Joint EU-MNE Programme for
Employment, Education and Social Welfare

WP 3 - Conducting of the Drug utilisation study – DUS of diclofenac, scientific analysis of obtained data on prescribing of diclofenac in PHC, preparational activities for publication of data in scientific journals

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DEV 3.2- Report "Assessment of compliance or deviation of diclofenac prescribing in PHC"

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1. Introduction

Obtained data on prescribing practice of diclofenac in PHC were analysed using BI tools. General overview has shown that diclofenac is widely prescribed to patients of all age groups, both genders and in all PHC units. Besides that, it was noticed that different pharmaceutical forms of diclofenac were available and that diclofenac is often prescribed as concomitant medicine simultaneously with numerous other medicines. However, despite the fact that diclofenac is mostly used in approved diagnoses, some important deviations regarding prescribing practice are noticed.

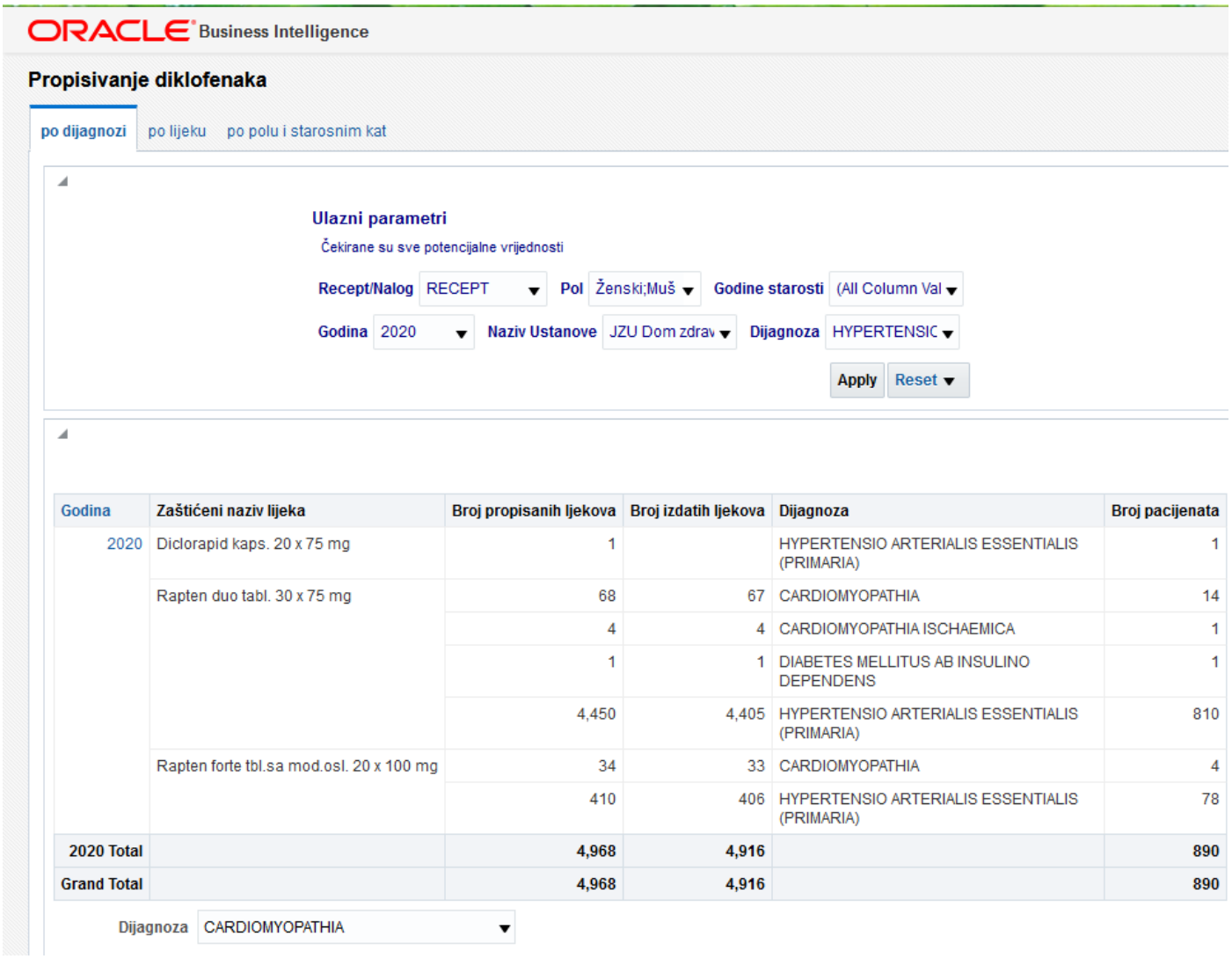
2.1 Diagnoses used

It was noted that prescribing of diclofenac was mostly related to diagnoses of inflammatory and painful conditions of the musculoskeletal system (e.g. arthralgia, myalgia, dorsalgia, lumbosciatica, spondylosis, extremity pain, hip osteoarthritis, intervertebral disc prolapse) which is in line with the approved indications. Besides that, prescribing of diclofenac was significantly present when it comes to numerous other diagnoses: primary arterial hypertension, insulin-dependent diabetes, hyperlipidemia, atrial fibrillation, angina pectoris, dyspepsia, acute pharyngitis, acute tonsillitis, acute bronchitis, breast cancer, urinary tract diseases, respiratory tract infections, renal colic, duodenal ulcer, Covid-19 infection...Some of these indications are connected to high risk of adverse reactions to diclofenac, especially regarding cardiovascular system. Patients with congestive heart failure and patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure the shortest duration possible and the lowest effective daily dose should be used.

Additional analysis of prescribing of diclofenac related to the diagnosis of primary arterial hypertension was carried out:

Year	No. of prescribed medicines	No. of patients
2016	35,373	9,413
2017	42,550	9,720
2018	45,593	10,162
2019	45,925	8,977
2020	46,653	7,869
2021	17,409	5,412

There is a significant number of patients diagnosed with the primary arterial hypertension who received diclofenac during observed time period.



ORACLE Business Intelligence

