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Costs and consumption of analgesics, with special reference to opiates in Serbia and Montenegro from 2015 to 2019

Troškovi i potrošnja analgetika, sa specijalnim osvrtom na opijate u Srbiji i Crnoj Gori od 2015. do 2019.

Katarina Mladenović*†, Viktorija Dragojević Simić†‡, Snežana Mugoša§‖, Nemanja Rančić†‡

Military Medical Academy, *Department of Anesthesiology and Intensive Care, ‡Center for Clinical Pharmacology, Belgrade, Serbia;†University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; §University of Montenegro, Faculty of Medicine, Department for Pharmacology, Podgorica, Montenegro; ‖Agency for Medicines and Medical Devices of Montenegro, Podgorica, Montenegro

Abstract

Background/Aim. Patients in developing countries do not always receive adequate pain-relieving treatment. Monitoring analgesics consumption is of great importance since this can help assess the quality of painful condition management. The aim of this paper was to present a five-year consumption and costs of drugs with analgesic effects in developing countries, exemplified by Serbia and Montenegro, and indicate the main reasons for their (in)adequate prescribing. **Methods.** The observational, retrospective, cross-sectional study was conducted in order to analyze the consumption of all analgesics, both opioid and non-opioid, in Serbia and Montenegro, as developing countries. The data concerning analgesic consumption and drug prices were obtained from annual editions of the publications of the Medicines and Medical Devices Agency of Serbia and Montenegro. The World Health Organization methodology with defined daily dose (DDD) as a unit of measure (defined by the number of DDD per 1000 inhabitants per day) was used in these publications. **Results**. Over the course of five years (from 2015 to 2019) in Serbia, the total allocations for analgesic therapy had a rising trend, from about 43.6 million to 63.3 million euros, while in Montenegro, expenditures showed annual variations with the highest value in 2018. Most of the money in both countries was invested in the M01A group of drugs, for which the highest consumption was also recorded. Significantly higher consumption of opioid analgesics in Montenegro compared with Serbia was observed in the same period, and it predominantly reflected the difference in fentanyl (N02AB03, transdermal patch) prescribing. In Montenegro, consumption of the M01AB group of drugs was prominently higher in comparison to the M01AE drugs group during the whole five-year period, like in Serbia, in which this was not the case just in 2018. **Conclusion**. Taking into account the importance of analgesics for everyday medical practice, more rational prescribing of these drugs is necessary both in Serbia and Montenegro in the future.

Key words:
analgesics; analgesics, opioids; developing countries; drug prescriptions; montenegro; pain; serbia.

Apstrakt

Uvod/Cilj. Pacijenti u zemljama u razvoju nemaju uvek adekvatan tretman za ublažavanje bolova. Praćenje potrošnje analgetika je od velike važnosti, jer može pomoći u proceni kvaliteta upravljanja terapijom bolnih stanja. Cilj rada bio je da predstavi petogodišnju potrošnju i troškove lekova sa analgetskim dejstvom u zemljama u razvoju, na primerima Srbije i Crne Gore, i ukaže na glavne razloge njihovog (ne)adekvatnog propisivanja. **Metode.** Opservaciona, retrospektivna studija preseka sprovedena je kako bi se analizirala potrošnja svih analgetika, opioidnih i neopioidnih, u Srbiji i Crnoj Gori kao zemljama u razvoju. Podaci koji se odnose na potrošnju lekova i nastale troškove korišćeni su iz publikacija koje svake godine izdaju naconalne agencije za lekove i medicinska sredstva Srbije i Crne Gore. U okviru ovih publikacija korišćena je metodologija Svetske zdravstvene organizacije sa definisanom dnevnom dozom (DDD) kao jedinicom mere (broj DDD na 1000 stanovnika na dan). **Rezultati.** Tokom petogodišnjeg perioda (od 2015. do 2019. godine) ukupna izdvajanja za terapiju analgeticima u Srbiji pokazala su trend porasta (od oko 43,6 miliona na 63,3 miliona evra), dok su troškovi u Crnoj Gori varirali na godišnjem nivou, sa najvišim vrednostima 2018. godine. Najveći deo sredstava u obe zemlje bio je investiran u lekove grupe M01A, za koje je

Correspondence to: Nemanja Rančić, University of Defence, Faculty of Medicine of the Military Medical Academy, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: nece84@hotmail.com

ujedno pokazana i najveća potrošnja. Značajno viša potrošnja opioidnih analgetika u Crnoj Gori, u poređenju sa Srbijom, zapažena je u ovom periodu i ona prevashodno odražava razlike u propisivanju fentanila (N02AB03, transdermalni flaster). U Crnoj Gori potrošnja lekova iz grupe M01AB bila je značajno viša u poređenju sa potrošnjom iz grupe M01AE u toku celog petogodišnjeg perioda, slično kao i u Srbiji, gde to nije bio slučaj samo u 2018. godini. **Zaključak.** Uzimajući u obzir značaj analgetika kao grupe lekova za svakodnevnu lekarsku praksu, neophodno je njihovo racionalnije propisivanje i u Srbiji i u Crnoj Gori u budućem periodu.

