	78.60	74.52
N06A	10.83	12.79	15.26	15.03	16.72	18.65
N06B	0.47	0.47	0.39	0.25	0.23	0.10
N06D	-	0.01	0.03	0.02	0.01	0.01
N06	11.30	13.17	15.68	15.30	16.96	18.76
Total	113.21	104.35	109.96	107.21	95.56	93.28

Legend: N05A - Antipsychotics; N05B – Anxiolytics; N05C - Hypnotics and sedatives; N05 – Psycholeptics; N06A – Antidepressants; N06B - Psychostimulants agents used for ADHD and nootropics; N06D - Anti-dementia drugs; N06 - Psychoanaleptics

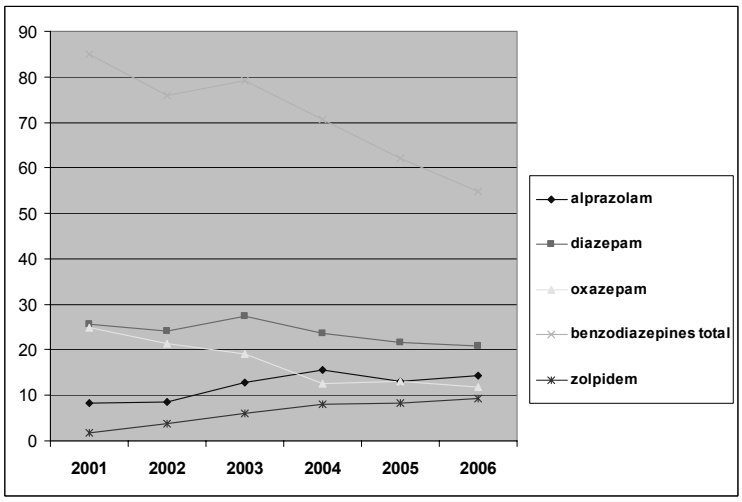
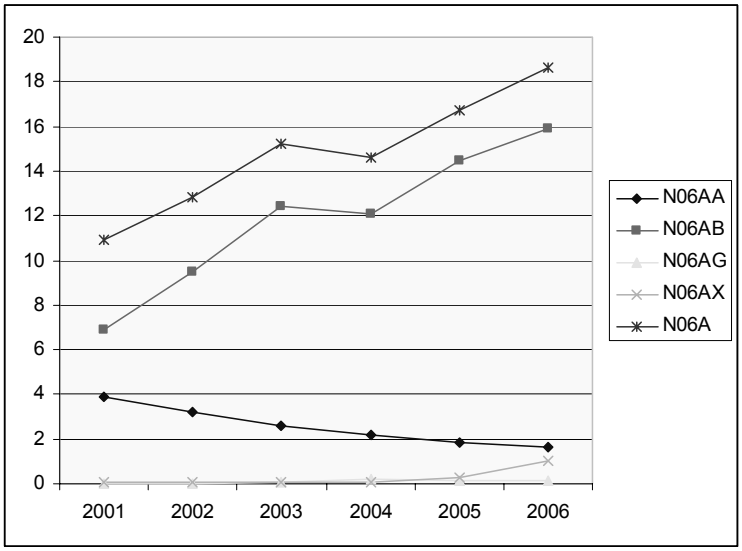


Figure 1. Outpatient utilization of benzodiazepines in the City of Zagreb 2001-2006 expressed as number of DDD/1000/day



Legend: N06AA - Non-selective monoamine reuptake inhibitors; N06AB - Selective serotonin reuptake inhibitors; N06AG - Monoamine oxidase A inhibitors; N06AX - Other antidepressants; N06A - Antidepressants

Figure 2. Outpatient utilization of antidepressants in the City of Zagreb 2001-2006 expressed as number of DDD/1000/day

Table 2. Psycholeptics and psychoanaleptics within Drug Utilization 90% (DU90%) segment expressed as number of DDD and cost *per* DDD in EUR within and beyond DU90% segment in Zagreb in 2001

