Utilization of psychiatric drugs in Serbia

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Ključne reči:
leki, korišćenje; psihotropni leki; farmakoepidemiologija.

Key words:
drug utilization; psychotropic drugs; pharmacoepidemiology.

Introduction

Drug utilization has been defined by the World Health Organization (WHO) as the „marketing, distribution, prescription and the use of drugs in a society, with a special emphasis on the resulting medical, social, and economic consequences“ 1. Drug utilization studies are usually aimed at drug use-related problem detection and quantification. These studies may be quantitative (with the objective to quantify drug usage at various levels of health-care system), or qualitative (L) (which assess the appropriateness of drug utilization) 2, 3.

Utilization of psychiatric drugs is often a subject of drug utilization studies. Increasing researchers’ interest in prescribing and utilization of psychiatric drugs is noted worldwide 4–8. It is understandable, bearing in mind that these drugs are, maybe more than other pharmacotherapeutic groups, related to different epidemiologic, social and economic variables. It is usually a high rate of prescribing of certain psychiatric drugs, as well as self-medicating (e.g. with benzodiazepines) that causes concern, as well as the consequences of such practice: development of tolerance and addiction, drug abuse, and increased treatment costs.

Over the last decade in Serbia several drug utilization studies on the usage of psychiatric drugs have been conducted. These studies have addressed certain major issues: drug use patterns, prescribing behavior, gaps between guidelines and actual utilization and factors responsible for poly-pharmacy. Both, quantitative and qualitative aspects of psychiatric drugs use have been analysed using up-to-date methodology. Such a modern methodological approach enables comparison of the data from Serbian studies with the data from other countries, thus pointing out certain prescribers’ habits and/or patients’ preferences that are characteristic for our milieu.

Methodology of drug utilization studies

Quantitative drug utilization studies can be conducted on different levels: national, regional, local or institutional 9. The data essential for these studies can be obtained from different sources, depending on the purpose of the study. In general, the ideal is a number of patients in a defined population who ingest a drug of interest during a particular time frame 9, 10. For qualitative studies, it is required to identify a proportion of patients who consummate a drug in a certain manner, of all those who receive that drug in that time frame. In many countries, even in most developed ones, such data are not easy to obtain. Just a few countries have developed databases that provide data on drug prescribing and morbidity (so-called "diagnosis-linked" data): e.g., the General Practice Research Database (GPRD), in the United Kingdom, is the world’s largest computerised database of anonymised longitudinal medical records from primary care 11. The majority of available data sources are not diagnosis-linked: drug sales data, medical insurance data, samples of prescriptions or data from hospital pharmacies and patients’ records. Therefore, many studies worldwide have some limitations regarding reliability of the data. However, some data sources, like wholesale data (from drug manufacturers), even if not entirely accurate, in general provide trustworthy insight in drug consumption in a certain population.

In Serbia, drug utilization studies in general rely on manufacturers’ data on wholesale (for population-based studies), or the data from patients’ records and/or hospital pharmacies (hos-
Since 2004, the Medicines and Medical Devices Agency of Serbia has been publishing “Annual reports of the trade and consumption of the medicinal products” 16. These publications comprise data on drugs wholesale and distribution, as well as calculated rates on drug consumption per 1 000 inhabitants of Serbia per day, thus becoming essential instrument for pharmacoepidemiologic studies.

One of the major problems of drug utilization studies is standardization of raw data (number of drug packages consumed, number of dosage forms, milligrams etc.) into comparable units. This problem was recognized in the 1960s, when drug utilization studies were at their earliest stage of development. At a symposium of WHO in Oslo in 1969 entitled The Consumption of Drugs, it was agreed that an internationally accepted classification system for drug consumption studies was needed. At the same symposium the Drug Utilization Research Group (DURG) was established and tasked with the development of internationally applicable methods for drug utilization research. Norwegian researchers developed a system known as the Anatomical Therapeutic Chemical (ATC) classification of drugs. In order to measure drug use, a technical unit of measurement called the Defined Daily Dose (DDD) to be used in drug utilization studies was developed. In 1996, WHO recognized a need to develop the use of ATC/DDD system as an international standard for drug utilization studies 17.

The DDD is the assumed average maintenance dose for the main indication of a particular drug 19. To estimate drug use in population, it can be expressed as DDD/1000 inhabitants/day (DID). In hospital settings, it is usually expressed as DDDs/100 bed-days (DBD). This method is useful in describing and comparing different patterns of drug utilization.

In studies of psychiatric drugs use, the ATC/DDD methodology has some significant limitations. Considering different potencies of antipsychotic drugs, for example, some authors questioned the reliability of DDDS in standardization of antipsychotic drugs, while others found no discrepancies between DDD methodology and classic chlorpromazine equivalents (CPZEs) 19, 20. Additional problems arise when a drug is used for more than one major indication (e.g. diazepam and other benzodiazepines), and when drugs are prescribed in combination with other drugs for the same disease 18. However, the ATC/DDD methodology is used by an increasing number of researchers worldwide 21-24.

