The Characteristics of the Outpatient Utilisation of Medicines in the Republic of Srpska in the period 2009-2017

Vanda Marković-Peković1, Ljubica Bojanić2, Svjetlana Stoisavljević-Šatara3

ABSTRACT

Background: Monitoring and measuring of the medicine utilisation enables to assess the quality of use of medicines, providing the evidence-based data for the improvement of the prescribing practice and a more rational use of medicines. The aim of this study was to analyse utilisation patterns of medicines and to compare the results with other countries.

Methods: A retrospective, observational study to analyse outpatient medicines utilisation in the Republic of Srpska between 2009 and 2017. Data of medicines utilisation were retrieved from the national database in the Public Health Institute of the Republic of Srpska and calculated and analysed by using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) methodology. The results were expressed as Defined Daily Doses (DDDs) per 1,000 inhabitants per day.

Results: Total medicines utilisation increased, from 448 DDDs in 2009 to 1,036 DDDs in 2017. Cardiovascular medicines (group C) were the most used medicines, and their share in the total utilisation increased from 36.6% in 2009 to 44.4% in 2017. Among them, the most frequently used were angiotensin-converting enzyme inhibitors, plain and in combinations with diuretics, namely enalapril. The share of medicines used in diabetes in the total utilisation increased from 3.9% in 2009 to 5.1% in 2017. Metformin and glimepiride accounted for about 83% of the blood glucose lowering medicines group (A10B). Among the antithrombotic medicines, the most frequently used were platelet aggregation inhibitors (B01AC), mainly acetylsalicylic acid whose use tripled since 2009. Diclofenac was the most frequently used non-steroidal anti-inflammatory and antirheumatic drug (M01).

Conclusion: The trend of increased medicines utilisation was observed in this study. This finding is comparable with other countries. Variations between countries in the preferred medicines within a class as well as the extent of medicines use were observed. These differences were probably consistent, but not solely attributable, to differences in local guidelines and reimbursement policies.

Key words: utilisation of medicines, ATC/DDD methodology, international comparisons, rational use.

INTRODUCTION

Medicines are only one component in the maintenance and restoration of the health of communities and individuals, and are segment in the prevention, diagnosis and treatment of diseases. If used appropriately, medicines have the potential to relieve suffering from disease and to restore health, which is why they are placed amongst the top priorities in every health sys-
tem.1 With their pharmacological properties, economic impact on health systems and environmental impact, utilisation of medicines exerts important effects on health systems. As in general, consumption of medicines continues to increase,2-4 the knowledge of the quantitative and qualitative patterns of medicines use is a key element for allocation of health care resources and development of sustainable health policy. In 2016, after inpatient and outpatient care, medicines represented the third largest item of health care spending and accounted for one-sixth of health expenditure in the European Union, thus confirming the vital role that medicines have in the health system.5

Systematic use of routinely collected data on medicines can be employed in assessing the value of medicines in use in health care systems, and can give an insight in the efficiency, quality and fairness of health services.6 Monitoring and measuring of the medicines use enables to assess quality use of medicines, to identify areas of suboptimal medicines use and provide feedback to prescribers, and thus improvement of pharmacotherapy. The volume of prescribed medicines may be affected by a number of factors, such as population size and age, disease prevalence, changes in medical practice, prescriber and patient behaviour, developments in medical practice, new medicines, reimbursement policies, new guidelines that adjust the recommended treatment per patient or which enlarge the population of patients who would benefit from the treatment.7, 8 Our country, like other countries in transition, is characterised by the demographic shift, with an increase in life expectancy and population aging.8 So, the major burden of diseases is shifted toward the whole range of chronic diseases, and clinical guidelines were developed for the most common non-communicable diseases.10 At the same time the legislative and organisational system for collecting the data on the medicines utilisation has been established.

Previous studies conducted by our research group have shown the importance of continuous monitoring and analysing of medicines utilisation and expenditure patterns in the population.4, 8 These studies enabled us to assess the influence of multiple measures introduced in our healthcare system in recent years to increase prescribing efficiency, and furthermore to suggest additional reforms or measures to further enhance the prescribing efficiency. With the aging of our population and the increasing prevalence of multiple medicinal conditions in the elderly, the share of the long-term medicine use has increased proportionally. This points out the public health importance of the utilisation patterns analyses in the elderly population with the aim to optimise drug prescribing for this group. Understanding of current patterns in medicines use is important to support pharmaceutical policy implementation as a part of a sustainable health policy, considering the expected health outcomes and the related impact to the medication expenditure.

