ORIGINAL ARTICLE

THE PREVALENCE OF INAPPROPRIATE USE OF NSAIDs BY CARDIOVASCULAR PATIENTS FOR MUSCULOSKELETAL DISORDERS

MARIA SUCIU [1#], LIANA SUCIU [1#], LAVINIA VLAIA [2*], MIRELA VOICU [1], VALENTINA BUDA [1], LIANA DRĂGAN [3], MINODORA ANDOR [4], VICENŢIU VLAIA [5], CARMEN CRISTESCU [1], MIRCEA HÎRJĂU [6]

[1]Department II – Pharmacology, Clinical Pharmacy, "Victor Babeş" University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041, Timişoara, Romania
[2]Department II – Pharmaceutical Technology, "Victor Babeş" University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041, Timişoara, Romania
[3]Department I – Drug Analysis, Environmental and Food Chemistry, Pharmaceutical Legislation, Management and Marketing, "Victor Babeş" University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041, Timişoara, Romania
[4]Department of Internal Medicine I – Medical Semiotics II, "Victor Babeş" University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041, Timişoara, Romania
[5]Department I – Organic Chemistry, "Victor Babeş" University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041, Timişoara, Romania
[6]Department of Pharmaceutical Technology and Biopharmacy , Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, 6 Traian Vuia Street, 020956, Bucharest, Romania

*corresponding author: vlaia.lavinia@umft.ro
#Authors with equal contribution.

Abstract

A prospective observational analysis of the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs)/paracetamol by cardiovascular (CV) patients over a 3-month period was performed. The aim of the study was to evaluate the potential inappropriate use of these drugs by CV patients and to identify the risk profile of the CV patient inclined towards self-medication with these molecules. The data obtained from the questionnaires completed by the respondents were statistically analysed using a SPSS statistical package (version 17.0) software. Our results showed that for both physicians and patients, the improvement of the patient's symptoms and quality of life prevail over future CV risks. Our results indicate that despite existing warnings from the FDA and EMA, there is still a high percentage of CV patients who use NSAIDs inappropriately, both as self-medication and with medical advice, and the pharmacist must play a more active role in preventing the problems related to the irrational consumption of NSAIDs.

Rezumat

O analiză observaţională prospectivă cu privire la consumul de antiinflamatoare nonsteroidiene (AINS)/paracetamol pe o durată de 3 luni a fost efectuată în rândul pacienţilor cu patologie cardiovasculari (CV). Scopul studiului a fost de a evalua o potenţială utilizare necorespunzătoare a acestor medicamente de către pacienţii CV şi de a identifica profilul de risc al pacientului cu boală CV înclinat spre automedicaţia cu aceste molecule. Analiza statistică a datelor obţinute după completarea integrală a chestionarelor aplicate respondenţilor a fost efectuată folosind pachetul statistic SPSS (versiunea 17.0). Rezultatele obţinute au arătat că atât pentru medici cât şi pentru pacienţi, ameliorarea simptomatologiei şi a calităţii vieţii acestora primează în faţa viitoarelor riscuri CV. Rezultatele noastre indică faptul că în ciuda avertismentelor existente de la FDA şi EMA, există încă o pondere mare de pacienţi CV care utilizează necorespunzător AINS-urile, atât ca automedicaţie, cât şi cu recomandare medicală, astfel încât farmacistul trebuie să joace un rol mai activ în prevenirea problemelor legate de consumul iraţional de AINS.

Keywords: NSAIDs, cardiovascular disease, inappropriate use, self-medication

Introduction

For all nonsteroidal anti-inflammatory (NSAID) molecules, independent of their selectivity on cyclo-oxygenase-2 (COX-2), it is well known today that their cardiovascular (CV) risk manifests itself in different degrees and clinical forms [1, 2]. This risk increases with the patient's age, the association of various comorbidities and concurrent consumption of various other drugs with which they can generate severe adverse events. Thus, over time, a number of decisions have been made regarding various molecules belonging to this large group of drugs, starting with the withdrawal of rofecoxib from the pharmaceutical market in 2004, and continuing with new contraindications and warnings for other COX-2 inhibitors [3] and warnings in case of

diclofenac [4] or even restrictions on use including avoidance recommendations in some categories of patients such as the elderly [5]. A recent Danish study suggested an increase in CV mortality even among healthy individuals (without a prior history of CV disease) using various NSAIDs, especially diclofenac and ibuprofen [6]. According to the guides, paracetamol, used for fever treatment and mild to moderate pain relief, should be the first choice of pain medication for people with increased risk of digestive or cardio-renal events, due to its intimate mechanisms of action, through which it intervenes in the process of nociception suppress at peripheral and central levels [7]. Generally, the main drug-related problems derive from the fact that the prescribed drugs are inappropriate, given the clinical context of each patient. The correct choice of co-administered drugs for the treatment of comorbidities for a CV patient is a factor just as important as the treatment of his underlying disease. Exposure of a large number of patients to NSAIDs consumption, according to their clinical potential for the development of different CV events, is a danger to their health, quality of life, respectively a serious public health problem, insufficiently known, but also under-recognized [2]. Considering all the above mentioned aspects, this study aimed: (1) to evaluate the prevalence and the factors associated with an inappropriate use of NSAIDs by CV patients and (2) to identify a risk profile of the CV patient inclined towards self-medication with NSAIDs.

Materials and Methods

Study design and data source
A prospective and cross-section observational study was performed to estimate the trends in the use of NSAIDs/paracetamol by CV patients, in Timișoara, Romania, from March 2018 until May 2018. The study was performed based on real-life practice data that were collected from a self-administered questionnaire, elaborated by the study working group and described in our previous work [8].

The patients of the study and procedures
The eligible target population included all NSAIDs/paracetamol users of both genders, over 18 years old, resident in Timișoara, Romania, not pregnant at the time of our survey, were willing to participate in a face-to-face interview and able to complete a questionnaire in Romanian language in a voluntary and anonymous manner. The questionnaires were distributed to patients of three community pharmacies by a pharmacist during their visit to purchase their medications containing paracetamol/NSAIDs, with or without prescription. The questionnaires were equally distributed among all interested participants, in each location, and in regard to gender. Patients were included only once, during the 3 months study, for each possible drug of interest. The complete responses rate of the questionnaire was 91.87%. A total of 381 women and 354 men contributed

with valid information and were included in the final analyses of the questionnaires. Patients with difficulties of comprehension and/or speaking of the Romanian language, with memory disorders that make it impossible to collect accurate data, which did not purchase the preparations for their own use, who refused to participate in the interview or recently participated in a similar study, were excluded from the study. Patient demographic characteristics, mentioned clinical data and the doctor's specialty who issued the prescription (if there was a medical prescription) were collected at the time of the purchase of NSAIDs/paracetamol. Also, medical history conditions of the patients and chronic concurrent therapy used in the last 12 months were identified by self-reporting and recorded for the patients enrolled in the study. By analysing of the socio-demographic characteristics, the respondents were divided into two categories based on marital status: married (who live with a partner) and unmarried (who live alone, for any reason). Further, the patients were included in one of the three levels of education, namely high, medium and low, according to the International Standard Classification of Educational Degrees (ISCED 2011) [9]. All situations in which the patient presented a prescription at the time of the purchase of the preparation were considered purchases with a medical prescription (MP), and the rest were all considered as self-medication (SM).