In studies on psychiatric drugs utilization in Serbia, the ATC/DDD methodology is applied, both in population-based studies 8, 12, 13 and in hospital-based studies 2, 14. The ATC/DDD methodology allows the comparison of the results on drug utilization in Serbia with other countries. Such comparisons give researchers an opportunity to identify drug over- or underuse, deviations from evidence-based medicine, and other problems that require educational interventions.

Utilization of psychiatric drugs in Serbia

The research conducted in late 1990s (1998–1999) pointed out certain characteristics of utilization of psychiatric drugs in Serbia in general population and in hospital settings 12. The most prominent was the domination of anxiolytic drugs (benzodiazepines), in psychiatric hospitals and in primary health care, with the increasing trend in anxiolytic drugs prescribing for unapproved indications. Prescribing of other psychiatric drugs in primary health care (other anxiolytics and hypnotics, antidepressants and antipsychotics) was virtually non-existent, while in psychiatric hospitals, the domination of first-generation antipsychotics and heterocyclic antidepressants was observed.

Based on this findings, further investigation was conducted and in 2006 Divac et al. 8 published a retrospective study on psychiatric drugs consumption in Serbia. This study covered a period of five years (2000–2004), and was conducted using the wholesale data collected by the drug manufacturers and distributors. The consumption of antipsychotics, antidepressants and anxiolytic drugs was in focus. The ATC/DDD methodology was applied and the results were expressed in DDDS/1000 inh./day (DID). This study pointed out the overall significant tendency of the psychiatric drugs consumption to increase (from 46.9 DID in 2000 up to 69.2 DID) 8. At the same time, in Slovenia, the use of psychiatric drugs was similar (50.9 DID), but in some Scandinavian countries (with a high level of health care) it was much higher (in Sweden it was 115.8 DID, in Norway 102.2 DID, in Iceland 168.8 DID in 2000) 25, 26.

So, this study showed that, apart from the increasing trend, the overall utilization of psychiatric drugs was lower than in some of the most developed European countries.

Antipsychotic drugs utilization in Serbia

In terms of consumption of the therapeutic subgroups of psychiatric drugs, the study of Divac et al 8 showed a mild surge of the use of antipsychotic drugs (from 1.8 DID in 2000 up to 3.0 DID in 2003, and 2.4 DID in 2004). A share of second generation antipsychotics was up to many times higher in 2004, compared with 2000. According to the available data, a total consumption of antipsychotics was about 2–3 times higher in more developed European countries at the same time (9.0 DID in Norway in 2000, 7.7 in Denmark in 2000). A share of atypicals was also higher, especially during a 2000–2002 period, when in Serbia it was 5.5–16.6%, while in Scandinavian countries it was between 33-38% and in Spain, for example, even higher (54% in 2001) 25, 27.

The study conducted in hospital settings put more light on the qualitative terms of antipsychotic drugs prescribing in Serbia. It was conducted at one of the leading psychiatric hospitals in Belgrade (Institute of Psychiatry, Clinical Centre of Serbia). The study was retrospective (2000–2005), and the data on therapy of patients diagnosed with psychosis (n = 120) were analysed 14. This study showed that the increase of the second generation antipsychotics prescribing referred mostly to clozapine, and from 2002, to risperidone. Bearing in mind the differences in indications for these two antipsychotics (clozapine is, according to up-to-date guidelines, reserved for patients with so-called therapeutic resistant schizophrenia, while risperidone is approved as first-line treatment by relevant guidelines) 28, the increase in clozapine utilization probably provided better social and functional...
perspectives for patients otherwise difficult to treat. On the other side, the participation of risperidone was still quite low in total antipsychotic prescribing, much lower than in many other countries 29–31. One of the possible reasons for this is that it was not available by mandatory health insurance, meaning the patients had to pay for the drug. It was until 2005, when risperidone finally found its place on the so-called “positive list” of drugs provided by the state. The participation of other atypical antipsychotics in the treatment of inpatients, as well as in wholesale terms, was minimal over the period when the study was performed. Olanzapine and quetiapine, for example, were available, but it remained unclear whether the lack of information, high treatment cost or other factors were responsible for such low prescribing of these drugs.

During this research, certain prescribing habits of Serbian psychiatrists were also noted and further investigated. The results of the antipsychotic drugs coprescribing in inpatients showed that more than 60% of patients treated in this hospital in a 2002–2005 period, received two or more antipsychotics concomitantly 14. That was approximately 100% higher than in some referent hospitals in developed European countries where similar research was performed 32,33. Also, in qualitative terms, these combinations also raised some questions. Mostly, first generation antipsychotics tended to be coprescribed within their own class. Overall, around 53% of coprescribing episodes were those with two first generation antipsychotics concurrently. In a proportion of 6% of coprescribing episodes three antipsychotics were used, belonging to the same antipsychotic class (two oral first generation antipsychotics and one depot first generation antipsychotic). The second generation antipsychotics were coprescribed in just 1.5% of cases. The coprescribing of antipsychotics of different classes occurred in 39.5% of hospitalizations 14. Also, although the majority of the existing trials and guidelines support mostly the utility of first + second generation combinations 28,32,33, in this study the prevalence of combinations of older generation drugs was observed 14.