In order to continue with the monitoring and evaluation of the utilisation of medicines in our country, the aim of this study was to analyse the utilisation patterns of medicines and to compare the results with the ones in other countries.

METHODS

This was a retrospective, observational study on outpatient medicines use over the period from 2009 to 2017. Data was retrieved from the national database located in the Public Institute of Health (PHI). Reports on all medicines dispensed to the patients in all retail pharmacies were sent annually to PHI for collation. This period was chosen as PHI has been collecting and processing data since 2009.

Medicines utilisation was calculated using the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) methodology,11 as the internationally accepted methodology for measuring medicines utilisation.12-16 The ATC system classifies medicines into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. Medicines were classified into ATC groups by its international non-propriet ary name. The results were expressed as a DDD per thousand inhabitants per day (DDDs). DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is a technical, statistical unit of measurement and does not necessarily reflect the recommended or actual used daily dose. DDD is a tool for national and international compar-
RESULTS

Total medicines utilisation increased, from 448 DDDs in 2009, to 1036 DDDs in 2017. The utilisation increased in almost all anatomical groups, and the highest increase was observed in groups C (cardiovascular system), B (blood and blood forming organs) and A (alimentary tract and metabolism). Group C medicines share in the total utilisation of medicines increased from 36.6% in 2009, to 44.4% in 2017 (Table 1). Medicines acting on the renin-angiotensin system (C09) and calcium channel blockers (C08) had a highest utilisation in the group C. The C09 group share in the total medicine utilisation increased from 15.7% (2009) to 24.6% (2017) (Table 2), and the most prescribed were angiotensin-converting enzyme inhibitors (ACEIs), plain (C09A) and in combinations (C09B) (Table 3). The share of the medicines used in diabetes (A10) in the total medicine utilisation increased from 3.9% (2009) to 5.1% (2017) (Table 2). In total medicines utilisation, the share of psycholeptics (N05) ranged from 4.5% (2009) to 3.4% (2017) and of psychoanaleptics (N06) from 1.3% (2009) to 1.9% (2017) (Table 2). Anxiolytics were the most prescribed among psycholeptics (Table 3), namely diazepam followed by alprazolam. Utilisation of antidepressants has grown steadily and has increased 3.5-fold during the observed period (4.7 DDDs in 2009 vs 16.7 DDDs in 2017).

Utilisation of drugs for obstructive pulmonary diseases (R03) has increased 2.5-fold in number of DDDs and the share in the total medicine utilisation increased from 1.4% (2010) to 1.9% (2017) (Table 2).

Among calcium channel blockers (CCBs), selective CCBs with mainly vascular effects (C08C) were prescribed the most, with about seven percent share in total medicines utilisation (Table 3). A continuous increase in the utilisation of drugs for acid-related disorders (A02) was
Table 3: Total utilisation of ten most prescribed pharmacological groups (ATC level III), in number of DDDs

