

# TRENDS IN THE OUTPATIENT UTILIZATION OF ANTIPSYCHOTIC DRUGS IN THE CITY OF ZAGREB IN THE TEN-YEAR PERIOD AS A TOOL TO ASSESS DRUG PRESCRIBING RATIONALITY

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## SUMMARY

**Background:** The aim was to determine distribution and trends in the outpatient utilization of antipsychotics to evaluate the rationality of antipsychotic drug prescribing during the ten year period.

**Subjects and methods:** The epidemiological method of descriptive and analytical observation was used. Data on drug utilization from Zagreb Municipal Pharmacy were used to calculate the number of defined daily doses (DDD) and DDD per 1000 inhabitants per day (DDD/TID) using the World Health Organization Anatomical-Therapeutic-Chemical methodology. The ratio of typical versus atypical antipsychotics served as an indicator on assessing the rationality of the utilization. Data on the use of anticholinergics in the treatment of neuroleptic side effects were also included.

**Results:** Outpatient utilization of antipsychotics showed a declining pattern from 14.17 in 2001 to 8.42 DDD/TID in 2010. The utilization of atypical antipsychotics increased by 60% (from 3.68 to 5.89 DDD/TID), while the utilization of typical antipsychotics decreased by 76% (from 10.49 to 2.53 DDD/TID). The drugs showing the largest increase were olanzapine (from 1.21 to 2.78 DDD/TID) and quetiapine (from 0 to 0.68 DDD/TID). The typical/atypical antipsychotic ratio changed from 1:0.4 in 2001 to 1:2.3 in 2010. A 2.3-fold decrease was recorded in the utilization of anticholinergics (from 2.05 to 0.91 DDD/TID).

**Conclusions:** Total consumption of neuroleptics significantly decreased. A decrease was also recorded in the utilization of anticholinergics. Study results pointed to two favorable features, i.e. low use of typical antipsychotics and the ratio of typical and atypical antipsychotics. Implementation of the new clinical guidelines for nervous system disorders and updating of the list of reimbursable drugs with the addition of new ones contributed to the observed improvement in the prescribing patterns during the study period. Using the WHO ATC/DDD methodology and rationality indicators in the assessment of trends in the outpatient utilization of psychopharmaceuticals over a ten-year period proved efficient in the evaluation of prescribing rationality.

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

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## INTRODUCTION

The group of mental disorders was the third most common cause of inpatient treatment in Zagreb, accounting for 10% of hospitalizations. These disorders account for every third hospital day, and schizophrenia has for years been associated with the highest rate of hospital days. Mental disorders were a significant factor of outpatient morbidity as well, with 3.9% of diagnoses made at the level of general medicine and 8% of illnesses and states managed by emergency service (Dr Andrija Štampar Institute of Public Health 2014, Polić Vižintin et al. 2005). 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 (Štimac et al. 2009).

The direct and indirect consequences of mental disorders lead to enormous health and social burdens, including negative economic effects. Therefore, analysis of drug utilization and monitoring of the prescribing habits are of greatest importance for policy-makers (Marković-Peković et al. 2010, Štimac 2012).

We were interested in finding out to what extent the prescribing habits in Zagreb followed modern principles of psychopharmacotherapy. The aim was to determine distribution and trends in the outpatient utilization of antipsychotics and to evaluate the rationality of antipsychotic drug prescribing during the 2001-2010 period.

## SUBJECTS AND METHODS

The epidemiological method of descriptive and analytical observation was used in this 10-year retrospective study. Data on outpatient drug utilization from Zagreb Municipal Pharmacy during the 2001-2010 period were used to calculate the number of defined daily doses (DDD) and DDD per 1000 inhabitants per day (DDD/TID) using the World Health Organization Anatomical-Therapeutic-Chemical (ATC) methodology. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults, and its use in DDD/TID is to enable a study of the extent of medicine utilization in a defined area and its changes over time. The DDD/TID is a useful indicator for

national and international comparisons, especially when the areas to be compared have a different number of inhabitants (EURO-MED-STAT group 2006, WHO 2009).

This study was focused on the utilization of antipsychotics (ATC subgroup N05A). In order to get the most realistic picture, data on the use of anticholinergics in the treatment of neuroleptic side effects were also included (ATC subgroup N04A) (Furst & Kocmur 2003).

The Eurostat ratio indicators were used on prescribing quality evaluation. The ratio of typical versus atypical antipsychotics served as an indicator on assessing the rationality of the utilization (EURO-MED-STAT group 2006).