No.	Drug name	DDD/TID	Share (%)	Cost/DDD
1	Diazepam	25.76	22.75	0.1
2	Oxazepam	24.92	22.01	0.2
3	Nitrazepam	6.24	5.51	0.1
4	Bromazepam	8.13	7.18	0.2
5	Lorazepam	10.41	9.20	0.1
6	Alprazolam	8.34	7.36	0.2
7	Fluoxetine	4.28	3.78	0.8
8	Promazine	9.31	8.22	0.2
9	Maprotiline	2.15	1.90	0.2
10	Fluphenazine	1.97	1.74	0.2
DU90% 1-10		101.51	89.65	0.2
Others 11-37		11.70	10.35	1.7
Total 1-37		113.21	100.00	0.6

Table 3. Psycholeptics and psychoanaleptics within Drug Utilization 90% (DU90%) segment expressed as number of DDD and cost per DDD in EUR within and beyond DU90% segment in Zagreb in 2006

No.	Drug name	DDD/TID	Share (%)	Cost/DDD
1	Diazepam	20.96	22.50	0.1
2	Alprazolam	14.34	15.39	0.2
3	Oxazepam	11.81	12.68	0.2
4	Zolpidem	9.32	10.00	0.2
5	Lorazepam	6.32	6.78	0.1
6	Paroxetine	4.55	4.88	0.6
7	Sertraline	4.11	4.41	0.6
8	Fluoxetine	2.74	2.94	0.4
9	Nitrazepam	2.65	2.85	0.1
10	Escitalopram	2.65	2.84	0.6
11	Olanzapine	2.40	2.58	3.6
12	Fluvoxamine	1.46	1.57	0.4
DU90% 1-12		83.31	89.42	0.6
Others 13-42		9.97	10.58	1.2
Total 1-42		93.28	100.00	0.9

The greater number of drugs within DU90% segment recorded in 2006 as compared with 2001 was simply a consequence of the increased number of psychopharmaceuticals registered in the Republic of Croatia in 2006. The antipsychotic thioridazine, the antidepressant trazodone and the anti-dementia agent rivastigmine were withdrawn from drug registry. In 2006, the following agents were newly registered in the Republic of Croatia: the antipsychotics ziprasidone, zuclopentixol and quetiapine; the hypnotic zaleplon; and the antidepressants escitalopram, citalopram, venlafaxine and mirtazapine. In 2001, six benzodiazepines, one SSRI antidepressant (fluoxetine), one antidepressant (maprotiline) and two first-generation antipsychotics were present within DU90% segment. In 2006, five benzodiazepines and the hypnotic zolpidem, five SSRI antidepressants and one third-generation antipsychotic (olanzapine) were found within

DU90% segment. A significant increase was recorded in the cost *per* DDD, both total and within DU90% segment.

DISCUSSION

The group of drugs used for the nervous system disorders (N) ranked second in total outpatient drug utilization in the City of Zagreb, with psychopharmaceuticals accounting for 70% of N group utilization and 9%-10% of total drug utilization (Štimac 2006). The high level of psychopharmaceutical utilization in Zagreb was substantiated by the respective morbidity indicators. The group of mental disorders and behavioral disorders was the third most common cause of inpatient treatment in Zagreb, accounting for 10% of hospitalizations. These disorders were a significant factor of outpatient morbidity as well, with 3.9% of diagnoses made at the level of general medicine and 10% of illnesses and states managed by emergency service. Mental disorders have for years been associated with the highest rate of hospital days, with a 30% share in the total number of hospital days, thus posing the greatest disease burden both in Zagreb and in Croatia as a whole. The group of mental disorders account for every third hospital day. Almost two thirds of all causes of hospitalization for mental disorders refer to four diagnostic groups, i.e. alcoholism (25.6%), schizophrenia (16.4%), depression and recurrent depressive disorder (10.3%), and major stress reaction including posttraumatic stress disorder (PTSD) (4.8%). During the study period, the rate of hospitalization for schizophrenia and depressive disorders increased, for PTSD decreased, and for alcoholism increased until 2002, then showing rise containment (Tešić et al. 2006). The group of psycholeptics accounted for more than two thirds of total group N utilization and has for years been one of the most frequently prescribed drug groups in Zagreb (Štimac 2006).