Propisivanje diklofenaka

po dijagnozi | po lijeku | po polu i starosnim kat

Ulazni parametri

Čekirane su sve potencijalne vrijednosti

Recept/Nalog: RECEPT | Pol: Ženski;Muš | Godine starosti: (All Column Val

Godina: 2020 | Naziv Ustanove: JZU Dom zdrav | Dijagnoza: HYPERTENSIC

Apply | Reset

Godina	Zaštićeni naziv lijeka	Broj propisanih ljekova	Broj izdatih ljekova	Dijagnoza	Broj pacijenata
2020	Diclorapid kaps. 20 x 75 mg	1		HYPERTENSIO ARTERIALIS ESSENTIALIS (PRIMARIA)	1
	Rapten duo tabl. 30 x 75 mg	68	67	CARDIOMYOPATHIA	14
		4	4	CARDIOMYOPATHIA ISCHAEMICA	1
		1	1	DIABETES MELLITUS AB INSULINO DEPENDENS	1
		4,450	4,405	HYPERTENSIO ARTERIALIS ESSENTIALIS (PRIMARIA)	810
	Rapten forte tbl.sa mod.osl. 20 x 100 mg	34	33	CARDIOMYOPATHIA	4
		410	406	HYPERTENSIO ARTERIALIS ESSENTIALIS (PRIMARIA)	78
2020 Total		**4,968**	**4,916**		**890**
Grand Total		**4,968**	**4,916**		**890**

Dijagnoza: CARDIOMYOPATHIA

Besides that, the analysis of prescribing diclofenac related to the other diagnoses, while focusing on the diagnoses related to the conditions requiring special attention when administering diclofenac (insulin-dependent diabetes, hyperlipidemia, angina pectoris, dyspepsia, duodenal ulcer) was performed. To illustrate,

in 2020 there were 179 prescriptions of diclofenac for patients diagnosed with insulin-dependent diabetes mellitus, while in 2019 there were 199 such prescriptions. During the whole period of time covered by the analysis (from 2016 to May 2021), there were 143 prescriptions of diclofenac for patients diagnosed with acute myocardial infarction. Covid-19 virus diagnosis was related with prescribing diclofenac in 1,630 cases. A high number of used diagnoses, many of which do not correspond to the approved indications, was registered in all health care institutions and during all periods covered by the analysis. Diclofenac was prescribed to patients with numerous comorbidities, with the large number of medicines used concomitantly.

2.2 Pharmaceutical forms

It was noticed that pharmaceutical form of diclofenac for oral use was predominantly prescribed during observed time period. As for the pharmaceutical forms for parenteral administration, the most prescribed medicine was Diclofenac solution for injection 5x3ml (75mg/3ml). When it comes to the pharmaceutical forms for oral administration, mostly prescribed medicines were Rapten duo tablets 30x75mg and Rapten forte modified-release tablets 20x100mg.

2.3 Gender and age groups

Diclofenac was often prescribed to the patients of both genders during the period observed. However the predominance of women was noted in each year.