Ključne reči:
analgetici; analgetici, opioidni; zemlje u razvoju; lekovi, propisivanje; crna gora; bol; srbija.

Introduction

Although pain management is one of the fundamental human rights [1], patients in developing countries do not always receive adequate pain-relieving treatment. It has been estimated that about 5.5 billion people, or 80% of the global population, have limited or no access to pain management [2]. Those are mainly low-income countries (LIC) or low-middle-income countries (LMIC).

Although access to pain management is low in many underdeveloped countries, it is believed that there is a "treatment gap" between what is being done and what could be done [3]. Barriers to the provision of effective pain management in developing countries are quite diverse. Most commonly, references are made to legislative regulations relating to medicines, i.e., accessibility and availability of some drugs, cumbersome medicine distribution process, and limited daily consumption of opioids, regardless of individual patient's needs [2–4]. It has been estimated that only 6.7% of the total consumption of natural opioid morphine is consumed by 74% of the global population in which the cancer-related mortality rate is the highest [5]. Existing obstacles can be related to health professionals that are overburdened by work and improperly trained in pain management, and frequently laden with prejudices relating to prescribing and administering opioids. There is also a fear of addiction to using opioids in the patients, frequently referred to as "opiophobia", but also a fear of respiratory depression and other serious adverse effects of this therapy [6]. On the other hand, patients also have prejudices. Many of them, particularly in underdeveloped countries, believe that complaining of pain is undignified, i.e., that pain is something to be endured. In some cultures and religions, it is even believed that pain is a "ticket to heaven" [7].

Whatever the reasons, overcoming these obstacles to pain management is crucial in developing countries. That can be achieved by harmonization and amendments to the laws, increased access to medicines, and their more affordable prices. Furthermore, education of both health professionals and the general population on the fundamental human right to pain relief and the administration of appropriate therapy has to be promoted.

Monitoring analgesic consumption is of great importance, particularly opioids, since this can help assess the quality of painful condition management. Moreover, consumption of non-opioid analgesics in many countries is significantly higher than in other groups of drugs, and one of the explanations is that many representatives from this group are available as over-the-counter (OTC) drugs. Therefore, they are among the best-selling drugs. However, due to their status, there is more and more evidence linking non-steroidal anti-inflammatory drugs (NSAIDs) and different side-effect profiles and their possible negative influence on human health [8].

It is expected that analgesics consumption will rise in the following years, and the reasons may vary as follows: higher rate of traffic-related injuries, wars, or terrorist actions, higher rate of patients with various comorbidities due to population aging, higher rate of surgical procedures, chronic painful conditions, and other [9]. Although there are many cheap, safe, and effective drugs on the market, pain management remains inadequate in numerous healthcare systems [10–13].

The aim of this paper was to present a five-year consumption and costs of drugs with analgesic effects, especially opioids, in developing countries, exemplified by Serbia and Montenegro, and indicate the main reasons for their (in)adequate prescribing.

Methods

The retrospective cross-sectional observational study was conducted in order to analyze consumption of all analgesics, both opioid and non-opioid, in Serbia and Montenegro as developing countries [The World Bank classifies countries by personal income into four groups: LIC, LMIC, upper-middle-income countries – UMIC, and high-income countries – HIC, depending on the gross national product (GDP) per capita] [14]. According to this classification, Serbia and Montenegro, with 7,030 USD and 9,060 USD GDP per capita, respectively, are classified as UMIC.

The data concerning analgesic consumption and drug prices from 2015 to 2019 in Serbia and Montenegro were directly obtained from editions of the publication "Marketing and Consumption of Medicinal Products in Human Medicine", issued annually by the Medicines and Medical Devices Agency of Serbia and the publication titled "Consumption of Medicines in Montenegro", issued by the Institute for Medicines and Medical Devices of Montenegro.

These data from the above-mentioned agency publications were expressed by the World Health Organization (WHO) methodology with a defined daily dose (DDD) as a unit of measure [15]. The method used to present the consumption of analgesics is determined by the number of DDD per 1000 inhabitants per day (DDD/1000 inhabitants/day) [16, 17].