Outpatient utilization of antipsychotics was reduced by almost a half during the study period. The utilization of anxiolytics showed a declining tendency, whereas the utilization of hypnotics and sedatives increased in 2006 as compared with 2001. The ratio of atypical to typical antipsychotics increased in 2006. The overall utilization of atypical antipsychotics including clozapine, olanzapine, quetiapine, sulpiride and risperidone was 5.31 DDD/1000/day, and of typical antipsychotics 2.93 DDD/1000/day. The ratio of typical to atypical antipsychotics changed significantly from 2:1 in 2001 to 1:1.81 in 2006. This tendency was supported by the absence of thioridazine in the list of antipsychotics registered in Croatia in 2006. The new, atypical antipsychotics have many advantages over typical antipsychotics, to mention only their much better tolerability and significantly lower incidence of extrapyramidal side effects (Jakovljević 2001). The utilization pattern of the anticholinergic biperiden, used in the treatment of extrapyramidal side effects, can be taken as an indirect indicator of the psychopharmaceutical prescribing quality, i.e. of the reduced rate of these side effects. The utilization of biperiden was 2.15, 1.71, 1.57, 1.4, 1.16 and 0.6 DDD/1000/day in 2001, 2002, 2003, 2004, 2005 and 2006, respectively. Currently, atypical antipsychotics are the first choice agents in the treatment of schizophrenia, and this international tendency has also been adopted in the City of Zagreb (Green et al. 2006, Štimac et al. 2007). However, the initial enthusiasm in prescribing atypical antipsychotics has been somewhat abated by recent pharmacoeconomic studies (Jones et al. 2006, Barbui et al. 2006, Polsky et al. 2006, Magnus et al. 2005). As atypical antipsychotics belong to most expensive drugs in general, and olanzapine with highest and continuously rising utilization in particular, the Croatian Institute of Health Insurance (CIHI) has restricted the prescription of this agent exclusively to cases refractory or intolerant to standard therapy with classic antipsychotics (Croatian Institute of Health Insurance). Considering all the advantages of atypical antipsychotics and their very high price, these agents should probably be reserved for young, active patients (Vrhovac 2007).

The utilization of hypnotics and sedatives increased due to the rising use of N05CF subgroup (benzodiazepine related drugs). In 2006, these drugs showed a utilization rate of 9.5 DDD/ 1000/day, primarily due to zolpidem which was among the 20 most frequently prescribed drugs in

the City of Zagreb. Zolpidem is a partial non-benzodiazepine agonist of benzodiazepine receptors, which reduces the stage of falling asleep and prolongs overall sleep time. Now, it is the first choice drug in the management of insomnia (Jakovljević et al. 2001, Rowlet et al. 2007, Estivill et al. 2003). The utilization of benzodiazepine sedatives (N05CD) showed a declining pattern from 2001 to 2006. In the group of anxiolytics, an increasing pattern was recorded for alprazolam, which could be attributed to its antidepressant and antipanic effects in addition to anxiolytic action (Vrhovac 2007, World Health Organization 2005). The use of oxazepam showed a decline. Along with an increase recorded in 2003, diazepam showed a mild decrease of utilization during the study period, yet remaining the most widely prescribed benzodiazepine agent in Zagreb. Although diazepam as a long-acting agent is associated with a lower potential of dependence development and lower price, and was the only benzodiazepine included in the CIHI List of Essential Drugs, all oral diazepam preparations from the List of Drugs had a prescribing restriction in the form of 10% prescription charge, while preparations of the more expensive oxazepam could be prescribed free of charge until 2006. Considering the potential adverse effects of inappropriate use of benzodiazepines (e.g., development of dependence), their utilization in Zagreb is still too high and inappropriate, significantly exceeding that in Scandinavian and West European countries while being comparable with their utilization in neighboring countries (Del Rio et al. 1996, Van Hulten et al. 2003, Divac et al. 2004).

The utilization of antidepressants showed a rising pattern from 2001, with the highest increase recorded for SSRI, while the use of non-selective monoamine reuptake inhibitors steadily declined. Although fluoxetine had highest utilization among antidepressants in 2001, the greatest utilization increase was recorded for paroxetine and sertraline, which were present in DU90% segment in 2006. The predominance of paroxetine in the outpatient drug utilization, characteristic of outpatient drug utilization not only in Zagreb but also in many other European countries, should probably be ascribed to the fact that it is the only drug approved by the Food and Drug Administration for the treatment of depressive disorders as well as all five anxious disorders, i.e. obsessive-compulsive disorder, panic disorder, social phobia, PTSD and generalized anxious disorder (Jakovljević 2004).