Ethical considerations
All participants who agreed to participate in the present study and were eligible provided written informed consent prior to personal interview and because the personal contact details of the patients were not collected, all information was stored in a secure manner, by irreversible data anonymization. Numbering the self-administered questionnaires completed with the requested information was used as a method of identifying each individual respondent. Therefore, being an observational study, our research group considered that an ethics committee approval was not required.

Statistical analyses
The data extracted from the questionnaires were analysed with Statistic Package for the Social Sciences (SPSS) software version Windows 17.0. The relationships between different variables were evaluated using descriptive statistics. Data were presented as odds ratio (OR) with 95% confidence intervals (CI) to assess different risk factors and Pearson's Chi-square test ($\chi2$) was used to compare differences between respondent characteristics and NSAID/paracetamol use. A p value of less than 0.05 was considered statistically significant to analyse the differences between the groups of patients.

Results and Discussion

Based on the inclusion criteria, a total of 735 respondents were included in this study. Due to the

high share of the CV disease (444; 60.40%) identified in our study, we further performed an analysis to identify the trends in the use of NSAIDs/paracetamol in two study groups, patients with and without associated CV comorbidities (CV patients and non-CV patients). More than three-quarters of NSAIDs users presented a CV comorbidity, a kidney or peptic ulcer disease. The CV disease subtypes identified by self-reported diagnosis among the participants were: hypertension (HT-252; 56.76%), chronic heart failure (CHF-129; 29.05%) and coronary artery disease (CAD-63; 14.19%). The socio-demographic characteristics and symptomatic status of the participants were presented in our previous published study [8]. From the first results, this study revealed an increased prevalence of current NSAIDs consumption among the groups of patients with risk to develop a significant adverse event or who have experienced major chronic medical conditions that represent relative contraindications to the use of this group of molecules. In the present study, NSAIDs/ paracetamol was purchased for the following five medical reasons: joint pain and low back pain (two forms of clinical manifestation of chronic pain), headache and toothache (two forms of acute pain) and fever.

As the biopsychosocial implications of chronic pain are well-known today and not neglected [10], more and more patients resort behaviourally to inappropriate trends of NSAIDs use (e.g. the molecule type, dose, duration of treatment) regardless of the consequences, for rapid and long-term suppression of the disabling symptomatology, but also for the induced physical and mental discomfort. In the light of the new findings, it is required to identify the modifiable behavioural risk factors, and also to develop and apply as early as possible various interventions, safe in CV terms, for the treatment of musculoskeletal comorbidities of CV patients to improve CV specific health outcomes and their quality of life [11].

According to the today Romanian pharmaceutical legislation, it is necessary for the patient to submit a prescription to the pharmacy for the medication that pose a direct or indirect danger to health [12]. Although, for some non-selective COX-2 NSAIDs (OTC), the acquisition is made without MP (for lower drug doses than those delivered with MP), and for COX-2 selective inhibitors only by MP, there were differences in the use of both drug types, regarding both the medical reason and the mode of request, as well as the analysed socio-demographic characteristics.

Trends of NSAIDs and paracetamol use by the patients of the two groups were assessed in relation to the following variables: (1) the medical reason – type of the chosen/used molecule – its request mode according to the types of real-life practices – related trends; (2) the socio-demographic characteristics – related trends and (3) concomitant drug treatment.

The medical reason – type of the chosen/used molecule – its request mode according to the types of real-life practices – related trends

From Table I, it can be observed that for the same main medical reason, *low back pain*, in the top of the CV patients requests was diclofenac (123; 66.13%), followed by etoricoxib (21; 11.29%), ibuprofen (12; 6.45%) and nimesulide (12; 6.45%). In comparison, the non-CV patients have requested mainly diclofenac (39; 54.17%) and etoricoxib (33; 45.83%).

Table I

Differences between the two groups in the use of NSAIDs/paracetamol depending on medical reasons and request mode

Drug	Joint pain CV MP	Joint pain CV SM	Joint pain nonCV MP	Joint pain nonCV SM	Low back pain CV MP	Low back pain CV SM	Low back pain nonCV MP	Low back pain nonCV SM	Headache CV MP	Headache CV SM	Headache nonCV MP	Headache nonCV SM	Toothache CV MP	Toothache CV SM	Toothache nonCV MP	Toothache nonCV SM	Fever CV MP	Fever CV SM	Fever nonCV MP	Fever nonCV SM	Total no. of patients
Diclofenac	-	15	3	-	18	105	-	39	-	-	-	-	-	-	-	-	-	-	-	-	180
Ibuprofen	-	15	-	12	-	12	-	-	-	12	-	42	-	6	-	39	-	6	-	9	153
Ketoprofen	3	36	-	12	-	6	-	-	-	-	-	3	-	-	-	3	-	-	-	-	63
Nimesulide	3	24	-	27	3	9	-	-	-	-	-	-	-	3	-	-	-	-	-	-	69
Indomethacin	30	-	6	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	39
Etoricoxib	27	-	24	-	21	-	33	-	-	-	-	-	-	3	-	-	-	-	-	-	108
Naproxen	39	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	42
Paracetamol	-	-	-	-	-	-	-	-	-	3	-	3	-	-	-	-	-	6	-	24	36
Meloxicam	9	12	-	-	6	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	30
Acetylsalicylic acid	-	-	-	3	-	-	-	-	-	3	-	-	-	-	-	-	-	-	-	9	15
Total no. of patients	111	105	33	54	51	135	33	39	-	18	-	48	-	12	-	42	-	12	-	42	735
patients	216		87		186		72		18		48		12		42		12		42		735