Results were obtained for the following groups of analgesics, according to the Anatomical Therapeutic Chemical (ATC) codes: NO2A – opioids; N02AA – natural opium alkaloids (N02AA01 morphine, N02AA03 hydromorphone, N02AA05 oxycodone, N02AA55 oxycodone and naloxone); N02AB – phenylpiperidine derivatives (N02AB02 pethidine, N02AB03 fentanyl); N02AJ – opioids in combination with non-opioid analgesics (N02AJ13 tramadol and paracetamol); N02AX – other opioids (N02AX02 tramadol); NO2B – other analgesics and antipyretics; N02BA – salicylic acid and derivatives (N02BA01 acetylsalicylic acid); N02BB pyrazolones (N02BB02 metamizole sodium); N02BE anilides (N02BE01 paracetamol); N02C – antimigraine preparations (N02CA ergot alkaloids, N02CA52 ergotamine, combinations excluding psycholeptics); N02CC – selective serotonin (5HT1) agonists (N02CC01 sumatriptan, N02CC03 zolmitriptan, N02CC07 frovatriptan); M01A – anti-inflammatory and antirheumatic products, non-steroids; M01AB – acetic acid derivatives and related substances (M01AB05 diclofenac, M01AB08 etodolac, M01AB11 acemetacin, M01AB15 ketorolac, M01AB16 aceclofenac, M01AB55 diclofenac, combinations); M01AC – oxicams (M01AC01 piroxicam, M01AC05 lornoxicam, M01AC06 meloxicam); M01AE – propionic acid derivatives (M01AE01 ibuprofen, M01AE02 naproxen, M01AE03 ketoprofen, M01AE09 flurbiprofen, M01AE17 dexketoprofen, M01AE51 ibuprofen, combinations); M01AH – coxibs (M01AH01 celecoxib, M01AH05 etoricoxib); M01AX – other anti-inflammatory and antirheumatic agents, non-steroids (M01AX17 nimesulide) [16]. Costs of analgesic treatment expressed in euros (EUR) are also presented from cited agency publications.

Results

Over the five years covered by this observational study in Serbia, the total allocations for all medicines had a rising trend – from 851,476,036 in 2015 to 1,176 million EUR in 2019 (Figure 1). The situation is similar to drugs with analgesic effects which also showed a rising trend, from about 43.6 to 63.3 million EUR. If the costs of analgesic therapy are expressed as a percentage of total expenditures for medicines, it can be concluded that about 5.5% (from 5.12% in 2015 to 5.68% in 2017) of the total sum accounts for the consumption of analgesics. Most of the money spent on analgesics was invested in the M01A group; the same result was obtained if DDD/1000 inhabitants/day was used as a consumption indicator (Tables 1 and 2).

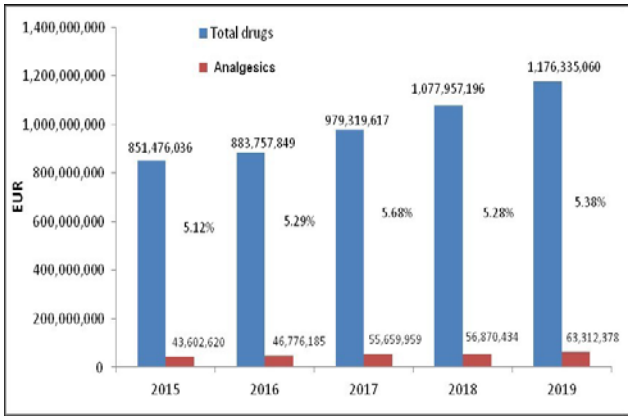


Fig. 1 – Total costs for medications as well as drugs with analgesic effects in Serbia during the five-year period (2015–2019).

Table 1

Expenditures and consumption of the main groups of analgesics, defined by ATC classification, in Serbia during the five-year period (2015-2019)

Analgesics	2015		2016		2017		2018		2019	
	EUR	DDD	EUR	DDD	EUR	DDD	EUR	DDD	EUR	DDD
N02A opioids	2,290,093	0.5630	2,245,910	0.5677	2,172,640	0.5244	2,205,030	0.5508	2,292,328	0.5683
N02B other analgesics and antipyretics	15,502,549	6.0390	19,712,955	7.9546	23,300,050	5.3067	26,603,908	7.0746	28,600,499	7.9010
N02C antimigraine preparations	284,822	0.0870	427,575	0.1606	541,720	0.1829	512,175	0.1575	661,829	0.2451
M01A anti-inflammatory and antirheumatic products, non-steroids	25,525,155	62.7660	24,389,745	58.2578	29,645,549	76.5431	27,549,320	59.0044	31,757,723	69.5517
Total	43,602,619	69.4550	46,776,185	66.9407	55,659,959	82.5571	56,870,433	66.7873	63,312,379	78.2661

ATC – Anatomical Therapeutic Chemical; DDD – defined daily dose; EUR – euro.

Table 2

Expenditures and consumption of analgesics, defined by ATC classification, in Serbia during the five-year period (2015-2019)