Year	No. of male patients	No. of female patients
2016	36,771	57,498
2017	36,936	58,176
2018	36,388	57,210
2019	36,768	56,667
2020	31,916	47,257
2021	18,351	28,996

In 2020 there was a decrease in the number of both male and female patients using diclofenac in comparison to previous years. Most patients prescribed with diclofenac belong to the group of 45 to 64 years of age, while the least number of patients belong to the group of up to 17 years.

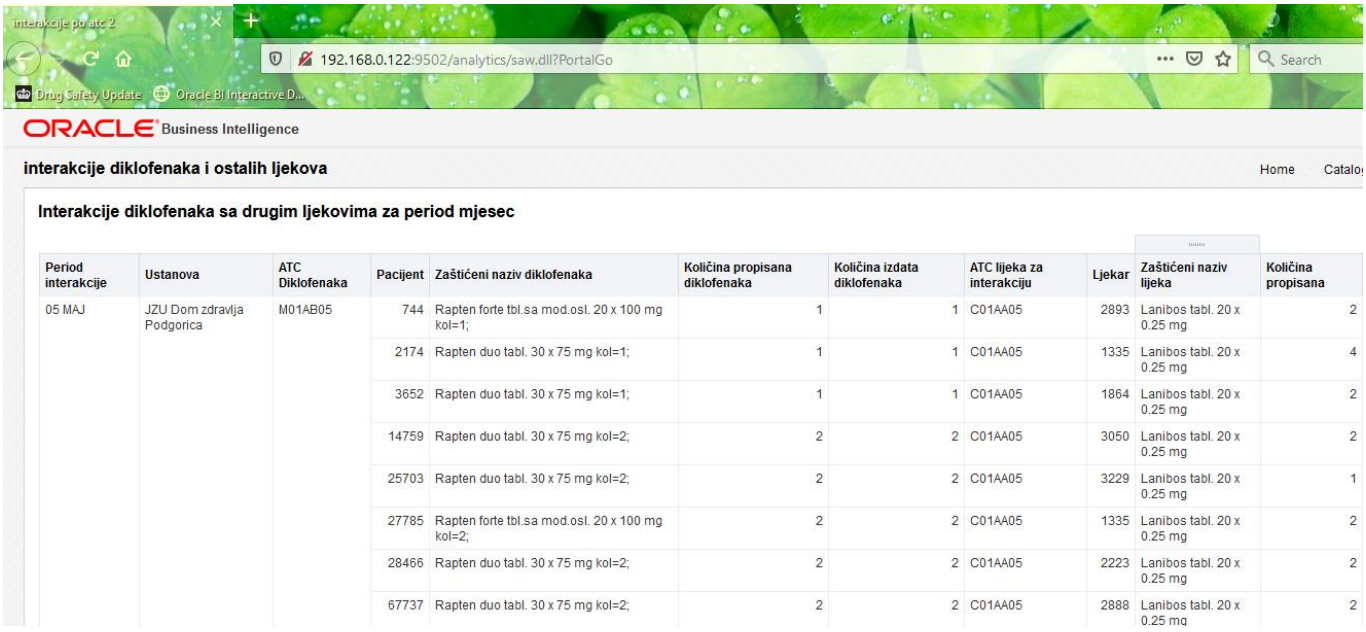
Additional analysis of prescription practice when it comes to women of reproductive age was also carried out, having in mind potential side effects of diclofenac on pregnancy, lactation and fertility:

Year	No. of prescribed medicines	No. of patients aged 18 to 44

2016	38,707	12,604
2017	40,060	12,390
2018	39,950	12,217
2019	40,582	12,475
2020	32,776	9,472
2021	11,446	4,143