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).

## RESULTS

### Antipsychotics

Outpatient utilization of antipsychotics (ATC subgroup N05A) in the City of Zagreb in the 2001-2010 period expressed as DDD/1000/day is presented in Table 1. Consumption of antipsychotics showed a declining pattern from 14.17 in 2001 to 8.42 DDD/TID in 2010. Antipsychotic drugs were divided into two subgroups for this overall analysis (Table 2).

**Table 1.** Utilization of antipsychotics in Zagreb 2001-2010 expressed as DDD/TID

ATC code	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Percentage*
N05AA	6.37	1.79	1.61	2.02	1.26	1.15	1.31	1.21	1.17	1.1	20.16
N05AB	2.19	1.77	1.93	1.44	0.69	0.66	0.66	0.67	0.69	0.6	12.00
N05AC	0.31	0.23	0.2	0.2	0.07	0	0	0	0	0	1.07
N05AD	1.62	1.15	1.14	1.82	1.03	0.95	0.88	0.88	0.87	0.83	11.86
N05AE	0	0	0	0	0	0.08	0.14	0.15	0.23	0.26	0.91
N05AF	0	0	0	0	0	0.12	0.08	0.13	0.08	0.08	0.52
N05AH	1.98	2.12	2.04	2.67	3.1	3.51	3.81	4.25	4.13	4.16	33.73
N05AL	0.94	0.82	0.76	1.41	1.1	0.83	0.97	0.6	0.56	0.54	9.06
N05AX	0.76	0.95	1.1	1.11	0.95	0.96	0.84	0.92	0.88	0.85	9.89
N05A	14.17	9.34	9.04	10.67	8.2	8.26	8.71	8.81	8.61	8.42	100.00

\*Mean share in total 10-year utilization of antipsychotics; DDD/TID = defined daily doses *per* 1000 inhabitants *per* day

**Table 2.** Utilization and ratio of typical/atypical antipsychotics in Zagreb 2001-2010 expressed as DDD/TID

Antipsychotics	DDD/TID									
	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Typical										
Chlorpromazine	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Levomepromazine	0.10	0.10	0.10	0.10	0.08	0.10	0.12	0.13	0.11	0.11
Promazine	6.27	1.69	1.51	1.92	1.18	1.05	1.19	1.08	1.06	0.99
Fluphenazine	1.97	1.31	1.46	1.23	0.69	0.66	0.66	0.67	0.69	0.60
Perazine	0.22	0.46	0.47	0.22	0.00	0.00	0.00	0.00	0.00	0.00
Thioridazine	0.31	0.23	0.20	0.20	0.07	0.00	0.00	0.00	0.00	0.00
Haloperidol	1.62	1.15	1.14	1.82	1.03	0.95	0.88	0.88	0.87	0.83
Total typical	10.49	4.94	4.88	5.48	3.06	2.75	2.86	2.75	2.73	2.53
Atypical										
Clozapine	0.76	0.69	0.24	0.72	0.61	0.66	0.67	0.73	0.70	0.70
Olanzapine	1.21	1.43	1.75	1.69	2.06	2.40	2.61	2.81	2.68	2.78
Risperidone	0.76	0.95	1.10	1.11	0.95	0.96	0.84	0.92	0.88	0.85
Ziprasidone	0.00	0.00	0.00	0.00	0.00	0.08	0.14	0.15	0.20	0.22
Quetiapine	0.00	0.00	0.06	0.25	0.43	0.45	0.54	0.71	0.75	0.68
Sulpiride	0.94	0.82	0.76	1.41	1.10	0.83	0.97	0.60	0.56	0.54
Zuclopenthixol	0.00	0.00	0.00	0.00	0.00	0.12	0.08	0.13	0.08	0.08
Sertindol	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.04	0.05
Total atypical	3.68	3.89	3.91	5.18	5.15	5.51	5.85	6.05	5.87	5.89
Typical/atypical ratio	1:0.4	1:0.8	1:0.8	1:0.9	1:1.7	1:2.0	1:2.0	1:2.2	1:2.2	1:2.3

DDD/TID = defined daily doses *per* 1000 inhabitants *per* day

The utilization of atypical antipsychotics increased by 60% (from 3.68 to 5.89 DDD/TID). The drugs showing the largest increase were olanzapine (from 1.21 to 2.78 DDD/TID) and quetiapine (from 0 to 0.68 DDD/TID). In 2010, olanzapine was the most popular atypical antipsychotic (47.1% of all atypical antipsychotics), followed by risperidone (14.4%), clozapine (11.9%) and quetiapine (11.5%). In contrast, the utilization of typical antipsychotics decreased by 76% (from 10.49 in 2001 to 2.53 DDD/TID in 2010). The drugs showing the largest decrease were promazine, then fluphenazine and haloperidol. However, in 2010, the three most popular typical antipsychotics were promazine (39.1% of total typical antipsychotic DDDs/1000/day), haloperidol (32.8%) and fluphenazine (23.7%). The typical/atypical antipsychotic ratio changed from 1:0.4 in 2001 to 1:2.3 in 2010.