Drugs	2015		2016		2017		2018		2019	
	EUR	DDD	EUR	DDD	EUR	DDD	EUR	DDD	EUR	DDD
N02A Opioids										
N02AA Natural opium alkaloids	805,535	0.1070	800,976	0.1018	675,274	0.0822	597,796	0.0815	861,585	0.1289
N02AB Phenylpiperidine derivatives	907,508	0.1130	873,586	0,1100	953,592	0.1178	1,031,318	0.1302	905,092	0.1138
N02AJ Opioids in combination with non-opioid analgesics									12,931	0.0080
N02AX Other opioids	577,050	0.3420	571,348	0.3560	543,774	0.3245	575,917	0.3391	512,720	0.3176
N02B Other analgesics and antipyretics										
N02BA Salicylic acid and derivatives	3,313,884	1.2430	2,365,001	0.7981	2,957,054	0.9986	2,650,783	0.7781	2,258,336	0.7408
N02BB Pyrazolones	1,750,252	1.8450	2,050,210	2.3514	1,954,986	1.8791	1,619,823	1.5569	1,942,372	1.9182
N02BE Anilides	10,438,413	2.9500	15,297,743	4.8050	18,388,010	2.4290	22,333,303	4.7396	24,399,791	5.2421
N02C Antimigraine preparations										
N02CA Ergot alkaloids			50,474	0.0306	87,377	0.0511			128,132	0.0764
N02CC Selective serotonin (5HT1) agonists	284,822	0.0870	377,101	0.1300	454,343	0.1318	512,176	0.1575	533,696	0.1686
M01A Anti-inflammatory and antirheumatic products, non-steroids										
M01AB Acetic acid derivatives and related substances	10,452,839	33,0110	9,214,272	27.2548	13,424,454	42.6273	9,107,148	23.2733	11,305,545	31.1431
M01AC Oxicams	1,556,009	3.3280	1,450,914	3.0859	1,359,410	2.8377	1,225,632	2.6577	1,047,199	2.2840
M01AE Propionic acid derivatives	10,330,280	19.2670	10,714,087	20.3967	12,598,539	23.0325	14,871,261	25.0473	17,133,916	28.3865
M01AH Coxibs	302,855	0.0280	258,876	0.0227	395,185	0.3254	531,460	0.4476	556,567	0.5199
M01AX Other anti-inflammatory and antirheumatic agents, non-steroids	2,883,171	7.1320	2,751596	7.4978	1,867,962	7.7203	1,813,819	7.5785	1,714,496	7.2181

ATC – Anatomical Therapeutic Chemical; DDD – defined daily dose; EUR – euro.

During the same five-year period in Montenegro, the total allocations for medicines also showed a rising trend, from about 66.1 million in 2015 to 101 million EUR in 2019 (Figure 2). The situation is similar with analgesic therapy which also shows a rising trend but with annual variations. In 2018, 1.25 million EUR were spent more than in 2015, while in 2019, a smaller sum (4,220,685) was spent than in the preceding year. The result is substantiated if DDD/1000 inhabitants/day is used as an indicator, and most of the money spent on analgesics was invested in the M01A group, like in Serbia (Tables 3 and 4).

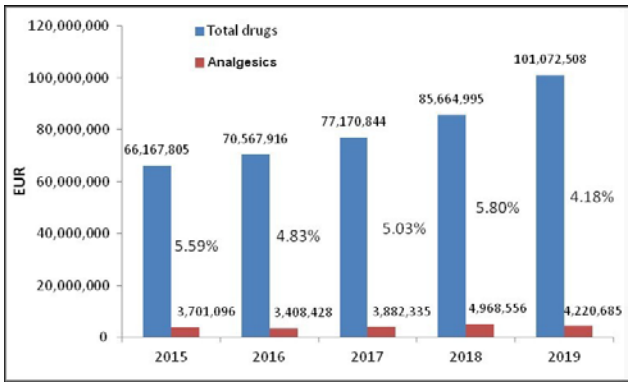


Fig. 2 – Total costs for medications as well as drugs with analgesic effects in Montenegro during the five-year period (2015–2019).

If we compare the use of opioid analgesics between Serbia and Montenegro, significantly higher consumption of these medicines could be observed in Montenegro (Figure 3). In Serbia, their consumption was relatively stable and maintained at about 0.50 DDD/1000 inhabitants/day. On the other hand, in Montenegro, it was significantly higher (0.96 and 1.00 DDD/1000 inhabitants/day in 2015 and 2016, respectively, falling to 0.76 in 2017 and again reaching the previous level in 2018 and 2019 (Figure 3). This difference in use reflects the difference in fentanyl (N02AB03, transdermal patch) prescribing (Table 5). Consumption of opioid fentanyl in Montenegro was 0.8 DDD/1000 inhabitants/day and higher in the observed period, except in 2017, when the value dropped to 0.62. In Serbia, the volume of this consumption was set from 0.11 to 0.12 DDD/1000 inhabitants/day in the same period. However, morphine sulfate consumption was prominently lower in Montenegro than in Serbia during the five years, while hydromorphone, oxycodone, and the combination of oxycodone and naloxone were not present in the Montenegrin market. Consumption of tramadol was also lower in Montenegro compared with Serbia but not as prominently as was the case with morphine sulfate.

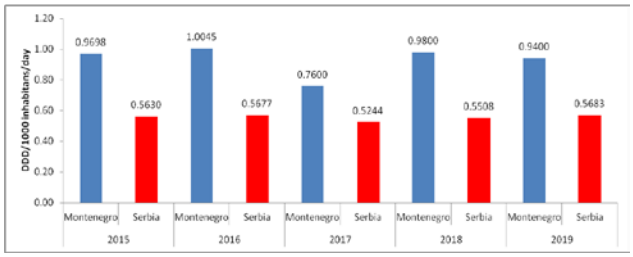


Fig. 3 – Total use of opioids in Serbia and Montenegro during the five-year period (2015–2019). DDD – defined daily dose.