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<tbody>
<tr>
<td>C09</td>
<td>Angiotensin-converting-enzyme (ACE) inhibitors, plain</td>
<td>46.7</td>
<td>70.9</td>
<td>93.7</td>
<td>91.6</td>
<td>96.8</td>
<td>109.3</td>
<td>118.7</td>
<td>147.2</td>
<td>154.8</td>
</tr>
<tr>
<td>B01A</td>
<td>Antiplatelet agents</td>
<td>46.7</td>
<td>70.9</td>
<td>93.7</td>
<td>91.6</td>
<td>96.8</td>
<td>109.3</td>
<td>118.7</td>
<td>147.2</td>
<td>154.8</td>
</tr>
<tr>
<td>C09B</td>
<td>Angiotensin-converting-enzyme (ACE) inhibitors, combinations</td>
<td>30.3</td>
<td>46.8</td>
<td>54.8</td>
<td>55.1</td>
<td>58.9</td>
<td>67.9</td>
<td>86.6</td>
<td>84.9</td>
<td>89.5</td>
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<tr>
<td>C08</td>
<td>Selective calcium channel blockers with mainly vascular effects</td>
<td>30.5</td>
<td>42.5</td>
<td>50.3</td>
<td>48.4</td>
<td>53.8</td>
<td>64.2</td>
<td>56.6</td>
<td>70.0</td>
<td>72.4</td>
</tr>
<tr>
<td>A10B</td>
<td>Antiinflammatory and antirheumatic products, non-steroids</td>
<td>12.7</td>
<td>18.0</td>
<td>28.9</td>
<td>28.3</td>
<td>30.4</td>
<td>34.5</td>
<td>35.8</td>
<td>44.9</td>
<td>46.8</td>
</tr>
<tr>
<td>B03B</td>
<td>Vitamin B12 and folic acid</td>
<td>15.3</td>
<td>27.1</td>
<td>35.6</td>
<td>30.0</td>
<td>29.6</td>
<td>33.9</td>
<td>30.9</td>
<td>35.3</td>
<td>32.1</td>
</tr>
<tr>
<td>B02B</td>
<td>Drugs for peptic ulcer and gastro-oesophageal reflux disease</td>
<td>10.3</td>
<td>11.9</td>
<td>18.6</td>
<td>21.1</td>
<td>20.8</td>
<td>22.6</td>
<td>21.6</td>
<td>27.6</td>
<td>30.3</td>
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<tr>
<td>NSB</td>
<td>Anxiolytics</td>
<td>17.5</td>
<td>24.9</td>
<td>28.8</td>
<td>25.5</td>
<td>25.2</td>
<td>27.4</td>
<td>28.8</td>
<td>30.4</td>
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observed, with the share in the total medicine utilisation of about 3% (Table 2). The most prescribed were drugs for peptic ulcer and gastro-oesophageal reflux disease (A02B) (Table 3), namely proton pump inhibitor pantoprazole and H2-receptor antagonist ranitidine (Table 4).
Among the antithrombotic medicines (Bo1A), the most frequently used were platelet aggregation inhibitors excluding heparin (Bo1AC), namely acetylsalicylic acid whose use tripled since 2009 (Table 4). The most frequently used were blood glucose lowering medicines, excluding insulin the combination of paracetamol with caffeine, codeine and propyphenazone. The high-ceiling diuretics comprised about 2/3 of diuretics (Co3) utilisation and furosemide was the most prescribed (Table 4).