### Anticholinergics

Anticholinergics from the subgroup of tertiary amines are used in psychiatry only to relieve some unwanted side effects of neuroleptics. In Croatia, biperiden was the only agent observed, which was included in the Croatian Institute of Health Insurance (CIHI) List of Drugs. Outpatient utilization of anticholinergics (ATC subgroup N04AA) in the City of Zagreb during the 2001-2010 period expressed as DDD/1000/day is illustrated in Table 3.

**Table 3.** Utilization of anticholinergics in Zagreb 2001-2010 expressed as DDD/TID

	Anticholinergics N04A
2001	2.05
2002	1.71
2003	1.58
2004	1.44
2005	1.16
2006	0.002
2007	1.02
2008	1.02
2009	0.90
2010	0.91

DDD/TID = defined daily doses *per* 1000 inhabitants *per* day

During the study period, a 2.3-fold decrease was recorded in the utilization of biperiden (from 2.05 in 2001 to 0.91 DDD/TID in 2010). The ratio between the use of typical antipsychotics and anticholinergics was 5.1 in 2001 and 2.8 in 2010.

## DISCUSSION

Study results showed that the total outpatient utilization of antipsychotics was reduced by almost a half during the 10-year period. In terms of DDD, total utilization of antipsychotics of 8.4 DDD/TID recorded

in this study was by far below that reported in Finland (20.26 DDD/TID), Norway (10.9 DDD/TID) and Denmark (12 DDD/TID) (Marković-Peković et al. 2010, Norwegian Institute for Public Health 2011, National Agency for Medicines Finland 2014).

The overall utilization of atypical antipsychotics increased, while the utilization of typical antipsychotics decreased. The ratio of typical to atypical antipsychotics changed significantly from 1:0.4 in 2001 to 1:2.3 in 2010. This tendency was supported by updating the list with the newer generation of atypical antipsychotics ziprasidone, zuclopentixol, quetiapine and sertindol, while the typical antipsychotic thioridazine was withdrawn from drug registry (Croatian Institute of Health Insurance 2006). This trend is similar to the global one found in most developed countries, such as Slovenia, Finland, Norway and Australia (Furst & Kocmur 2003, National Agency for Medicines Finland 2014, Norwegian Institute for Public Health 2011, Stephenson et al. 2013).

The leading atypical antipsychotic was olanzapine. While some large-scale studies suggest that olanzapine may be a more efficacious first-line treatment for psychosis than other atypical antipsychotics, the clinical significance of these benefits has been questioned (Komossa et al. 2010, Seabury et al. 2014, Leucht et al. 2009). Olanzapine also carries a higher risk of adverse metabolic effects than most other atypicals (Stephenson et al. 2013, Komossa et al. 2010).

As atypical antipsychotics belong to the most expensive drugs in general, and olanzapine with highest and continuously rising utilization in particular, the Croatian Institute of Health Insurance (CIHI) has restricted prescription of these agents exclusively to cases refractory or intolerant to standard therapy with classic antipsychotics (Croatian Institute of Health Insurance 2006).

Clozapine, an atypical antipsychotic with similar metabolic risks, has shown a slight utilization decrease over the decade and remains the most effective antipsychotic for treatment of resistant schizophrenia (Leucht et al. 2009, Mackin & Thomas 2012). Clozapine has been shown to be more effective than many of the newer antipsychotics and is often significantly cheaper than other antipsychotic drugs (Attard & Taylor 2012). 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). Currently, atypical antipsychotics are the first-line agents in the treatment of schizophrenia, and this international tendency has also been adopted in the City of Zagreb (Štimac & Čulig 2009, Green et al. 2006). It is considered that the advantages of atypical antipsychotics should be reserved for younger, active patients, as their quality of life is improved by the lower level of extrapyramidal side effects, while the price difference is still too high for atypical antipsychotics to be prescribed as first line therapy in all schizophrenic patients (Vrhovac et al. 2007).