As far as non-opioid analgesics are concerned, consumption of the N02B group of drugs was constantly rising both in Serbia and Montenegro, as well as Serbian expenditures for these drugs (except in 2017) (Tables 1 and 3). As far as the N02BB group is concerned (pyrazolones), only metamizole was present on the market of both countries (Tables 2 and 4). Metamizole costs varied

Table 3

Expenditures and consumption of the main groups of analgesics, defined by ATC classification, in Montenegro during the five-year period (2015-2019)

Analgesics	2015		2016		2017		2018		2019	
	EUR	DDD	EUR	DDD	EUR	DDD	EUR	DDD	EUR	DDD
N02A Opioids	89,115	0.9698	86,776	1.0045	66,411	0.7600	119,747	0.9800	122,164	0.9400
N02B Other analgesics and antipyretics	1,230,236	7.3088	959,075	7.7828	1,337,056	7.5000	835,494	7.5300	1,362,607	8.0700
N02C Antimigraine preparations	61,687	0.0834	62,302	0.1634	63,872	0.1800	67,639	0.1900	72,907	0.2000
M01A anti-inflammatory and antirheumatic products, non-steroids	2,320,058	72.9602	2,300,275	68.4748	2,414,996	74.5400	2,587,188	73.3000	2,663,007	75.3900
Total	3,701,096	81.3222	3,408,428	77.4255	3,882,335	82.9800	3,610,068	82.0000	4,220,685	84.6000

ATC – Anatomical Therapeutic Chemical; DDD – defined daily dose; EUR – euro.

Table 4

Expenditures and consumption of analgesics, defined by ATC classification, in Montenegro during the five-year period (2015-2019)

N02A Opioids	2015		2016		2017		2018		2019	
	EUR	DDD	EUR	DDD	EUR	DDD	EUR	DDD	EUR	DDD
N02AA Natural opium alkaloids	14,385	0.0113	17,464	0.0154	12,555	0.0100	16,695	0.0200	19,884	0.0200
N02AB Phenylpiperidine derivatives	61,476	0.8219	57,705	0.8598	42,115	0.6200	86,783	0.8400	83,198	0.8000
N02AJ Opioids in combination with non-opioid analgesics	774	0.0001	424	0.0001	340	0.0001	194	0.0001	298	0.0001
N02AX Other opioids	12,480	0.1366	11,153	0.1293	11,400	0.1300	16,075	0.1300	18,783	0.1100
N02B Other analgesics and antipyretics										
N02BA Salicylic acid and derivatives	216,585	1.0722	206,116	1.0476	205,107	0.8900	190,712	0.7300	182,574	0.7000
N02BB Pyrazolones	266,991	3.3598	279,268	3,3662	277,539	3.3400	264,644	3.2600	294,762	3.2300
N02BE Anilides	746,660	2.8768	473,691	3.3690	854,409	3.2700	1,290,850	3.5400	885,271	4.1300
N02C antimigraine preparations										
N02CA Ergot alkaloids	34,302	0.1104	37,365	0.1199	42,373	0.1400	43,420	0.1400	42,541	0.1400
N02CC Selective serotonin (5HT1) agonists	27,385	0.0417	24,937	0.0435	21,499	0.0400	24,219	0.0500	30,365	0.0600
M01A Anti-inflammatory and antirheumatic products, non-steroids										
M01AB Acetic acid derivatives and related substances	966,223	45.3044	819,712	39.9800	842,036	44.5500	1,210,354	45.7600	1,290,080	49.7700
M01AC Oxicams	58,073	2.2097	74,272	2.3100	77,554	2.3700	46,805	1.2200	41,565	1.1000
M01AE Propionic acid derivatives	1,150,506	21.2335	1,200,789	22.4459	1,235,481	22.9400	1,219,430	23.4400	1,278,751	23.7400
M01AH Coxibs	13,484	0.1104	18,815	0.1589	23,956	0.2000	27,826	0.2400	30,359	0.2600
M01AX Other anti-inflammatory and antirheumatic agents, non-steroids	131,772	2.6657	186,687	3.5800	235,969	4.4800	82,773	2.6400	22,252	0.5200

ATC – Anatomical Therapeutic Chemical; DDD – defined daily dose; EUR – euro.