Regarding the request mode in case of low back pain, diclofenac as NSAID prototype was requested by SM by 56.45% of CV patients, *versus* 54.17% of non-CV patients. Etoricoxib was the second molecule as pharmacological therapeutic alternative, but it was requested based on a specialist MP for 21 (11.29%) CV patients compared to 33 (45.83%) non-CV patients. Significant difference in the choice of various NSAID molecules was also observed between the two groups of patients in case of *joint pain* treatment, which

included a broader range of therapeutic options: for CV patients, naproxen molecule was more frequently prescribed (42; 19.44%), followed closely by ketoprofen (39; 18.06%), indomethacin (30; 13.89%), etoricoxib (27; 12.50%) and nimesulide (27; 12.50%); instead, for non-CV group, the main NSAID molecule prescribed was nimesulide (27; 31.03%), followed by etoricoxib (24; 27.59%). As self-medication, the CV patients requested mainly ketoprofen (36; 16.67%), followed by nimesulide (24; 11.11%), while the non-CV patients preferred nimesulide as first therapeutic option. For the treatment of symptoms such as headache, tooth-ache and fever, the results revealed that ibuprofen as SM was the most commonly used NSAID, totalizing 24 (57.14%) CV and 90 (68.18%) non-CV patients (Table I). Both categories of patients have acquired the paracetamol molecule as a SM, only for the treatment of headache and fever symptoms, manifested concomitantly or independently of each other (Table I). Based on all observations of the present study, it can be suggested that different other considerations are operational in the NSAIDs use trend, for both CV patients and physicians. Although, our results cannot be generalized, being a small study and limited only to the urban environment, it is possible that factors, other than those assessed (e.g. the patient's rapid urge to suppress the pain, lack of time for a specialized medical consultation, previous experience, the cost *per* molecule, habit and medical routine, but also the sponsored advertising of some drugs such as ibuprofen), can be taken more quickly into account when choosing a molecule (by the CV patient, doctor or pharmacist). It seems that the CV associated comorbidities have a lesser influence on the pharmacological therapeutic management decisions of different painful chronic clinical contexts. As etoricoxib (the only selective COX-2 in our study) and diclofenac (non-selective COX-2) are delivered only on MP, our results suggest that their risks for developing or worsening a CV disease, in general population or in the target group, are considered acceptable (rare/or low severity) or are ignored by many clinicians and pharmacists in daily clinical practice. Also, other factors could contribute to the inappropriate choice of the NSAIDs molecule, such as: the short duration of clinical visits (10 - 15 minutes) which does not allow an optimal assessment of the patient's relative contraindications to NSAID therapy, erroneous perception of the risks (by patient, physician, pharmacist), and according to other studies even the level of medical knowledge of older physicians generations [13].

The results of the Chi-square test for independence (Table II) performed to explore the relationship between the presence/absence of CV comorbidities and two analysed variables (the medical reasons and the main four NSAIDs), revealed a statistically significant relationship ($p < 0.05$) between the abovementioned variables and the presence of CV comorbidities, excepting the ketoprofen molecule ($p = 0.0614$), whose use appears to be unrelated with the presence of CV comorbidities. Also, a statistically significant relationship ($p < 0.05$) between the request mode and the presence of CV comorbidities in the general patient population as well as in the two subgroups (with join pain and low back pain) was indicated by the results of Chi-square test for independence applied in case of these two variables (Table II).

Table II

Results of a Chi-square test of independence between CV comorbidities and the medical reasons, the main four NSAIDs used and their request mode

Variables	CV patients 444	non-CV patients 291	χ^2 statistics[a] (df)	p-value[b]	χ^2 statistics[a] of group (global df)	p-value[b]
A. Medical reasons						
Joint pain	216	87	25.5106 (1)	< 0.05	125.8677 (4)	p < 0.00001
Low back pain	186	72	22.6952 (1)	< 0.05		
Headache	18	48	33.2881 (1)	< 0.05		
Toothache	12	42	35.5336 (1)	< 0.05		
Fever	12	42	35.5336 (1)	< 0.05		
B. NSAIDs use						
Diclofenac	138	42	26.3461 (1)	< 0.05	72.7088 (3)	p < 0.00001
Ibuprofen	51	102	59.2224 (1)	< 0.05		
Ketoprofen	45	18	3.4991 (1)	0.061403		
Etoricoxib	51	57	9.2037 (1)	0.002415		
Paracetamol	9	27	19.8435	0.000008	-	-
C. Request mode						
General population MP/SM	156/288	66/225	12.9348 (1)	0.000323	-	-
Joint pain subgroup MP/SM	111/105	33/54	4.5041 (1)	0.033814	-	-
Low back pain subgroup MP/SM	51/135	33/39	8.0155 (1)	0.004638	-	-

[a]χ^2 - Chi square test; df - degrees of freedom; [b]p - level of statistical significance; the mean difference is significant at the 0.05 level

The socio-demographic characteristics – related trends

The socio-demographic characteristics of patients leave an important mark on the trends of use of NSAIDs/ paracetamol by the two categories of patients. First, all the patients of our study who have shown *low back pain* were male, independent of the presence/absence of associated CV comorbidities (Table III). Although, the molecule diclofenac ranked first in the top of the requests, for both categories of male patients, 123 (66.13%) of CV patients and respectively 39 (54.17%) of non-CV patients, their socio-demographic characteristics were different. CV male patients were mostly married (75; 40.32%), middle-aged (96; 51.61%) and with middle education levels (72; 38.71%), while the non-CV male were mainly unmarried (21; 29.17%), younger (33; 45.83%) and belonged to a higher educational level (21; 29.17%) (Tables IV, V and VI).

Table III

Trends of NSAIDs/paracetamol use by the patients of the two groups in relation to their gender as socio-demographic characteristic

Symptom	Patient type/Gender		Drug used/No. of patients										Total no. of patients	
			DCF	IBU	KPF	NMS	IND	ECX	NPX	PCM	MLX	AAS		
Joint pain	CV	M	6	-	-	6	-	3	-	-	3	-	18	216
		F	9	15	39	21	30	24	42	-	18	-	198	
	non-CV	M	-	3	-	-	-	6	-	-	-	-	9	87
		F	3	9	12	27	6	18	-	-	-	3	78	
Low back pain	CV	M	123	12	6	12	3	21	-	-	9	-	186	186
		F	-	-	-	-	-	-	-	-	-	-	-	
	non-CV	M	39	-	-	-	-	33	-	-	-	-	72	72
		F	-	-	-	-	-	-	-	-	-	-	-	
Headache	CV	M	-	-	-	-	-	-	-	-	-	-	-	18
		F	-	12	-	-	-	-	-	3	-	3	18	
	non-CV	M	-	6	3	-	-	-	-	3	-	-	12	48
		F	-	36	-	-	-	-	-	-	-		36	
Toothache	CV	M	-	6	-	-	-	-	-	-	-	-	6	12
		F	-	-	-	3	-	3	-	-	-	-	6	
	non-CV	M	-	27	3	-	-	-	-	-	-	-	30	42
		F	-	12	-	-	-	-	-	-	-	-	12	
Fever	CV	M	-	-	-	-	-	-	-	3	-	-	3	12
		F	-	6	-	-	-	-	-	3	-	-	9	
	non-CV	M	-	3	-	-	-	-	-	6	-	9	18	42
		F	-	6	-	-	-	-	-	18	-	-	24	