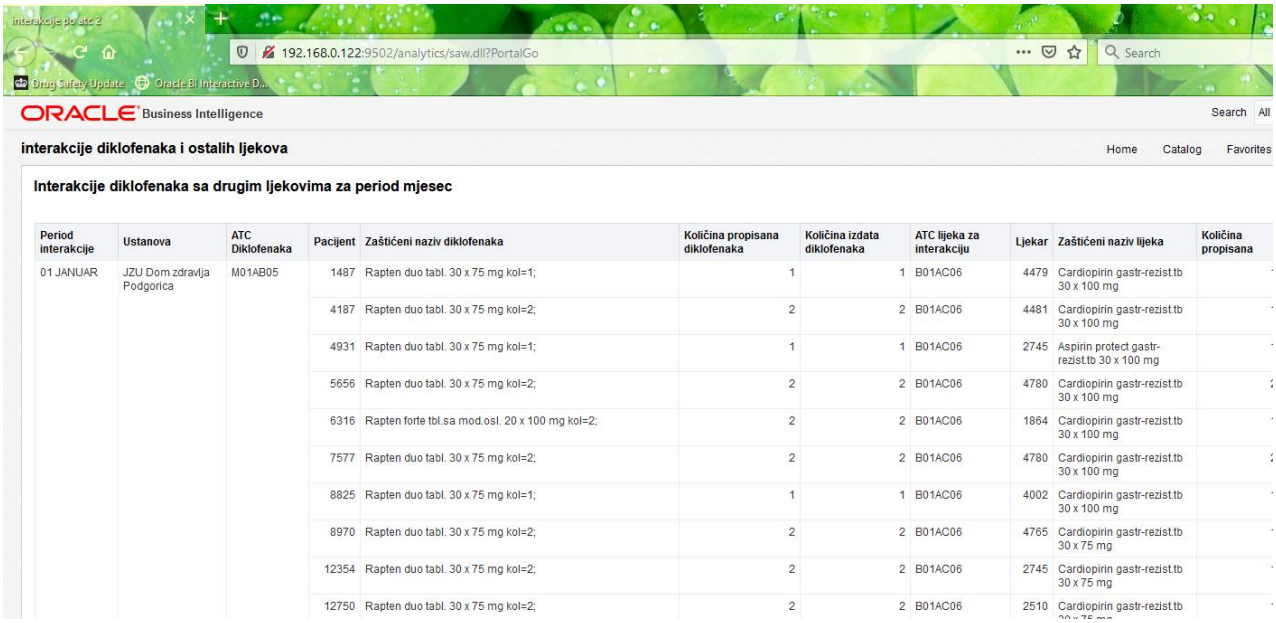
2.4 Interactions

During the whole period of monitoring, it was noticed that diclofenac had often been prescribed concomitantly with a large number of other medicines. Prescribing of diclofenac concomitantly with the medicines whose summary of product characteristics contains information on significant interactions was analysed with special attention. Diclofenac was prescribed to a significant extent in the same period as the medicines for which major interactions were identified: antihypertensives (beta-blockers), other nonsteroidal anti-inflammatory drugs (acetylsalicylic acid), heart disease therapy medicines (digitalis glycosides).



Period interakcije	Ustanova	ATC Diklofenaka	Pacijent	Zaštićeni naziv diklofenaka	Količina propisana diklofenaka	Količina izdata diklofenaka	ATC lijeka za interakciju	Ljekar	Zaštićeni naziv lijeka	Količina propisana
05 MAJ	JZU Dom zdravlja Podgorica	M01AB05	744	Rapten forte tbl.sa mod.osl. 20 x 100 mg kol=1;	1	1	C01AA05	2893	Lanibos tabl. 20 x 0.25 mg	2
			2174	Rapten duo tabl. 30 x 75 mg kol=1;	1	1	C01AA05	1335	Lanibos tabl. 20 x 0.25 mg	4
			3652	Rapten duo tabl. 30 x 75 mg kol=1;	1	1	C01AA05	1864	Lanibos tabl. 20 x 0.25 mg	2
			14759	Rapten duo tabl. 30 x 75 mg kol=2;	2	2	C01AA05	3050	Lanibos tabl. 20 x 0.25 mg	2
			25703	Rapten duo tabl. 30 x 75 mg kol=2;	2	2	C01AA05	3229	Lanibos tabl. 20 x 0.25 mg	1
			27785	Rapten forte tbl.sa mod.osl. 20 x 100 mg kol=2;	2	2	C01AA05	1335	Lanibos tabl. 20 x 0.25 mg	2
			28466	Rapten duo tabl. 30 x 75 mg kol=2;	2	2	C01AA05	2223	Lanibos tabl. 20 x 0.25 mg	2
			67737	Rapten duo tabl. 30 x 75 mg kol=2;	2	2	C01AA05	2888	Lanibos tabl. 20 x 0.25 mg	2

During each year covered by the project, there were cases of prescribing diclofenac and bisoprolol from the group of beta-blockers (ATC: C07AB07) during the same month. When used concomitantly, diclofenac may reduce the antihypertensive effect of diuretics and antihypertensive medicines (e.g. beta-blockers, ACE inhibitors). When used concomitantly it is recommended to pay special caution, as well as to periodically monitor blood pressure, especially with the elderly population. Diclofenac was also very often prescribed in the same month as digoxin from the group of cardiac glycosides (ATC: C01AA05). Concomitant use of diclofenac with the digitalis glycosides may lead to increase of concentration of plasma glycosides and exacerbation of cardiac disorder. Along with that, it was noticed that diclofenac is often prescribed with the other nonsteroidal anti-inflammatory drugs, such as acetylsalicylic acid (ATC: B01AC06). Concomitant use of diclofenac and other NSAIDs (including aspirin) or corticosteroids may increase the risk of gastrointestinal adverse effects.