Table 5

Consumption of opioids (in DDDs/1000 inhabitants/day) in Serbia and Montenegro during the five-year period (2015-2019)

N02A Opioids	2015		2016		2017		2018		2019	
	Serbia	Montenegro	Serbia	Montenegro	Serbia	Montenegro	Serbia	Montenegro	Serbia	Montenegro
N02AA01 Morphine-sulfate	0.1080	0.0113	0.1018	0.0154	0.0493	0.0100	0.0497	0.0200	0.0616	0.0200
N02AA03 Hydromorphone	0.0490		0.0523		0.0330		0.0269		0.0353	
N02AA05 Oxycodone							0.0048		0.0249	
N02AA55 Oxycodone, naloxone									0.0072	
N02AB02 Pethidine	0.0010		0.0019		0.0023	0.0001	0.0020	0.0001	0.0016	0.0001
N02AB03 Fentanyl	0.1120	0.8219	0.1080	0.8598	0.1155	0.6200	0.1282	0.8400	0.1122	0.8000
N02AJ13 Tramadol, paracetamol						0.0001		0.0001	0.0080	0.0001
N02AX02 Tramadol	0.3420	0.1366	0.3560	0.1293	0.3245	0.1300	0.2971	0.1300	0.3176	0.1100

DDD – defined daily dose.

from year to year in Serbia, but it was higher at the end of the observed period compared to 2015. A similar situation was with its consumption. Neither consumption nor costs for metamizole changed significantly during the entire observed period in Montenegro (Tables 2 and 4). A rising trend of expenditures for paracetamol (N02BE anilides) was noticed in the entire monitored period in Serbia, while it varied from year to year in Montenegro. Paracetamol consumption in Serbia was significantly higher in 2019 compared to 2015, although its lowest value was recorded in 2017, not accompanied by a decrement in cost. A similar situation was in Montenegro, but the lowest value of its consumption was not as prominent as in Serbia in 2017.

Most prominent expenditures and consumption of all analgesics recorded in both Serbia and Montenegro during the whole observed period referred to the M01A group of drugs (Tables 1 and 3). Consumption of the M01AB group of drugs was higher than that of the M01AE group in Serbia during the observed period except in 2018 when it was lower. As far as costs were concerned, they were similar for both groups of drugs from 2015 to 2017, while expenditures for the M01AE group were higher than for the M01AB group in 2018 and 2019. In Montenegro, consumption of the M01AB group of drugs was prominently higher compared to the M01AE group during the whole five-year period. However, expenditures for the M01AE group of drugs were higher from 2015 to 2017, while they were very similar for both groups of drugs during the remaining two years of the observed period. In both countries over the five years, the expenditures and consumption of coxibs were the lowest among other anti-inflammatory drugs.

Discussion

In our study, the trends in analgesic consumption and expenditures in Serbia and Montenegro from 2015–2019 were examined. The total consumption of all drugs on the markets of both countries and their prices increased during this period. The highest overall consumption of analgesics was observed in 2017 in Serbia (82.55 DDD/inhabitants/day), while in Montenegro, it was detected in 2019 (84.60 DDD/inhabitants/day). Although the corresponding consumption decreased in 2016 and 2018, the total costs were steadily rising in Serbia, while in Montenegro, it varied annually, and the highest costs for analgesics were in 2019 when their consumption was also highest. Occasionally observed increase in costs of analgetics parallel with the decline in their consumption, which alternates with the reduction of costs in the supervenient year in Serbia, could be explained by government decrees that seek to limit drug prices in accordance with its other economic measures [18]. In both countries, results showed that the M01A group of drugs had the highest consumption associated with the highest costs of all analyzed analgesics. The second highest consumption was related to the N02B group of drugs (other analgesics and antipyretics), followed by opioids (N02A). About 0.22% of the total expenditures for medicines in Serbia were spent on opioids. Consumption of opioids was substantially lower than the consumption of anti-inflammatory medicines and antipyretics. This trend can be partly explained by the fact that most of the latter ones are in the OTC status, i.e., a doctor's prescription is not required. The comparison of the use of opioids over the five years in two countries has led us to the conclusion that it was consistently and more prominent in Montenegro.

In Serbia, during the observed period, consumption of morphine, hydromorphone, fentanyl transdermal formulation, and tramadol was relatively stable, while pethidine use showed a downward trend. In Montenegro, the consumption of morphine, pethidine, and tramadol was stable and lower than in Serbia during the whole observed period. The increase in whole opioid consumption recorded in Montenegro was actually at the expense of fentanyl, of which usage ranged from 0.62 to 0.84 DDD/1000 inhabitants/day. In the same period, from 2015 to 2019, consumption of fentanyl in Serbia was in the range from 0.1080 to 0.1282, while in Croatia, it accounted for 0.63, 0.61, 0.59, 0.60, and 0.63 DDD/1000 inhabitants/day, respectively [19]. A European study concerning the consumption of opioids in severe pain from 1990 to 2016 showed that in 2016 fentanyl use in Sweden, Denmark, and Norway (countries with well-developed pharmacotherapeutic practice) was 5.10, 6.41, and 5.55 times higher than in Serbia [20]. Trends of fentanyl use largely corresponded to those of total opioids in all European countries, and it steadily increased from 2004 onwards. Easy administration, good adherence of the patient to the drug, and a strong marketing campaign have contributed to the increase in its consumption. It is obvious that its use in Serbia is inadequate and that education of both healthcare providers and patients is urgently needed.