M – male; F – female; DCF – diclofenac; IBU – ibuprofen; KPF – ketoprofen; NMS – nimesulide; IND – indomethacin; ECX – etoricoxib; NPX – naproxen; PCM – paracetamol; MLX – meloxicam; AAS – acetylsalicylic acid

Similarly, for both groups of patients with low back pain, on the second place was the etoricoxib molecule with small differences in terms of their socio-demographic characteristics. Thus, if the 21 (11.29%) male CV patients were mostly unmarried (12; 6.45%), elderly, over 65 (12; 6.45%), and had medium educational level (15; 8.06%), the 33 male non-CV patients were also mainly unmarried (18; 25%), over 65 years old (18; 25%), but equally with medium or high education levels (15/15; 20.83%). The potential CV risk of diclofenac is recognized today and the safety advice for diclofenac issued by the European Medicines Agency states that this molecule is contraindicated for use in patients with CAD, HT, CHF, cerebro-vascular disease or peripheral artery disease [14]. It is also known, that the use of selective COX-2 inhibitory NSAIDs (such as celecoxib in the present case) is associated with an increased risk of CV events [15], especially thromboembolic events, which led to the withdrawal of the rofecoxib molecule from the pharmaceutical market on 30 September 2004 [16]

and to the FDA recommendations on 7 April 2005 for precautions in terms of CV safety of coxibs. The results obtained in our study, namely the excessive use of diclofenac or etoricoxib among patients with pre-existing CV disease, could be attributed to various other reasons, valid for both physicians and patients such as: an insufficient level of knowledge, their different perceptions about the importance of the risks of NSAIDs treatment, the expected benefits of this therapy among CV patients and their attitudes towards their painful physical disabilities. Even though the patients are aware of the potential adverse effects, it is possible that some of them still use diclofenac, etoricoxib or other NSAIDs inappropriately, because these molecules give them a faster pain suppression, which they cannot obtain by other means or with other molecules. Our findings on the predominant use of diclofenac or etoricoxib in CV patients require additional investigations to understand all the real reasons for their inappropriate use. If for non-CV male patients, the therapeutic options described above were the only

ones identified in our study, for CV male patients, the palette of pharmacological therapeutic molecules, purchased to alleviate the discomfort due to physical disability produced by low back pain, was much wider, including, in descending order, other representatives such: ibuprofen (12; 6.45%), nimesulide (12; 6.45%) and meloxicam (9; 4.84%). All of them had mostly the same common socio-demographic characteristics presented in Tables III - VI. It can be suggested that also this wider range of painkiller molecules used by CV patients supports the previously presented idea that the need for rapid pain suppression determine the patient's behaviour, urging him to experience the efficacy of several molecules, irrespective of the consequences of this inappropriate use.

If the low back pain was predominant in the male gender patients, the *joint pain* was the prevalent symptom in female patients, independent of the existence of CV comorbidities, for 198 CV women and 78 non-CV (Table III). All female patients have acquired a much broader range of NSAIDs molecules for the treatment of their locomotor pain and reduction of joint dysfunctions, compared to male patients for the treatment of low back pain, independent of group membership (Table III). The preferences of CV females, in descendent order were: naproxen (42; 21.21%), ketoprofen (39; 19.70%), indomethacin (30; 15.15%), etoricoxib (24; 12.12%) and nimesulide (21; 10.61%). The female CV users of naproxen were mainly un-married (36; 85.71%) older than 65 years (33; 78.57%) and with middle graduate education (21; 50%). From

these first results it can be observed that the naproxen molecule (associated with less CV risk and recommended by guidelines to be used for this category of patients [17] is ranked first in the top of the individual preferences of female CV patients. For ketoprofen, the analysis of socio-demographic characteristics of female CV patients revealed that most of them were married (21; 53.85%), middle-aged (33; 84.62%) and with middle educational level (24; 61.54%).

The NSAID molecules recommended or preferred by the female non-CV populations were different, on first place being nimesulide (27; 34.62%), followed by etoricoxib (18; 23.08%), ketoprofen (12; 15.38%), ibuprofen (9; 11.53%) and indomethacin (6; 7.69%). More than half of the female non-CV patients using nimesulide were unmarried (18; 66.67%), both young (12; 44.44%) and middle-aged in equal proportions (12; 44.44%), but mostly with higher education level (15; 55.56%). The female non-CV patients requesting the etoricoxib molecule were almost all married (15; 83.33%), both middle age and over 65 years in equal proportions (9/9; 50%), and as an educational level belonged to the elementary education (12; 66.67%). Analysing the obtained results for this subgroup of patients, it can be observed that female CV patients, although mostly have an average educational level and belong to the second and third decades of age, experienced a much wider range of NSAID molecules than men and much more correctly chosen in terms of their CV and gastro-intestinal safety.

Table IV

Trends of NSAIDs/paracetamol use by the patients of the two groups in relation to their marital status as socio-demographic characteristic

Symptom	Patient type/ Marital status		Drug used/No. of patients										Total no. of patients	
			DCF	IBU	KPF	NMS	IND	ECX	NPX	PCM	MLX	AAS		
Joint pain	CV	M	6	6	21	-	30	15	6	-	15	-	111	216
		uM	9	9	18	-	-	12	36	-	6	-	105	
	non-CV	M	3	9	6	9	-	21	-	-	-	3	51	87
		uM	-	3	6	18	6	3	-	-	-	-	36	
Low back pain	CV	M	75	9	6	9	-	9	-	-	9	-	117	186
		uM	48	3	-	3	3	12	-	-	-	-	69	
	non-CV	M	18	-	-	-	-	15	-	-	-	-	33	72
		uM	21	-	-	-	-	18	-	-	-	-	39	
Headache	CV	M	-	6	-	-	-	-	-	3	-	3	12	18
		uM	-	6	-	-	-	-	-	-	-	-	6	
	non-CV	M	-	30	-	-	-	-	-	-	-	-	30	48
		uM	-	12	3	-	-	-	-	3	-	-	18	
Toothache	CV	M	-	3	-	-	-	-	-	-	-	-	3	12
		uM	-	3	-	-	-	3	-	-	-	-	9	
	non-CV	M	-	6	-	-	-	-	-	-	-	-	6	42
		uM	-	33	3	-	-	-	-	-	-	-	36	
Fever	CV	M	-	6	-	-	-	-	-	6	-	-	12	12
		uM	-	-	-	-	-	-	-	-	-	-	-	
	non-CV	M	-	6	-	-	-	-	-	9	-	3	18	42
		uM	-	3	-	-	-	-	-	15	-	6	24	