Recent independent studies have posed a number of questions about comparative advantages of atypical antipsychotics because the results of independent clinical trials are not as favorable as the results of early studies sponsored by pharmaceutical industry (Jakovljević 2007). Most authors agree that schizophrenia therapy should be tailored for each patient individually (Jakovljević 2007, Thibaut 2014). Both classic and atypical antipsychotics are efficacious in the treatment of acute schizophrenia as well as in relapse prevention, where typical antipsychotics are associated with a higher risk of extrapyramidal side effects, whereas atypical antipsychotics bear a higher risk of metabolic and cardiovascular side effects (Thibaut 2014). In psychiatry, the principle of personalized medicine has introduced modifications in the theory and practice of clinical trials, trying to provide the best psychiatric health care based on valid evidence to patients suffering from schizophrenia. Development of individualized, personalized psychopharmacotherapy is not possible without an adequate number of different and modern antipsychotics available as first choice therapy in the management of schizophrenia (Jakovljević 2007, Jakovljević 2009).

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 (Furst & Kocmur 2003, Štimac & Čulig 2009).

Considering the similar use of typical antipsychotics in Zagreb (2.53 DDD/1000/day) in comparison with Norway and Finland (1.33-2.03 DDD/1000/day), we would expect a lower use of anticholinergics in Zagreb (National Agency for Medicines Finland 2014, Norwegian Institute for Public Health 2011). Although the utilization of anticholinergics in Zagreb decreased significantly, it is still up to three times higher than in Nordic countries. While Norwegian psychiatrists prescribe 1 daily dose of anticholinergics per 5.8 daily dose of typical antipsychotics, Finnish 1 per 5.9 and Slovenian 1 per 2.1, the psychiatrists in Zagreb prescribe 1 per 2.8 (National Agency for Medicines Finland 2014, Norwegian Institute for Public Health 2011, Furst & Kocmur 2003). Such extensive prescribing of anticholinergics burdens the patients with additional adverse effects.

In Croatia, drug prescribing is characterized by continuous efforts to use the restrictive financial resources for drugs in the most rational way. Despite some improvement observed in the prescribing quality, additional rationalization is necessary. One of the ways to rationalize drug utilization and upgrade the quality of drug prescribing is promotion of prescribing generic drugs. Results of the study conducted in the City of Zagreb revealed a significant decrease in the share of generic psychopharmaceuticals in total drug utilization recorded by DDD/1000/day, in spite of the fact that the

number of generic drugs included in the CIHI List of Drugs increased during the ten-year period. In the therapeutic subgroup of antipsychotics the share of generic drugs decreased significantly by 30.9% according to DDD/1000/day. The declining trend recorded in the utilization of generic antipsychotics could in part be attributed to the decreasing use of typical antipsychotics (only generic agents included in the CIHI List of Drugs in 2010) and the increasing use of atypical antipsychotics, where ever more generic and brand name drugs were available, and physicians tended to more frequently prescribe the more expensive brand name ones (Polić Vižintin et al. 2014).

## CONCLUSION

During the study period, total consumption of neuroleptics decreased significantly. The utilization of anticholinergics decreased. Study results pointed to two favorable features, i.e. low use of typical antipsychotics and the ratio of typical and atypical antipsychotics. Implementation of new clinical guidelines for nervous system disorders and updating the list of reimbursable drugs with the addition of new ones contributed to the observed improvement in prescribing patterns during the study period. Despite some improvement observed in the prescribing quality, additional rationalization is necessary.

Clinicians should determine individual treatment for patients with schizophrenia and keep in mind the efficacy, side effects and costs of various antipsychotic drugs. On prescribing anticholinergics, it would be useful to take professional guidelines into consideration. Using the WHO ATC/DDD methodology and rationality indicators in the assessment of trends in the outpatient utilization of psychopharmaceuticals over a ten-year period proved efficient in the evaluation of prescribing rationality. A more precise evaluation of the drug prescribing quality and rationality would require data on the diagnosis for which a particular drug has been prescribed and verification of patient compliance with therapy prescribed; this would help explain the increased use of atypical antipsychotics in spite of CIHI restrictions.

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### Contribution of individual authors:

M. Polić Vižintin and D. Štimac: study design and conception, acquisition of data, drafting the manuscript;  
I. Tripković: participate in coordination of the study and helped to analyse data, statistical analyses  
Z. Šostar: conceived of the study, participate in analysis and interpretation of data;  
M. Orban: literature searches, interpretation of data

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