**Table 4: Twenty most prescribed medicines, in DDDs**

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<tr>
<td>C09AA02</td>
<td>enalapril</td>
<td>34.3</td>
<td>49.0</td>
<td>63.3</td>
<td>61.7</td>
<td>67.2</td>
<td>74.5</td>
<td>80.3</td>
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<td>96.5</td>
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<td>B01AC06</td>
<td>acetylsalicylic acid</td>
<td>45.7</td>
<td>45.5</td>
<td>49.6</td>
<td>50.1</td>
<td>53.6</td>
<td>63.1</td>
<td>81.0</td>
<td>78.2</td>
<td>82.2</td>
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<td>C08CA01</td>
<td>amldipine</td>
<td>32.6</td>
<td>35.5</td>
<td>41.6</td>
<td>40.1</td>
<td>45.0</td>
<td>53.6</td>
<td>45.9</td>
<td>53.8</td>
<td>53.8</td>
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<tr>
<td>C09BA02</td>
<td>enalapril, hydrochlorothiazide</td>
<td>15.5</td>
<td>23.1</td>
<td>28.8</td>
<td>27.6</td>
<td>32.0</td>
<td>33.1</td>
<td>39.1</td>
<td>41.7</td>
<td>52.7</td>
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<tr>
<td>C09AA05</td>
<td>ramipril</td>
<td>3.1</td>
<td>6.1</td>
<td>11.1</td>
<td>12.6</td>
<td>13.0</td>
<td>13.8</td>
<td>17.6</td>
<td>26.3</td>
<td>30.3</td>
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<tr>
<td>A10BA02</td>
<td>metformin</td>
<td>5.1</td>
<td>7.6</td>
<td>11.1</td>
<td>15.9</td>
<td>13.6</td>
<td>16.2</td>
<td>18.0</td>
<td>23.6</td>
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<td>M01AB05</td>
<td>diclofenac</td>
<td>10.3</td>
<td>16.2</td>
<td>19.1</td>
<td>19.5</td>
<td>19.4</td>
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<tr>
<td>B03BB01</td>
<td>folic acid</td>
<td>0.6</td>
<td>0.7</td>
<td>20.3</td>
<td>21.1</td>
<td>18.5</td>
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<td>18.3</td>
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</tr>
<tr>
<td>N02BE51</td>
<td>codeine, caffeine, paracetamol, propyphenazone</td>
<td>3.4</td>
<td>26.3</td>
<td>19.8</td>
<td>22.1</td>
<td>20.3</td>
<td>19.5</td>
<td>19.0</td>
<td>16.8</td>
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<tr>
<td>C03CA01</td>
<td>furosemide</td>
<td>5.5</td>
<td>11.1</td>
<td>10.6</td>
<td>12.8</td>
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<td>12.3</td>
<td>13.5</td>
<td>16.8</td>
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<tr>
<td>N02BE01</td>
<td>paracetamol</td>
<td>3.1</td>
<td>3.4</td>
<td>4.3</td>
<td>5.6</td>
<td>9.2</td>
<td>6.8</td>
<td>7.5</td>
<td>9.6</td>
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<tr>
<td>C07AB02</td>
<td>metoprolol</td>
<td>5.9</td>
<td>8.6</td>
<td>10.6</td>
<td>10.1</td>
<td>11.2</td>
<td>12.3</td>
<td>14.2</td>
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<tr>
<td>A02BC02</td>
<td>pantoprazole</td>
<td>0.6</td>
<td>1.2</td>
<td>2.1</td>
<td>2.8</td>
<td>4.1</td>
<td>7.0</td>
<td>7.3</td>
<td>11.4</td>
<td>14.0</td>
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<td>ranitidine</td>
<td>7.2</td>
<td>6.8</td>
<td>11.9</td>
<td>14.2</td>
<td>13.0</td>
<td>12.6</td>
<td>12.0</td>
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<td>A11GA01</td>
<td>levothyroxine</td>
<td>16.1</td>
<td>13.3</td>
<td>12.7</td>
<td>10.7</td>
<td>16.0</td>
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<td>ascorbic acid</td>
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<td>3.0</td>
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<td>13.1</td>
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<tr>
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<td>lisinopril</td>
<td>2.2</td>
<td>3.3</td>
<td>5.1</td>
<td>5.6</td>
<td>5.9</td>
<td>6.7</td>
<td>8.1</td>
<td>10.8</td>
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<tr>
<td>A10BB12</td>
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<td>1.4</td>
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<td>8.3</td>
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<tr>
<td>C10AA05</td>
<td>atorvastatin</td>
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<td>7.8</td>
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<td>8.0</td>
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<tr>
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<td>bisoprolol</td>
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<td>0.1</td>
<td>2.1</td>
<td>2.6</td>
<td>3.8</td>
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<td>6.4</td>
<td>9.8</td>
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INN, International Non-proprietary Name

Four out of five most prescribed medicines were cardiovascular medicines. Plain ACEI enalapril was the most frequently used, with the increased share in the total medicines’ utilisation from 7.6% (2009) to 9.3% (2017). Amlodipine was the dominantly prescribed selective CCBs. Consumption of non-opioid analgesics (No2B) dominated among analgesics (No2), namely

**DISCUSSION**

This study revealed an increasing trend toward the utilisation of medicines, and given the previous studies it was not a surprising finding. Similar trend was observed in other studies. The quantity of medicines tends to increase over time in most therapeutic classes, which may be explained by population ageing, the rise in the prevalence of chronic diseases such as cancer and diabetes, the availability of new medicine treatments or changes in the physicians’ prescribing practices, that may have had an influence on our patterns of medicines utilisation, too.
Medicines classes used for treatment of the most common chronic non-communicable diseases were of the highest degree of utilisation, as in other countries. Premature mortality related to the major non-communicable diseases can be reduced if appropriate, timely and collective action is taken. Among the other activities undertaken towards improvement of health of the population, an update of reimbursable medicines list was carried out precisely to provide better therapeutic choice of medicines, contributing thus to the reduction of morbidity and mortality. Although major non-communicable diseases affect people of all ages, they are often associated with older age groups. Our population is evidently aging as the share of elderly (≥ 65 years) has increased, from 18% (2007) to 22% (2014), and of people aged 50-64 years, from 19% (2010) to 23% (2014). As the trend in ageing of population has significantly increased over the time, it directly influenced the volume of medicines needed for care of elderly people since they have multiple chronic diseases and requires larger number of prescriptions. A recent study among elderly patients has showed an increase of those who use more medicines for longer period of time, with an increased polypharmacy prevalence (use of ≥ 5 different medicines).