M – married; uM – unmarried; DCF – diclofenac; IBU – ibuprofen; KPF – ketoprofen; NMS – nimesulide; IND – indomethacin;
ECX – etoricoxib; NPX – naproxen; PCM – paracetamol; MLX – meloxicam; AAS – acetylsalicylic acid

Analysing the socio-demographic characteristics of patients who purchased ibuprofen for the treatment of *headache* (Tables III - VI), it can be observed that they are all women (12; 100%) in the CV group, unmarried and married in equal parts (6/6, 50%/50%), mostly by medium age (9; 75%) and with high educational level (6; 50%). Also, in the group of non-CV patients, most of them were female (36; 75%), married (30, 62.5%), younger (33; 68.75%) and with high education level (36; 75%) (Tables III - VI). Compared to other studies revealing a higher incidence of headache among males [18], in our study the prevalence of headache was higher in female patients, independent of associated CV comorbidities, possibly in close relationship with other factors such as socio-cultural or hormonal changes characteristic for this

age period (pre-menopausal, menopause, and possible the use of replacement sex hormones), integral part of the normal female life cycle. According to the results presented in the Table III, the *toothache* was mainly observed for the male patients from both groups, and for its treatment also ibuprofen was the main required molecule. In the group of CV patients, ibuprofen was used by 6 (50%) male patients, middle-aged, with higher education, married and unmarried in equal proportions, while nimesulide and etoricoxib molecules were requested by the other 6 (50%) patients who were female in equal numbers. Nimesulide was requested by middle-aged female patients, unmarried and with high educational level and etoricoxib by elderly female patients, unmarried and with elementary education level.

Table V

Trend of NSAIDs/paracetamol use by the patients of the two groups in relation to their age as socio-demographic characteristic

Symptom	Patient type/Age		Drug used/No. of patients										Total no. of patients	
			DCF	IBU	KPF	NMS	IND	ECX	NPX	PCM	MLX	AAS		
Joint pain	CV	20 - 44	-	-	-	-	-	-	-	-	-	-	-	216
		45 - 65	6	12	33	15	18	-	9	-	9	-	102	
		> 65	9	3	6	12	12	27	33	-	12	-	114	
	non-CV	20 - 44	-	-	3	12	-	3	-	-	-	-	18	87
		45 - 65	-	12	9	12	3	12	-	-	-	3	51	
		> 65	3	-	-	3	3	9	-	-	-	-	18	
Low back pain	CV	20 - 44	9	-	-	-	-	-	-	-	-	-	9	186
		45 - 65	96	12	6	12	-	9	-	-	3	-	138	
		> 65	18	-	-	-	3	12	-	-	6	-	39	
	non-CV	20 - 44	33	-	-	-	-	-	-	-	-	-	33	72
		45 - 65	6	-	-	-	-	15	-	-	-	-	21	
		> 65	-	-	-	-	-	18	-	-	-	-	18	
Headache	CV	20 - 44	-	3	-	-	-	-	-	-	-	-	3	18
		45 - 65	-	9	-	-	-	-	-	3	-	3	15	
		> 65	-	-	-	-	-	-	-	-	-	-	-	
	non-CV	20 - 44	-	33	3	-	-	-	-	3	-	-	39	48
		45 - 65	-	9	-	-	-	-	-	-	-	-	9	
		> 65	-	-	-	-	-	-	-	-	-	-	-	
Toothache	CV	20 - 44	-	-	-	-	-	-	-	-	-	-	-	12
		45 - 65	-	6	-	3	-	-	-	-	-	-	9	
		> 65	-	-	-	-	-	-	3	-	-	-	3	
	non-CV	20 - 44	-	33	3	-	-	-	-	-	-	-	36	42
		45 - 65	-	6	-	-	-	-	-	-	-	-	6	
		> 65	-	-	-	-	-	-	-	-	-	-	-	
Fever	CV	20 - 44	-	-	-	-	-	-	-	-	-	-	-	12
		45 - 65	-	6	-	-	-	-	-	6	-	-	12	
		> 65	-	-	-	-	-	-	-	-	-	-	-	
	non-CV	20 - 44	-	9	-	-	-	-	-	15	-	-	24	42
		45 - 65	-	-	-	-	-	-	-	9	-	9	18	
		> 65	-	-	-	-	-	-	-	-	-	-	-	

DCF – diclofenac; IBU – ibuprofen; KPF – ketoprofen; NMS – nimesulide; IND – indomethacin; ECX – etoricoxib; NPX – naproxen; PCM – paracetamol; MLX – meloxicam; AAS – acetylsalicylic acid

Given that the toothache is an acute moderate pain, the NSAIDs used for its treatment have been selected considering that they provide a faster and superior analgesic and anti-inflammatory effect than other molecules, and because of their gastro-intestinal safety

profile, but ignoring their potential CV risk assuming a short period of use. In comparison with the group of CV patients, the patients of the non-CV group, who requested NSAID molecules for the suppression of toothache, were more numerous for both genders,

the male gender prevailing (30; 71.43%). The main molecule they requested was ibuprofen for both genders, and the 27 (64.29%) male respondents were mainly unmarried (24; 88.89%), young (24; 88.89%), and with a high educational level (18; 66.67%). Choosing ibuprofen as first option in the treatment of headache and toothache (acute pain) can be related to several factors such as: (i) its intimate mechanism of action; (ii) legislative reasons (it is an OTC); (iii) the high educational level of the patients and (iv) its advertisements sponsored over time, which plays an important role in his choice. Paracetamol was mainly used as antipyretic by the 6 CV patients, in equal numbers by both sexes and much less as headache analgesic by 3 female patients, who were all middle-aged, married and the most with high education level (Tables III - VI). The paracetamol molecule was also used for fever treatment by 24 non-CV patients, which were mainly female (18; 75%), equally young and middle-aged (9/9), unmarried and married (9/9) and most graduated a higher level of education (15; 62.50%).