Interakcije diklofenaka sa drugim ljekovima za period mjesec

Period interakcije	Ustanova	ATC Diklofenaka	Pacijent	Zaštićeni naziv diklofenaka	Količina propisana diklofenaka	Količina izdata diklofenaka	ATC lijeka za interakciju	Ljekar	Zaštićeni naziv lijeka	Količina propisana
01 JANUAR	JZU Dom zdravlja Podgorica	M01AB05	1487	Rapten duo tabl. 30 x 75 mg kol=1;	1	1	B01AC06	4479	Cardiopirin gastr-rezist.tb 30 x 100 mg	
			4187	Rapten duo tabl. 30 x 75 mg kol=2;	2	2	B01AC06	4481	Cardiopirin gastr-rezist.tb 30 x 100 mg	
			4931	Rapten duo tabl. 30 x 75 mg kol=1;	1	1	B01AC06	2745	Aspirin protect gastr-rezist.tb 30 x 100 mg	
			5656	Rapten duo tabl. 30 x 75 mg kol=2;	2	2	B01AC06	4780	Cardiopirin gastr-rezist.tb 30 x 100 mg	
			6316	Rapten forte tbl.sa mod.osl. 20 x 100 mg kol=2;	2	2	B01AC06	1864	Cardiopirin gastr-rezist.tb 30 x 100 mg	
			7577	Rapten duo tabl. 30 x 75 mg kol=2;	2	2	B01AC06	4780	Cardiopirin gastr-rezist.tb 30 x 100 mg	
			8825	Rapten duo tabl. 30 x 75 mg kol=1;	1	1	B01AC06	4002	Cardiopirin gastr-rezist.tb 30 x 100 mg	
			8970	Rapten duo tabl. 30 x 75 mg kol=2;	2	2	B01AC06	4765	Cardiopirin gastr-rezist.tb 30 x 75 mg	
			12354	Rapten duo tabl. 30 x 75 mg kol=2;	2	2	B01AC06	2745	Cardiopirin gastr-rezist.tb 30 x 75 mg	
			12750	Rapten duo tabl. 30 x 75 mg kol=2;	2	2	B01AC06	2510	Cardiopirin gastr-rezist.tb	

3. Conclusion

The analysis of the available data indicates certain deviations when it comes to prescribing practice in PHC. Diclofenac is often prescribed to patients with concomitant diseases that increase the risk of adverse effects on the cardiovascular system. Dicklofenac is also often prescribed at the same time as other drugs with which it interacts significantly. A revision of prescribing practices is necessary in order to make the use of diclofenac more rational and safer.

Joint EU-MNE Programme for
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WP3

Consumption of non-steroidal antiinflamatory drugs (NSAID)with special reference to diclofenac

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1. Introduction

Non-steroidal antiinflammatory drugs (NSAIDs) comprise a heterogeneous group of non-opioid drugs with effective analgesic, antiinflammatory and antipyretic properties. Overall, NSAIDs are well tolerated, especially when used short-term in low doses (Ong et al., 2007), but because of the enormous usage globally, they are often implicated in adverse drug reactions. These reactions, mostly gastrointestinal, cardiovascular and renal complications, have been shown to be dose-dependent, range from mild to severe and can result in hospitalizations and deaths. Some authors report that NSAIDs cause 100 000 hospitalizations and 17 000 deaths annually (Bhala et al., 2013; Szeto et al., 2020; Rane et al, 2020). Besides, the cost of treating adverse effects associated with NSAID use are also high. Some estimates suggest that direct costs for NSAID-related GI complications alone range from $1800 to $8500 per patient per hospitalization. In the elderly, the medical costs of adverse GI events associated with NSAID use likely exceed $4 billion per year. NSAID use is also associated with costly adverse events impacting the cardiovascular (CV) and renal systems. For example, NSAID use has been associated with increased risk for hospitalization due to myocardial infraction (MI) as well as for heart failure (HF). According to data from the USA Agency for Healthcare Research and Quality, the average hospitalizations for acute MI and congestive HF cost $18,500 and $10,500, respectively. Likewise, acute renal failure, which is also associated with NSAID use can ultimately lead to expensive dialysis treatment (Fine, 2013).

Because of that, it is important to regularly monitor the consumption/use of NSAIDs and take timely measures to make it rational and safe.