Antidepressant drug utilization in Serbia

The low consumption of antidepressant drugs in Serbia was observed by Divac et al. 8 during a 2000–2004 period. In 2000, it was approximately 20 times lower than in Scandinavian countries (2.3 DID vs. 47.3 DID in Sweden and 41.4 DID in Norway 8,25 and around 10 times lower than in Spain 34. However, the consumption of antidepressants in Serbia showed a tendency to increase, and in 2004 it rose almost three-fold (6.8 DID). The selective serotonin reuptake inhibitors’ share in the total antidepressant expenditure surged more than six-fold, showing positive shift in Serbian psychiatrists’ prescribing habits towards newer generation drugs 8.

The prescribing of antidepressants in Serbian primary health care is minimal, which implies possible underdosing of affective disorders in general practice 8. To the contrary, other Western European countries and the USA, especially during the last decade, face the opposite situation: high rates of antidepressants prescribing and consumption, influenced, among other factors, by aggressive marketing of the pharmaceutical companies 34,35.

Anxiolytic/hypnotic drugs utilization in Serbia

Some indicators of the high rates of anxiolytic/hypnotic drugs utilization, especially benzodiazepines, were noted in former Yugoslavia in 1980s 36. During 1990s, Miljković and Đukić 37 showed that the most often prescribed drug in primary health care, among all drugs, in Serbia was the anxiolytic diazepam.

High consumption of benzodiazepines in a society may be an indicator of stress, especially in the case of some economic or social hardship, wars, or natural disaster 38. Therefore, it was almost expected that the utilization of benzodiazepines in Serbia would steadily and significantly increase in 1990s (from 23.1 DID in 1991 to 42.5 in 1998), with sudden but explainable surge in 1999 (year of NATO air strikes), when it amounted to 133.1 DID 10. This trend of increase continued in 2000s, when it rose from 42.8 DID in 2000 up to 60.0 DID in 2004 4. In a study in which these results were published, apart from the analysis on general consumption of benzodiazepines, qualitative approach was also applied and the pattern of prescribing of benzodiazepines in primary health care was investigated. It was shown that benzodiazepines were most frequently prescribed to patients with cardiovascular (e.g. hypertension) and other nonpsychiatric diseases, without any reference to possibly existing anxiety disorder, insomnia or any other approved indication for benzodiazepines 13.

Further investigation of the use of benzodiazepines in the treatment of hypertension in Serbia was conducted in 2005, at the Institute for Nephrology and Haemodyalisis, the Clinical Center Niš, and at the Institute for Cardiovascular Diseases, the Clinical Center of Serbia. A questionnaire was used for the assessment of utilization of benzodiazepines in patients with hypertension (n = 171) 39. This study showed that almost one half of patients (46.2%) treated for hypertension also received benzodiazepines (mostly prescribed, with around 24% of cases of self-medication). As the reason for taking benzodiazepines, most of the patients stated anxiety (62%) and insomnia (17%). There were no significant differences of values of blood pressure between patients treated with benzodiazepines and those treated with antihypertensive therapy only 39. The practice of introducing benzodiazepines in the treatment of hypertension is controversial, since there are no firm evidences that anxiety and psychological characteristics (personality type A, anxiety, aggression, etc.) contribute to the development of hypertension 40. On the other hand, recent findings of Sowden and Huffman 41 pointed out that the impact of mental health on cardiovascular diseases is in general largely overlooked. According to their findings, anxiety disorders are among important cardiac risk factors and benzodiazepines are effective therapeutic interventions for these patients, but more research is required to support this hypothesis 41. However, the tendency of general practitioners and cardiologists to prescribe benzodiazepines for cardiologic indications is widespread in Serbia but might not necessarily represent misuse or abuse of these drugs.

Conclusion

Pharmacoepidemiologic studies on psychiatric drugs prescribing conducted in Serbia mostly belong to the group of drug utilization studies. These studies are not interventions, but are rather aimed at problem detection and quantification. In that sense, the studies cited in this review have contributed to better understanding of certain therapeutic controversies, like the domination of typical antipsychotics and tendency towards coprescribing (especially within the same class), low consumption of antidepressants and high, still increasing trend of the utilization of anxiolytic/hypnotic drugs. Among positive trends, steady increase in the use of atypical antipsychotics and SSRI antidepressants have been noted.

The major limitation of these studies was the lack of electronic data-bases at the time when they were conducted.

The investigators faced tremendous efforts in collecting data from patients’ charts, hospital pharmacies records and wholesale reports from pharmaceutical factories. Introduction of up-to-date data-bases would allow further development of pharmacoepidemiology in Serbia, as well as comparing data between institutions, regions or other countries. It is necessary not only to conduct drug utilization studies, but also to provide feedback for prescribers and include follow-up measures in order to improve the quality of drug use and health care in general.

Acknowledgement

This work was supported by the Ministry of Science and Environmental Protection of Serbia, project number 145001.

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The paper received on July 18, 2008.