Table VI

Trends of NSAIDs/paracetamol use by the patients of the two groups in relation to their educational level as socio-demographic characteristic

Symptom	Patient type/ Educational level		Drug used/No. of patients										Total no. of patients	
			DCF	IBU	KPF	NMS	IND	ECX	NPX	PCM	MLX	AAS		
Joint pain	CV	E	6	6	3	9	9	15	12	-	3	-	63	216
		M	6	3	24	15	18	9	21	-	12	-	108	
		H	3	6	12	3	3	3	9	-	6	-	45	
	non-CV	E	3	-	-	3	-	12	-	-	-	-	18	87
		M	-	6	3	9	6	12	-	-	-	3	39	
		H	-	6	9	15	-	-	-	-	-	-	30	
Low back pain	CV	E	9	-	3	-	-	3	-	-	-	-	15	186
		M	72	6	3	9	-	15	-	-	9	-	114	
		H	42	6	-	3	3	3	-	-	-	-	57	
	non-CV	E	-	-	-	-	-	3	-	-	-	-	3	72
		M	18	-	-	-	-	15	-	-	-	-	33	
		H	21	-	-	-	-	15	-	-	-	-	36	
Headache	CV	E	-	3	-	-	-	-	-	3	-	-	6	18
		M	-	3	-	-	-	-	-	-	-	3	6	
		H	-	6	-	-	-	-	-	-	-	-	6	
	non-CV	E	-	-	-	-	-	-	-	-	-	-	-	48
		M	-	6	-	-	-	-	-	-	-	-	6	
		H	-	36	3	-	-	-	-	3	-	-	42	
Toothache	CV	E	-	-	-	-	-	3	-	-	-	-	3	12
		M	-	-	-	-	-	-	-	-	-	-	-	
		H	-	6	-	3	-	-	-	-	-	-	9	
	non-CV	E	-	-	-	-	-	-	-	-	-	-	-	42
		M	-	6	-	-	-	-	-	-	-	-	6	
		H	-	33	3	-	-	-	-	-	-	-	36	
Fever	CV	E	-	-	-	-	-	-	-	-	-	-	-	12
		M	-	-	-	-	-	-	-	6	-	-	6	
		H	-	-	-	-	-	-	-	6	-	-	6	
	non-CV	E	-	-	-	-	-	-	-	-	-	-	-	42
		M	-	3	-	-	-	-	-	3	-	-	6	
		H	-	6	-	-	-	-	-	21	-	9	36	

E – elementary; M – medium; H – high; DCF – diclofenac; IBU – ibuprofen; KPF – ketoprofen; NMS – nimesulide; IND – indomethacin; ECX – etoricoxib; NPX – naproxen; PCM – paracetamol; MLX – meloxicam; AAS – acetylsalicylic acid

Analysing the use trends of NSAIDs/paracetamol by the patients of the two studied groups, in relation to their socio-demographic characteristics, some observations are to be mentioned. First, symptoms such as joint pain, headache and fever were reported more frequently by the female patients, while symptoms like low back pain and dental pain were reported by the male gender, independent of the presence of any associated CV disease [19]. Second, the CV female patients, used a wider range of NSAIDs compared to CV male patients and 21% of CV women used a correct NSAID (naproxen), compared to the totally inappropriate molecules used by CV men. Thirdly, we identified gender differences in their inappropriate preferences for certain NSAIDs, depending on their COX-1/COX-2 selectivity. The CV women benefited from drugs with higher degrees COX-2 selectivity, including newer COX-2 inhibitors. Interestingly, COX-2-inhibitors played no important role in medical prescriptions related to male CV patient [20], who are mainly users of classical NSAIDs, non-

selective COX inhibitors. All these differences could be a consequence of the unsatisfactory improvement in the symptomatology, the increased incidence of gastrointestinal discomfort when female patients used previously traditional NSAIDs with higher COX-1 selectivity, their different perceptions to drug efficacy, their easier acceptance of new molecules, several other psycho-social elements. There are some specifications in the literature according to which this osteo-articular suffering and disability present mainly in females is strongly associated with their social situation and support [21]. Our previous results also support this idea, because 105 (48.61%) CV female patients with joint pain and 69 (37.10%) CV men patients with low back pain are unmarried.

Regarding the influence of age on the use of different NSAIDs, the obtained results revealed that particularly older CV patients with joint pain used mainly naproxen molecule, complying with current guidelines, but also the etoricoxib molecule, which was less well-chosen taking into account the profile of their associated comorbidities. The NSAIDs used by elderly CV patients were acquired based on a MP and were recommended either in accordance with their CV safety profile (naproxen) or with therapeutic benefit (etoricoxib), ignoring other possible risks. On the contrary, middle-aged CV patients used classical NSAIDs: such as ketoprofen, ibuprofen and indomethacin by women with joint pain, respectively diclofenac and

ibuprofen by the men with low back pain. Medium or high educational level had not an important impact on the type of the acquired NSAIDs, there are no significant differences in the type of molecule chosen among CV patients with joint pain and low back pain. Most CV patients with joint pain (n = 108, 50%) and with low back pain (n = 114; 61.30%), possessing medium educational level, have requested ketoprofen (n = 24; 22.22%) and naproxen (n = 21; 19.45%) for the treatment of the first symptom and diclofenac (n = 72; 63.16%) and etoricoxib (n = 15; 13.16%) for the second. Similarly, but in a smaller proportion, patients with a high educational level have chosen approximately the same molecules to suppress the pain induced by the presence of the two chronic physical disabilities, the results being shown in Table VI. Thus, it seems that in our study the choice of the molecule type is much more dependent on the patient's gender than on its educational level. There are quite few studies who evaluated the role played by other social variables, such as the educational level of the patients, in acquiring the NSAID molecule by the two categories of patients (CV *vs.* non-CV).

Table VII presents the results of a SPSS Chi-square independence test, performed to establish the independence between the socio-demographic characteristics and the presence/absence of CV comorbidity among the patients using different NSAIDs molecules.