In 2006, another two SSRIs were found within DU90% segment: escitalopram and fluvoxamine. Although citalopram has a very similar action but lower price than escitalopram, some studies support the Zagreb pattern of prescribing antidepressants, arguing that escitalopram is most selective of all SSRIs and more efficacious than citalopram (Fantino et al. 2007, Wade et al. 2005, Hemels et al. 2004, Demyttenaere 2005). The decreasing utilization of anxiolytics as agents with symptomatic action and increasing utilization of antidepressants characterized by etiologic action indicate improvement in the psychopharmaceutical prescribing quality (Furst et al. 2003, Ciuna et al. 2004). During the study period, the ratio of anxiolytic/antidepressant outpatient utilization was reduced significantly from 7.5:1 in 2001 to 3:1 in 2006.

In the group of antidepressants, the next was the subgroup of non-selective monoamine reuptake inhibitors (N06AA), led by maprotiline, present in DU90% segment in 2001. Although included in this group according to ATC classification, maprotiline is a selective norepinephrine reuptake inhibitor by its action. It belongs to second-generation antidepressants and is characterized by higher selectivity, thus being associated with fewer side effects than other agents of this subgroup. The subgroup of other antidepressants (N06AX) ranked third, with highest utilization of mirtazapine (0.66 DDD/1000/day) in 2006. In the group of antidepressants, the subgroup of monoamine oxidase type A inhibitors, which included only one agent, moclobemide, showed lowest utilization. During the study period, the overall utilization of antidepressants rose almost twofold, primarily due to the high utilization of SSRI.

Although total outpatient utilization of psychopharmaceuticals showed a declining pattern during the study period, their consumption

expressed in financial terms actually increased due to the prescribing of new, more different and thus more expensive drugs. The mean cost *per* psychopharmaceutical DDD was 0.6 and 0.9 EUR in 2001 and 2006, respectively, yielding a rise by 0.3 EUR/DDD. The highest rise was recorded in the cost/DDD within DU90% segment, first of all due to olanzapine and a greater number of new antidepressants. However, on choosing rational therapy all factors influencing the length and outcome of treatment should be taken in consideration, such as patient compliance, possible side effects and their treatment options, number of complications, hospitalization and rehospitalization as an indicator of treatment quality at primary health care level, and number of lethal outcomes. Non-rational use of less expensive drugs may frequently entail higher overall cost than appropriate use of a more expensive agent. This clearly applies to the data presented above. The utilization of benzodiazepines has been continuously decreased; however, these drugs still show highest utilization in the group of psycholeptics. In 2006, three benzodiazepine anxiolytics were still present among the leading 20 drugs according to utilization in the City of Zagreb, with the addition of zolpidem, a benzodiazepine related hypnotic (Čulig et al. 2007). Considering the side effects that may occur on non-rational use of these agents, to mention only the potential of tolerance and dependence development, efforts should be invested to reduce their overprescribing and reserve them exclusively for cases where these drugs are necessary and indicated; they should be prescribed in optimal dosage, over the shortest period of time and occasionally rather than permanently, if possible. According to literature data, benzodiazepines should be administered for four months or even for only two to four weeks at the most (Vrhovac et al. 2007, Jakovljević et al. 2001). Therefore, primary practitioners should receive continuous education on the rational use of drugs; the population at large should be regularly informed on the possible adverse events associated with the use of drugs; patient compliance with medication protocol should be followed up; and drug policy should be based on professional, evidence based guidelines.

CONCLUSION

The general insight in the quality of psychopharmaceutical prescribing in Zagreb points to improvement of prescribing patterns in primary health care. In Zagreb, benzodiazepines as a symptomatic rather than etiologic therapy still accounted for more than 50% of psychopharmaceutical utilization, pointing to the need of respective guidelines as a measure of rationalization. Pharmacoeconomic analysis should be introduced on including drugs on the Croatian List of Drugs; and problems should be more precisely defined and priorities identified through monitoring of drug utilization at the national level.

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