Cardiovascular (CV) medicines were the most frequently prescribed, like in other countries. The trend of steady increase in the CV medicines use has been seen over the last few decades as they are key elements in preventing and treating CV diseases, which are the leading cause of death and disability worldwide. It has also been a leading cause of our population’s mortality for the last 20 years. The health policy planners therefore focused their attention on a national CV programme, implementation of the national and European guidelines and selection of the reimbursable medicines. A decrease in CV mortality, from 53.6% in 2002 to 48.7% in 2016 might be attributable to improved CV care, including pharmacotherapy, as the association between the increase in CV medicines use and a decrease in CV mortality was confirmed. Despite the significant increase in CV medicines use, the mortality rate was rather high and CV diseases has remained a leading cause of morbidity and mortality.

The highest utilisation of antihypertensive medicines, such as ACEIs, CCBs and beta blockers, and the increased utilisation of diuretics, are in accordance with clinical guidelines for hypertension. These medicines, with ARBs, are major classes for the treatment of hypertension, used either as monotherapy or in combination with other drugs (mainly diuretics). Over the past 20 years a constant increase in utilisation of these classes was noticed. Enalapril as a monotherapy and in combination with hydrochlorothiazide was the most used ACEI, followed with ramipril (monotherapy) and lisinopril (combination). As a monotherapy, the ACEIs were also frequently prescribed in Serbia, Finland and Norway. High use of ACEIs in combination with diuretics was not surprising, because treatment of hypertension should be preferentially based on combinations of ACEIs or ARBs with a CCB and/or a thiazide diuretic as the most effective evidence-based treatment strategy to improve blood pressure. These combinations are available on our market in a single pill and in a range of doses, enabling simplification of treatment, flexible prescribing and better patient adherence. Country differences were noticed in the preferred ACEIs and ARBs. They may be influenced by the recommendation to assess the clinical effects, which are proven to be divergent today, of each medicine and their indications in light of the comorbidities.

Although amlodipine was the most preferred CCB, an increase in lercanidipine utilisation was notable (rising from 0.5 DDDs in 2011 to 11 DDDs in 2017). This trend was noticed in other countries, and could be explained by more favourable tolerability profile. It is a medicine of a higher cost within the class, and value for money is also an important consideration when choosing a preferred medicine. Patients should be provided with a medication appropriate to their clinical needs and at the lowest cost to them and health system. Acetylsalicylic acid was the most frequently used among the antithrombotic medicines, as generally considered effective for the secondary prevention of cardiovascular disease and one of the most frequently used drugs worldwide.

Among statins, atorvastatin was the most prescribed, with the growth in rosuvastatin use (0.7 DDDs in 2011; 5.6 DDDs in 2017). The cross-country variations in the statin use was also noticed by other authors. Atorvastatin reference prices were higher than those of simvastatin, while rosuvastatin was the most expensive
The utilisation of medicines showed an increasing trend, which is similar to other countries. In addition to the similarities, certain differences in the use of medicines were also observed among the countries, as variations in the preferred medicines within a class and the extent of medicines use. These differences were probably consistent, but not solely attributable, to differences in local guidelines and reimbursement policies. Value for money, for health system and patients who pay for their own medicines, is an important consideration when choosing a preferred medicine according to scientific evidence and the patient’s needs.

**CONCLUSION**

The utilisation of medicines showed an increasing trend, which is similar to other countries. In addition to the similarities, certain differences in the use of medicines were also observed among the countries, as variations in the preferred medicines within a class and the extent of medicines use. These differences were probably consistent, but not solely attributable, to differences in local guidelines and reimbursement policies. Value for money, for health system and patients who pay for their own medicines, is an important consideration when choosing a preferred medicine according to scientific evidence and the patient’s needs.
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