Table VII

Results of the SPSS Chi-square test of independence on the patient's sociodemographic variables and the presence of CV comorbidities

Variables		χ2statistics (df)	p-value	χ2statistics (df)	p-value	χ2statistics (df)	p-value
		General population (CV *vs.* non-CV)		Subgroup with joint pain (CV *vs.* non-CV)		Subgroup with low back pain (CV *vs.* non-CV)	
Gender	Male	0.0163 (1)	0.898516	0.3092 (1)	0.5782	-	-
	Female						
Marital status	Married	7.0793 (1)	0.007798	1.3037 (1)	0.25354	6.2146 (1)	0.01267
	Unmarried						
Age	20 - 44	248.21 (2)	p < 0.00001	-	-	71.0441 (2)	p < 0.00001
	45 - 64			14.9833 (1)	0.000108		
	> 65						
Educational level	Low	86.976 (2)	p < 0.00001	6.6733 (2)	0.035486	8.7014 (2)	0.012898
	Medium						
	High						

χ2 – Chi square test value; df – degrees of freedom; p – level of statistical significance (the mean difference is significant at the 0.05 level)

Because the calculated values of Chi-square score are higher (7.0793, 248.21 and 86.976) than the critical value at the 0.05 level of significance (3.841 for df = 1 and 5.991 for df = 2), it can be suggested that the presence/absence of CV comorbidities in general population is related to the studied socio-demographic variables, except for the patients gender, for which $\chi2$ (1) = 0.0163, p = 0.898516. After eliminating the insignificant variables (p > 0.05) and counting only cells that contain a number greater than 5, a similar analysis of the degree of independence between the

same socio-demographic variables (marital status, age and educational level) and the presence/absence of CV comorbidity in the subgroups of patients with joint pain and low back pain revealed a significant and close relationship of dependence of those with of CV disease, especially in the subgroup with low back pain (Table VIII). According to the obtained results, the consumption of NSAIDs and paracetamol to suppress mainly painful symptoms with different localizations, can contribute to the development and decompensation of CV comorbidities, depending on

the socio-demographic factors, the main place being occupied by age, followed closely by the educational level, and last but not least, the patient's marital status.

Concomitant drug treatment

Finally, the various NSAIDs described were used together with a series of commonly prescribed CV medication according to the type of CV disease presented individually by each patient. For the patients with chronic *versus* non-chronic conditions, the uses of the NSAIDs were as follows: diclofenac 31.08% *versus* 0%, etoricoxib 10.81% *versus* 0.67%, ibuprofen 6.08% *versus* 5.41% (p < 0.0001), and a history of hypertension was present in 50.00% *versus* 6.76% (p < 0.05) and the chronic heart failure was present in 27.70% *versus* 1.35% (p < 0.05), respectively (Table VIII).

Chronic NSAIDs users also were more likely to use CV drugs. Thus, for chronic NSAIDs users *versus* non-chronic NSAID users, diuretic consumption was 38.51% *versus* 6.08% (p < 0.01) and angiotensin receptor blockers (ARBs) use was 12.84% *versus* 3.38% (p < 0.001) (Table VIII).

There were also patients who had two or more associated cardiovascular drugs as well as other medications for various other comorbidities. According to a recent study [22], all NSAIDs have an increased risk of developing time-dependent myocardial infarction (it seems after 7 days of continuous use for diclofenac, ibuprofen, or after 30 days of use for celecoxib), a risk that increases in case of a CV medical history and concurrent use of the CV therapy.

Table VIII

Concurrent drugs used by CV patients dependent by chronic/non-chronic medical conditions

Variables	Chronic medical conditions for NSAIDs use (n=402)	Non-chronic medical conditions for NSAIDs use (n=42)	OR (95% CI)	p value
A. Type of molecule, (%)				
Diclofenac	138 (34.33)	-	-	-
Ibuprofen	27 (6.72)	24 (57.14)	0.0540 (0.0261 to 0.1115)	p < 0.0001
Ketoprofen	45 (11.19)	-	-	-
Nimesulide	39 (9.70)	3 (7.14)	1.3967 (0.4124 to 4.7303)	p = 0.5914
Etoricoxib	48 (11.94)	3 (7.14)	1.7627 (0.5244 to 5.9254)	p = 0.3595
Acetylsalicylic acid	-	3 (7.14)	-	-
Naproxen	42 (10.45)	-	-	-
Indomethacin	33 (8.21)	-	-	-
Meloxicam	30 (7.46)	-	-	-
Paracetamol	-	9 (21.43)	-	-
B. History of, (%)				
Hypertension	222 (55.22)	30 (71.43)	0.4933 (0.2455 to 0.9912)	p = 0.0472
Coronary artery disease	57 (14.18)	6 (14.28)	0.9913 (0.3996 to 2.4592)	p = 0.9850
CHF (class I to III)	123 (30.60)	6 (14.28)	2.6452 (1.0863 to 6.4409)	p = 0.0322
C. Medications, (%)				
Diuretics	171 (42.54)	27 (64.29)	0.4113 (0.2123 to 0.7968)	p = 0.0085
ACEIs	117 (29.10)	9 (21.43)	1.5053 (0.6985 to 3.2440)	p = 0.2965
ARBs	57 (14.18)	15 (35.71)	0.2974 (0.1491 to 0.5933)	p = 0.0006
Beta-blockers	102 (25.37)	12 (28.57)	0.8500 (0.4195 to 1.7223)	p = 0.6519
Digoxin	72 (17.91)	3 (7.14)	2.8364 (0.8529 to 9.4329)	p = 0.0891
Anti-platelets drugs	42 (10.45)	6 (14.29)	0.7000 (0.2786 to 1.7591)	p = 0.4481
Calcium channel blockers	63 (15.67)	3 (7.14)	2.4159 (0.7242 to 8.0591)	p = 0.1513
Nitrates drugs	42 (10.45)	6 (14.29)	0.7000 (0.2786 to 1.7591)	p = 0.4481
Diabetes medication	51 (12.69)	6 (14.29)	0.8718 (0.3499 to 2.1719)	p = 0.7683
Bronchodilators drugs	9 (2.24)	3 (7.14)	0.2977 (0.0774 to 1.1455)	p = 0.0780
Anti-secretory agents	24 (5.97)	-	-	-

ACEIs – Angiotensin Converting Enzyme Inhibitors; ARBs – Angiotensin Receptor Blockers

But it is also known that the concurrent use of diuretics, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) with NSAIDs drugs is a triple association with high risk of adverse events: decreases the effectiveness of antihypertensive drugs and increases the risk of nephrotoxicity [23]. From analysing all the variables, our patients with pre-existing CV comorbidities appeared to have a significantly higher risk for CV events associated with the chronic use of diclofenac, etoricoxib, ketoprofen,

or ibuprofen compared with patients without these conditions. Details on the types of CV disease, type of the purchased NSAIDs and non-studied medications (but routinely prescribed) used concomitantly are summarized in the Table VIII.