2. Analysis of NSAID consumption in the world

NSAIDs, including low dose aspirin, are one of the most commonly prescribed classes of medication, accounting for approximately 5–10% of prescriptions globally (Onder et al., 2004). Two decades ago, >30 million people were estimated to take NSAIDs daily (Singh and Triadafilopoulos, 1999). Pharmacoepidemiological studies indicate that NSAID use is increasing. A 2010 National Health Interview Survey (CDC, USA) reported increases of 57% and 41% in aspirin and NSAID use, respectively, over 5 years (Zhou et al., 2014), but this may still be an underestimate given the wide availability of some of these drugs as over-the-counter (OTC) formulations. Telephone surveys of

United States OTC NSAID users found that drugs were often used/taken inappropriately with with more than 25% of respondents exceeding recommended doses (Goldstein and Lefkowith, 1998; Wilcox et al., 2005; Goldstein and Cryer, 2015).

In Germany, analgesic use significantly increased from 19.2% in 1998 to 21.4% in 2008–2011. This rise was found to be attributed exclusively to the use of OTC formulations increasing from 10.0 to 12.2% (prescribed analgesic use remained constant at 7.9%). Ibuprofen was most commonly used, followed by aspirin (Sarganas and et al., 2015). Higher frequencies of ibuprofen use have also been documented in Denmark (Olsen and et al., 2011) and Spain (Gómez-Acebo et al., 2018). In contrast, however, diclofenac was reported as the most frequently used NSAID (followed by ibuprofen) in a study across 15 countries (Australia, Bangladesh, Canada, China, China (Hong Kong), England, Indonesia, Malaysia, New Zealand, Pakistan, Philippines, Singapore, Taiwan, Thailand, and Vietnam) (McGettigan and Henry, 2013). Similarly, in the same period, diclofenac and ibuprofen were the most frequently used NSAIDs in Serbia (Perić et al, 2013). The trend for increasing analgesic use has also been reported in Australia. Between 2001 and 2009, there was a 15% increase in the use of ibuprofen, naproxen and diclofenac (Stosic et al., 2011).
In general practice, NSAID use by the elderly is increased at 96% (96% in males, 96.7% in females) in patients > 65 years (Pilotto et al., 2003), which opens the possibility for a greater degree of manifestation of their adverse effects.

The European Medicine Agency (EMA) is the principal regulatory authority in the European Union, which constantly evaluates and regularly updates information on the balance of benefits and risk of medicines. Consequent recommendations are considered mandatory in all Member States and should serve as guidelines for relevant decision making. Since 2005, the EMA has restricted the use of certain NSAIDs due to concerns about safety. For example, in 2005, the EMA Committee for Medicinal Products for Human Use (CHMP) restricted the use of COX-2 inhibitors taking into account the results of studies showing their potential CV risk. Following these precautions, the utilization of coxibs decreased extremely in Denmark and Norway. Studies in other countries also showed that the use of COX-2 inhibitors declined (e.g., in 2005 following rofecoxib withdrawal in Australia, celecoxib prescription declined by 23%). As a result, a slight increase in paracetamol use was observed (Barozzi and Tett, 2007). However, in some countrie, like Lithuania, neither unfavorable results of clinical trials nor the EMA precautions had any impact on trends in COX-2 utilization — a consistent increase in COX-2 utilization with no (even transient) decrease was observed (Kasciuškeviciute et al, 2018).

In 2013, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) concluded that the effects of diclofenac on the heart and circulation when given systemically were similar to those of selective COX-2 inhibitors and recommended to apply the same CV precautions as for selective COX-2 inhibitors. Morales et al (2020) performed a study that measured the impact of the regulatory

action on the prescribing of systemic diclofenac in Denmark, The Netherlands, England, and Scotland. It was shown that overall, diclofenac prescription initiations fell during the observation periods of all countries (Figure 1). Compared with Denmark where there appeared to be a more limited effect, the regulatory action was associated with significant immediate reductions in diclofenac initiation in The Netherlands (−0.42%, 95% CI, −0.66% to −0.18%), England (−0.09%, 95% CI, −0.11% to −0.08%), and Scotland (−0.67%, 95% CI, −0.79% to −0.55%); and falling trends in diclofenac initiation in the Netherlands (−0.03%, 95% CI, −0.06% to −0.01% per quarter) and Scotland (−0.04%, 95% CI, −0.05% to −0.02% per quarter). However, there was no significant impact on diclofenac discontinuation in any country. The regulatory action was associated with modest differences in switching to other pain medicines following diclofenac discontinuation. Interestingly, in Scotland, the EMA regulatory action was associated with an increase in switching to opioids.

Contrary to this, in Lithuania, in the period 2013-2016, diclofenac utilization did not decrease and reached the largest diclofenac utilization indicators over the last 11 years (Kasciuškeviciute et al, 2018).