On the Montenegrin market, hydromorphone, oxycodone, or the combination of the latter with naloxone were not available at all. Oxycodone appeared on the Serbian market in 2018, while the combinations of oxycodone and naloxone, as well as tramadol and paracetamol, were launched in 2019. The latter combination has also been

present on the Montenegrin market since 2017. Regardless of the rising trend of opioid use in both countries, their consumption remains low. Our previous results indicated that consumptions of opioids in Serbia were 0.517 and 0.519 in 2012 and 2013, respectively, while morphine use was also low and amounted to 0.031 and 0.068 DDD/1000 inhabitants/day in the same years, respectively [21]. At the same time, total opioid costs amounted to 2,637,364.9 and 2,499,864.2 EUR in 2012 and 2013, compared to 2,290,093, 2,245,910, 2,172,640, 2,205,030, and 2,292,328 EUR in 2015, 2016, 2017, 2018, and 2019, respectively. On the other hand, the consumption of opioids in Croatia was 8.83 and 8.55 times higher than in Serbia in 2012 and 2013, respectively, while the Croatian health system was willing to pay 6.35 and 6.22 times more for these drugs in the same period, respectively [21]. That trend continued since the consumption of opioids was 4.13, 4.25, and 16.20 in 2017, 2018, and 2019 in Croatia, respectively [19]. Therefore, it was still far more than in Serbia and Montenegro in the same period.

One of the explanations is the high level of caution in the prescription routine by medical doctors, bearing in mind possible adverse effects and risk of abuse, especially in primary health care in Serbia [22]. A similar situation also exists in other countries [23]. However, the low consumption rate not only in Serbia and Montenegro but also in some other countries, mostly in Southern and Eastern Europe, can suggest insufficiently developed palliative care and numerous administrative obstacles that may still be related to prejudices concerning opioids, but also lack of adequate training of healthcare professionals, still inadequate available formularies and limited economic resources [24, 25]. Namely, there is a globally widespread inequity in access to analgesics, primarily opioids. In 2020, Duthey and Sholten [26] found that only 7.5% of the world population has moderate or adequate access to analgesics. Almost 2 billion people worldwide have no access to essential medicines, resulting in higher pain and suffering, prolonged disease, unnecessary disability, and avoidable fatal outcomes [27]. That applies mostly to opioids that are faced with an abundance of legal obstacles. Moreover, it was shown that there is no correlation between access to potent analgesics and obstacles in legal regulations in eleven East European countries, suggesting that other factors, beyond legislation and regulation, affect inadequate access to medicines [28]. Even though Serbia and Montenegro belong to the UMIC group, they are in the group of about 75% of countries with middle income and inadequate access to analgesics [29].

Due to its pharmacological properties and low price, morphine should be widely used in treating severe pain, particularly cancer. However, 90% of global morphine consumption is used by only 20% of the global population, particularly in developed countries and the ones with high middle income [30]. Although Serbia and Montenegro are in the group of UMIC, consumption of morphine was very low, about 0.10 DDD/1000/day in 2015 and 2016, after that from 0.04 to 0.06 in Serbia (2017–2019), and from 0.01 to 0.02 DDD/1000/day in Montenegro, in the examined five-year period. In 2016, morphine consumption in Serbia was 12.52, 12.58, and 15.9 times lower than in Sweden, Norway, and the European Union, respectively. At the same time, this difference was even more prominent in the same period concerning Montenegro [20]. In our previous study concerning the utilization of parenteral morphine in the tertiary care hospital in Serbia, a low level of morphine use was demonstrated in comparison to other European countries [31], and one of the reasons was a low marketing price connected with no-brand names. In addition, better education and training of staff and a multidisciplinary approach should enable more rational use of opioids, not only in the hospital.

Problems relating to opioids in developing countries do not pertain to morphine only. It also frequently happens that the prices of opioids in some developing countries are higher than in developed ones [32]. There is a study that shows that the price of morphine in the oral immediate-release (IR) formulations (10 mg) in LMIC is 5.8 times higher than in HIC [33]. Moreover, in developing countries, it frequently happens that the cheapest formulation, such as the oral IR formulations, are sold at prices higher than transdermal or sustained-release formulations [34]. Furthermore, not all formulations of medicines are always available in these countries. Often, the ones most needed (oral morphine preparations, IR tablets) are missing. Therefore, many obstacles should be removed, not only in developing countries, to make opioid use more rational and accomplish patient-tailored pain management.

Consumption of the N02B group of drugs was constantly rising both in Serbia and Montenegro, as well as Serbian expenditures for these drugs. As far as the N02BB group is concerned (pyrazolones), only metamizole is present on the market of both countries. In this study, it was shown that neither consumption nor costs for metamizole changed significantly during the entire observed period. In our study published in 2018 [35], it was demonstrated that utilization of this drug was 3.31-fold higher in Serbia than in Croatia and that the expenditure of metamizole in the same period (from 2010 to 2015) was 5.29-fold higher in Serbia than in Croatia. Although metamizole use was gradually decreasing with a minimal value of 0.5 DDD/1000/day in 2015, it rose again and accounted for 1.91 DDD/1000/day in Serbia in 2019. Consumption in Montenegro was even higher, from 3.23 to 3.34 DDD/1000/day, while data from Croatian Medicine and Medical Devices Agency indicate that in the same period, like in our study, it was in the range from 0.41 to 0.92 DDD/1000/day [19]. In most European countries, metamizole has not been on the market for a relatively long time due to serious adverse effects, such as agranulocytosis, thrombocytopenia, aplastic and haemolytic anemia, etc. [36]. Therefore, although metamizole is widely used, its prescribing should be strictly based on the indications and appropriate duration of therapy according to its current Summary of product characteristics.