Conclusions

The results of our pharmaco-epidemiological study indicate that there is a large number of CV patients

using NSAIDs inappropriately, as a type of molecule, as a mode of acquisition, but also as a potential risk of interactions with the medication. Conventional NSAIDs, like diclofenac and etoricoxib were the most purchased by CV patients, despite the fact that at the time of their acquisition they already had a potential risk of CV events, from the perspective of their CV history. The use of NSAIDs without a prescription was common among patients with increased CV risk, especially in men. In summary, the results from this observational study indicate that the profile of the CV patient inclined towards self-medication with NSAIDs molecules is male, middle-aged, unmarried and with average education. In order to minimize the CV risks, the appropriate NSAIDs prescribed by the doctor/recommended by the pharmacist based on the patient's characteristics and the different safety profiles of the numerous NSAIDs available on the pharmaceutical market are essential for their appropriate and safe administration. Self-medication with NSAIDs should be monitored more closely and awareness of the potential risks due to irrational consumption should be increased through a series of educational programs among the community in general, and the categories of patients at high risk in particular. Healthcare providers, physicians, but especially pharmacists (as direct drug providers), should be aware of this increased prevalence of inappropriate NSAIDs use in the community and pay more attention to both the problem and the CV patient, in particular.

The small size of the sample, the small number of pharmacies participating in the study, the short duration of the study, the inclusion in the study only of the subjects from the urban area who agreed to participate, or the fact that the purchasing of the NSAIDs does not equally mean consumption, are some of the limits of our study. So, further studies in this regard need to be performed.

Conflict of interest

The authors declare no conflict of interest.

References

1. McGettigan P, Henry D, Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk: an examination of sales and essential medicines lists in low-, middle- and high-income countries. *PLoS Med.*, 2013; 10(2): e1001388: 1-10.
2. Varga Z, Sabzwari SRA, Vargova V, Cardiovascular Risk of Nonsteroidal Anti-Inflammatory Drugs: An Under-Recognized Public Health Issue. *Cureus*, 2017; 9(4): e1144: 1-12.
3. European Medicines Agency. European Medicines Agency concludes action on COX-2 inhibitors. 2005; www.ema.europa.eu.
4. European Medicines Agency. PRAC recommends the same cardiovascular precautions for diclofenac as for selective COX-2 inhibitors. 2013; www.ema.europa.eu.
5. American Geriatrics Society, 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.*, 2019; 67(4): 674-694.
6. Fosbøl EL, Folke F, Jacobsen S, Rasmussen JN, Sørensen R, Schramm TK, Andersen SS, Rasmussen S, Poulsen HE, Køber L, Torp-Pedersen C, Gislason GH, Cause-Specific Cardiovascular Risk Associated with Nonsteroidal Antiinflammatory Drugs Among Healthy Individuals. *Circ Cardiovasc Qual Outcomes*, 2010; 3(4): 395-405.
7. Gupta A, Jakobsson J, Acetaminophen, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 selective inhibitors: an update. *Plast Reconstr Surg.*, 2014; 134(4 Suppl 2): 24S-31S.
8. Suciu M, Suciu L, Vlaia L, Voicu M, Buda V, Drăgan L, Andor M, Vlaia V, Cristescu C, Prevalence and the patterns of use of non/-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol among the general population. *Farmacia*, 2019; 67(2): 337-345.
9. United Nations Educational Scientific and Cultural Organization (UNESCO). International Standard Classification of Education (ISCED). Montreal, Canada: UNESCO; 2011.
10. Wijma AJ, van Wilgen CP, Meeus M, Nijs J, Clinical biopsychosocial physiotherapy assessment of patients with chronic pain: The first step in pain neuroscience education. *Physiother Theory Pract.*, 2016; 32(5): 368-384.
11. Suciu L, Cristescu C, Tomescu M, Balaș M, Mureșan L, Vlaia V, Voicu M, Suciu M, Grădinaru R, Vlaia L, Drăgănescu D, The impact of hypertension and associated comorbidities on quality of life assessment questionnaire SF-36 V2. *Farmacia*, 2013; 61(3): 503-517.
12. ***Ministry of health order 1602/2010 for the approval of the Norms on classification for the release of medicinal products for human use. Official Gazette of Romania, Part I, 27/12.01.2011, (available in Romanian).
13. Ray WA, Stein CM, Byrd V, Shorr R, Pichert JW, Gideon P, Arnold K, Brandt KD, Pincus T, Griffin MR, Educational program for physicians to reduce use of non-steroidal anti-inflammatory drugs among community-dwelling elderly persons: a randomized controlled trial. *Med Care*, 2001; 39(5): 1352-1353.
14. European Medicines Agency. Assessment report for diclofenac containing medicinal products (systemic formulations). 2013; www.ema.europa.eu.
15. Solomon SD, McMurray JJ, Pfeffer MA, Wittes J, Fowler R, Finn P, Anderson WF, Zauber A, Hawk E, Bertagnolli M, Adenoma Prevention with Celecoxib (APC) Study Investigators, Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *N Engl J Med.*, 2005; 352(11): 1071-1080.
16. Food and Drug Administration. FDA public health advisory: safety of Vioxx, www.sciencedaily.com.
17. Conaghan P, A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. *Rheumatol Int.*, 2012; 32(6): 1491-502.
18. Carrasco-Garrido P, de Andrés AL, Barrera VH, Jiménez-Trujillo I, Fernandez-de-Las-Peñas C, Palacios-Ceña D, García-Gómez-Heras S, Jiménez-García R, Predictive factors of self-medicated analgesic use in

Spanish adults: a cross-sectional national study. *BMC Pharmacol Toxicol.*, 2014; 15: 36: 1-9.

19. Unruh AM, Gender variations in clinical pain experience. *Pain*, 1996; 65(2-3): 123-167.

20. Dominick KL, Ahern FM, Gold CH, Heller DA, Gender differences in NSAID use among older adults with osteoarthritis. *Ann Pharmacother.*, 2003; 37(11): 1566-1571.

21. Peat G, Thomas E, Handy J, Croft P, Social networks and pain interference with daily activities in middle and old age. *Pain*, 2004; 112(3): 397-405.

22. Bally M, Beauchamp ME, Abrahamowicz M, Nadeau L, Brophy JM, Risk of acute myocardial infarction with real-world NSAIDs depends on dose and timing of exposure. *Pharmacoepidemiol Drug Saf.*, 2018; 27(1): 69-77.

23. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S, Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *BMJ.*, 2013; 346: e8525: 1-11.