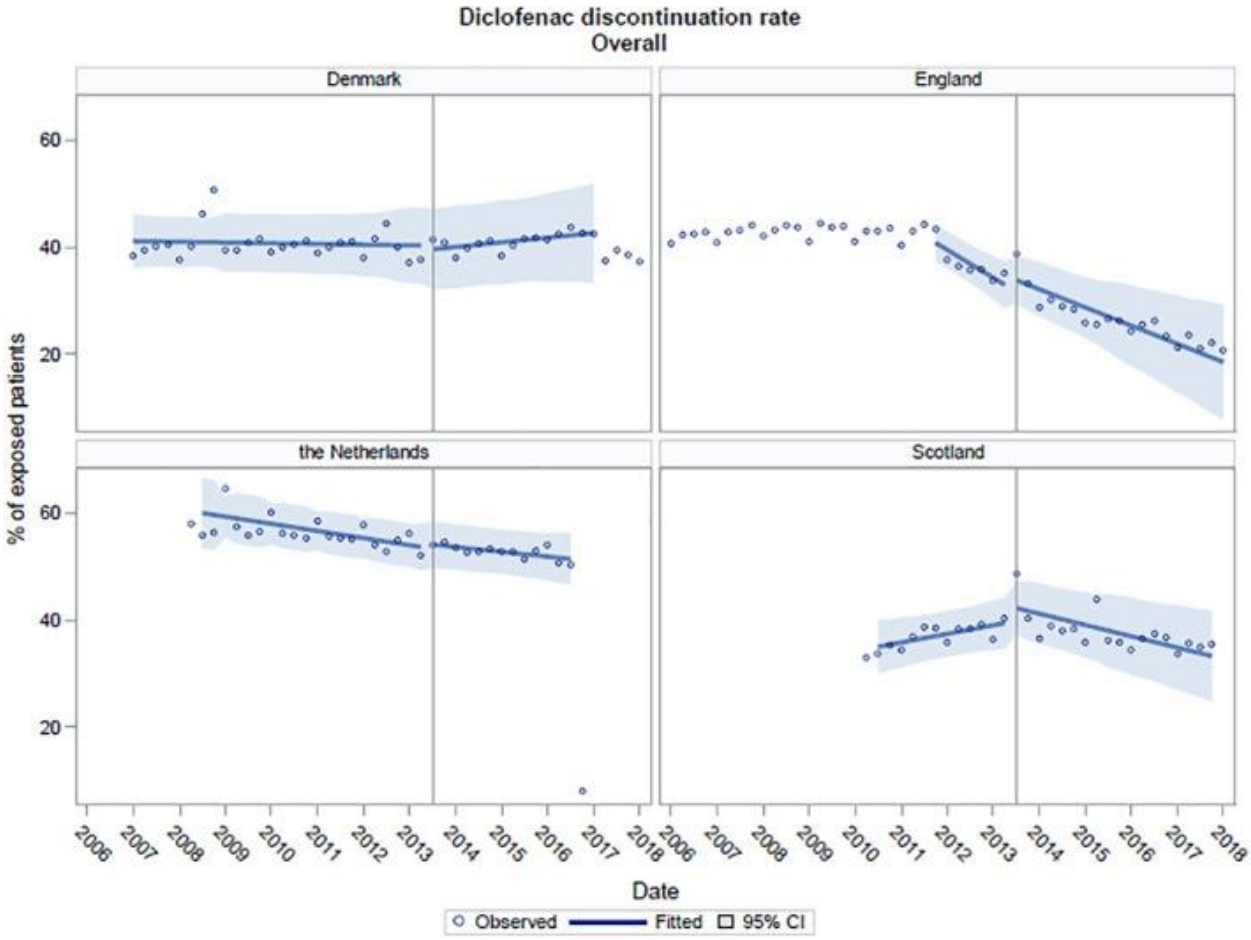

Fig. 1 - Trends in diclofenac discontinuation in Denmark, the Netherland, England, and Scotland after new contraindications and warnings for prescribing diclofenac were recommended by the EMA in 2013 (Morales et al., 2020)

3. Analysis of NSAID consumption in Montenegro

Data on the consumption of NSAIDs and, in particular, diclofenac (ATC code: M01AB05), in Montenegro (expressed as DDD / 1000 inhabitants / day), in the period from 2010 to 2020, are shown in Table 1. For comparison, data on the consumption of these drugs in the same period in countries in the region (Serbia and Croatia), and Norway as a country known for the rational use of drugs are also given. It can be seen, that within the group of drugs used in the treatment of the musculoskeletal system diseases (ATC code – M), NSAIDs (ATC code M01) have the largest share (about 80-90%). In the observed period, there was a constant

increased consumption of these drugs, especially diclofenac, in Montenegro. On average, the consumption of diclofenac in Montenegro was 1.65, 3.55 and 4.75 times higher than in Serbia, Croatia and Norway, respectively.