A consistently rising trend of both expenditures and consumption of paracetamol was noticed in the entire monitored period in both countries, only less prominently in Montenegro than in Serbia. Miljković et al. [35] showed that from

2010–2015 paracetamol was the most frequently prescribed analgesic in both Serbia and Croatia, and its consumption continued to increase during the whole period. This trend continued in both of these countries, with the average use from 4.7 to 5.0 DDD/1000/day, probably due to a very good risk/benefit ratio and affordable prices, which makes it the most commonly prescribed antipyretic and analgesic in children, not only in Serbia, Montenegro, and Croatia but also in Finland, as a representative country for comparison [19, 36]. Referring to the M01 group, the most prominent expenditures and consumption of all analgesics were recorded in both Serbia and Montenegro during the whole observed period. Consumption of the M01AB group of drugs (diclofenac, etodolac, ketorolac, etc.) was higher than that of the M01AE group (propionic acid derivatives) in Serbia during the observed period, except in 2018 when it was lower. In Montenegro, consumption of the M01AB group of drugs was prominently higher in comparison to the M01AE group during the whole five-year period. This trend has existed in Serbia for a long time, according to studies from 2005 onwards [35, 37]. Mijatović et al. [37] even showed that diclofenac accounted for 50% of NSAID consumption in Serbia from 2005–2008, followed in much smaller amounts by ibuprofen. A similar situation was noted in Croatia, while in Denmark, ibuprofen consumption was higher compared to diclofenac from 2005 onwards [38]. In 2018 and 2019, the consumption of the M01AB group of drugs was still high both in Serbia and Montenegro, compared to Croatia, while consumption and expenditures of ibuprofen and propionic acid derivatives were steadily rising in all three countries [19]. These findings can be explained by a higher awareness of the lower adverse effects rate of ibuprofen compared to the corresponding one in the M01AB group, especially diclofenac [38]. That was especially emphasized after the announcement of the European Medicines Agency in 2013 that diclofenac use was associated with increased cardiovascular risks similar to those of COX-2 inhibitors [39]. This regulatory action caused a significant reduction in overall diclofenac initiation, which varied by country since it was investigated in Scotland, England, Denmark, and the Netherlands [40]. Interestingly, there was no impact on discontinuation and variable impact on switching of diclofenac. One of the ways to overcome the present bad prescribing practices in Serbia and Montenegro is to target education and adherence to the principles of evidence-based medicine [41].

In Serbia and Montenegro, over the five years, the expenditures and consumption of coxibs were the lowest among other anti-inflammatory drugs. That can be explained by their high price and limited indications due to the profile of adverse drug reactions, necessitating a patient-tailored approach [42, 43].

The WHO List of Essential Medicines includes only three medicines under the “non-opioid and anti-inflammatory medicines”: paracetamol, acetylsalicylic acid, and ibuprofen. The most commonly used NSAIDs are aspirin (88 countries), ibuprofen (90 countries), diclofenac (74 countries), indomethacin (56 countries), and naproxen (27 countries). In the group of 15 countries, uniformly distributed into low, middle, and high-income countries, it appears that diclofenac and etoricoxib account for a third of the total consumption of NSAIDs. As far as these medicines are concerned, there was no significant difference in their use in countries with low, middle, and high incomes [44, 45].

We did not provide detailed insight into the consumption trend for all the specific types of NSAIDs since national studies related to analgesics are rare. Nevertheless, we believe our analysis of NSAIDs consumption and price contributes to the understanding of the main reasons for their continuous irrational use, especially in middle-developed countries such as Serbia and Montenegro.

Conclusion

In both Serbia and Montenegro, allocations for analgesics are substantial, with a rising trend noted for the five years of observation (2015–2019). However, only about 0.22% of the total expenditures for medicines in Serbia were spent on opioids. Moreover, the distribution and consumption in these two countries classified as developing ones are faced with more or less the same obstacles as other developing countries. Both have a low number of opioid medicine types, either as single active substance drugs or combined formulations. Despite necessary caution in prescribing practice, more should be done to remove administrative obstacles that make them barely accessible to patients. Moreover, education of both the general population and healthcare professionals could help dispel prejudices relating to the consumption of opioids in both countries.

Non-opioid analgesics in the M01A and N02B groups of drugs are most frequently used. That can be explained by numerous indications for their use and OTC status. More rational prescribing, taking into consideration drugs with lower incidence of adverse drug reactions, like ibuprofen, should be present in practice.

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