Table 1. Consumption of NSAIDs and diclofenac (in DDD/1000 inhabitants/day) in Montenegro, Serbia, Croatia and Norway in the period 2010-2020*

Year	Montenegro		Serbia		Croatia		Norway	
	M (M01)	M01AB05	M (M01)	M01AB05	M (M01)	M01AB05	M (M01)	M01AB05
2010	89.84 (n.a)	46.38	49.19 (45.84)	19.95	52.14 (42.43)	14.01	58.89 (45.50)	11.36
2011	92.78 (n.a)	48.95	64.55 (60.57)	34.66	50.74 (40.79)	12.47	60.07 (46.75)	11.43
2012	92.94 (n.a)	46.74	60.38 (54.34)	34.66	51.35 (41.59)	13.17	57.93 (47.51)	10.83
2013	66.62 (n.a)	40.99	62.58 (55.62)	28.83	52.84 (43.27)	12.82	57.97 (46.88)	10.13
2014	65.30 (n.a)	40.22	70.50 (63.08)	35.20	53.80 (44.87)	12.16	56.99 (45.92)	8.30
2015	101.98 (n.a)	43.57	71.08 (62.77)	31.09	56.91 (48.39)	12.26	57.60 (47.05)	7.96
2016	74.01 (n.a)	38.10	66.87 (58.26)	25.24	61.70 (51.31)	12.38	62.57 (47.48)	7.25
2017	80.39 (n.a)	42.71	84.81 (76.72)	40.43	65.82 (54.89)	11.77	63.38 (48.50)	6.85
2018	79.28 (n.a)	42.29	69.63 (59.45)	20.99	72.93 (61.04)	11.76	57.59 (47.32)	6.31
2019	82.40 (n.a)	43.92	81.23 (69.78)	28.56	77.81 (66.17)	11.38	63.24 (47.96)	5.92
2020	85.72 (n.a)	45.80	n.a.	n.a.	80.99 (67.95	11.63	65.03 (49.19)	5.62

*data are taken from publications on drug consumption freely available on the official websites of the medicines agencies of the countries in question (Montenegro: www.calims.me; Serbia: www.alims.sr; Norway: www.fhi.no)
M – Muskuloskeletal system; M01 – Antiinflammatory and antirheumatic products;
M01AB05 – diclofenac; n.a. – not available.

Although data on the consumption of diclofenac in Montenegro accounts for more than 50% of total consumption for drugs used to treat diseases of the musculoskeletal system, which is not the case in the region and especially in Norway. Moreover, in the period observed, diclofenac has been one of the first five most prescribed drugs in Mentenegro, and most frequently prescribed among NSAIDs. This speaks in favor of the enormous and unjustified consumption of diclofenac in Montenegro. In addition, while in Croatia and Norway there is a downward trend in diclofenac consumption of

subgroup M01 (in Montenegro data on consumption of this subgroup were not available), it can be seen that consumption in the period after 2013, when the new EMA recommendations on limiting the use of diclofenac were published, its consumption is maintained at an equally high level in Montenegro at all times. The situation is similar in Serbia, although in this country there is a certain trend of a slight decrease in the consumption of this medicine.

Due to all the above, there are great expectations from the new IT solutions in electronic drug prescribing which will signal to the doctor which categories of patients should not be prescribed, and which, but with caution, should be prescribed diclofenac. In that way, the use of this druge will be rationalized, which, we believe, will be reflected in the reduction of its consumption, and thus in the reduction of its potential adverse effects.

4. Conclusion and recommendation

NSAIDs, especially diclofenac, are still one of the most widely used drugs, although there is evidence of serious risks if used for a long time in high doses, in the elderly, and those with pre-existing cardiovascular diseases or the risk of developing them.

The consumption of diclofenac is unjustified high in Monteenegro.

As the elderly most often suffer from diseases for which these drugs are used (rheumatic problems), and often already have some of the cardiovascular diseases, they are at special risk from the use of the drug.

Therefore, in further analyses of the use of diclofenac, besides the drug consumption by using DDD / 1000 inhabitants / day, it should be considered which age groups are prescribed this drug the most, in which doses and for how long and whether any disorders have been registered during the administration of the drug that could be related to that administration.

These analyses should, in addition to prospectively, be conducted retrospectively (for an earlier period), in order to fully see the usefulness of new IT solutions that will provide the most optimal prescribing of diclofenac through an integrated health care system.

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