



APPLICATION OF DRUG-RELATED PROBLEMS APPROACH TO ANALYSIS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS' SAFETY

A.V. Matveev^{1,2}, A.E. Krashenninikov¹, E.A. Egorova², E.I. Konyaeva²

¹ National Pharmacovigilance Research Center,
2/2, Malaya Sukharevskaya sq., Moscow, Russia, 127051

² Medical Academy n. a. S.I. Georgievsky of Vernadsky CFU,
5/7, Lenin Avenue, Simferopol, Republic of Crimea, Russia, 295051

E-mail: elena212007@rambler.ru

Received 15 June 2019

Review (1) 3 August 2019

Review (2) 14 August 2019

Accepted: 20 August 2019

Summary. A Drug-Related Problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.

The aim of the study was the analysis of the adverse drug reactions (ADR) associated with prescription of the non-steroidal anti-inflammatory drugs (NSAIDs) using the DRP PCNE V5.01 qualification system.

Materials and methods. The objects of the study were 415 notification forms about adverse drug reactions of NSAIDs recorded in the regional database of spontaneous reports and called ARCADE (Adverse Reactions in Crimea, Autonomic Database) for the period from 1 January 2009 to 31 December of 2018. The study and analysis of the problems associated with drugs were carried out using the qualification system DRP PCNE V5.01 (Pharmaceutical Care Network Europe) 2006 in the modification of Prof. Zimenkovsky.

Results. Among other representatives of the NSAID group, Ibuprofen and Diclofenac became the "leaders" in the incidence of ADR. The frequency of ADR cases for Ibuprofen was 142 reports (34.22% of the total number of ADR for NSAIDs), and for Diclofenac it was 90 cases (21.69%). The calculation of DRP values for each of the presented cases made it possible to determine that in 81 (19.51%) and 91 (21.9%) cases, the DRP value was 6 and 7, respectively. DRP values in the range of 8–10 were found in 92 reports. The highest DRPs value was observed after the administration of Parecoxib (13 problems but only one case was found in the database), the DRPs value of Dexketoprofen was 12.5 (95% CI: 7–17) and the DRPs value of Diclofenac combinations was 10 DRPs; 95% CI: 5–17 DRP). The minimum DRPs values were associated with Naproxen, Rofecoxib, and Etoricoxib prescriptions.

Conclusion. Using the DRP system in the analysis of NSAIDs, ADRs allow to identify the medicines which have a high risk of causing safety problems, such as Parecoxib, Dexketoprofen and Diclofenac combinations. The prescription of these drugs should be carried out with special cautions and control to the indications and contraindications, the dose and duration of treatment, as well as to a possible interaction of them with concomitant drugs.

Keywords: drug-related problems (DRPs), non-steroidal anti-inflammatory drugs (NSAIDs), adverse drug reactions (ADRs)

List of abbreviations: DRP – drug-related problems; MP – medicinal products; ADRs – adverse drug reactions; NSAIDs – non-steroidal anti-inflammatory drugs; COX – cyclooxygenase; ATC-code – code of product according to Anatomical Therapeutic Chemical (ATC) classification system.

For citation: A.V. Matveev, A.E. Krashenninikov, E.A. Egorova, E.I. Konyaeva. Application of drug-related problems approach to analysis of non-steroidal anti-inflammatory drugs' safety. *Pharmacy & Pharmacology*. 2019;7(4): 215–223. DOI: 10.19163/2307-9266-2019-7-4-215-223

© A.B. Матвеев, А.Е. Крашенинников, Е.А. Егорова, Е.И. Коняева, 2019

Для цитирования: А.В. Матвеев, А.Е. Крашенинников, Е.А. Егорова, Е.И. Коняева. Применение системы проблем, связанных с лекарственными препаратами (drug-related problems), на примере группы нестероидных противовоспалительных средств. *Фармация и фармакология*. 2019;7(4): 215–223. DOI: 10.19163/2307-9266-2019-7-4-215-223

ПРИМЕНЕНИЕ СИСТЕМЫ ПРОБЛЕМ, СВЯЗАННЫХ С ЛЕКАРСТВЕННЫМИ ПРЕПАРАТАМИ (DRUG-RELATED PROBLEMS), НА ПРИМЕРЕ ГРУППЫ НЕСТЕРОИДНЫХ ПРОТИВОВОСПАЛИТЕЛЬНЫХ СРЕДСТВ

А.В. Матвеев^{1,2}, А.Е. Крашенинников¹, Е.А. Егорова², Е.И. Коняева²

¹Автономная некоммерческая организация «Национальный научный центр Фармаконадзора», 127051, Российская Федерация, Москва, ул. Малая Сухаревская площадь, д. 2, корп. 2

²Медицинская академия им. С.И. Георгиевского ФГАОУ ВО «КФУ им. В.И. Вернадского», 295051, Российская Федерация, г. Симферополь, бул. Ленина, 5/7

E-mail: elena212007@rambler.ru

Получено 15.06.2019

Рецензия (1) 03.08.2019

Рецензия (2) 14.08.2019

Принята к печати 20.08.2019

Проблемы, связанные с лекарственными препаратами (drug-related problems, DRP), – это события или изменения, связанные с фармакотерапией, которые реально или потенциально препятствуют достижению желаемых результатов в процессе лечения.

Цель – анализ случаев нежелательных реакций (НР) на препараты группы нестероидных противовоспалительных средств (НПВС) с помощью квалификационной системы DRP PCNE V5.01.

Материалы и методы. Объектами исследования стали 415 карт-извещений о нежелательных реакциях НПВС, зарегистрированные в региональной базе спонтанных сообщений ARCADE (Adverse Reactions in Crimea, Autonomic Database) за период 2009–2018 гг. Изучение и анализ проблем, связанных с лекарственными препаратами, проводился с использованием квалификационной системы DRP PCNE V5.01 (Pharmaceutical Care Network Europe) 2006 г. в модификации А.Б. Зименковского.

Результаты. «Лидерами» по частоте развития НР среди отдельных представителей группы НПВС стали препараты ибупрофен и диклофенак. Частота встречаемости случаев НР для ибупрофена составила 142 случая (34,22% от всего количества случаев НР на НПВС), а для диклофенака – 90 случаев (21,69%). Расчет значений DRP для каждого из представленных случаев НР позволил определить, что в 81 (19,51%) и 91 (21,9%) случае значение DRP было равно 6 и 7 соответственно. Значения DRP в пределах значений 8–10 встречались в 92 случаях. Наиболее высокие значения DRP наблюдались при назначении парекоксиба – 13 проблем (зарегистрирован 1 случай), декскетопрофена – 12,5 DRP (95% ДИ: 7–17) и комбинированных препаратов, содержащих диклофенак – 10 DRP (95% ДИ: 5–17 DRP). Минимальные значения DRP были выявлены при назначении напроксена, рофекоксиба и эторикоксиба.

Заключение. Использование системы проблем, связанных с лекарственными препаратами (DRP), для проведения анализа нежелательных реакций препаратов группы НПВС позволило выделить отдельных представителей группы, обладающих высоким риском развития неблагоприятных последствий при их применении в практической медицине. Среди таких препаратов стоит отметить парекоксиб, декскетопрофен и комбинированные препараты, содержащие диклофенак. Назначение представленных выше препаратов должно проводиться со строгим учетом показаний и противопоказаний к применению, дозы и курса лечения, а также вероятности возможного взаимодействия этих препаратов с сопутствующими лекарственными средствами.

Ключевые слова: проблемы, связанные с лекарственными препаратами, DRP, нестероидные противовоспалительные средства

Список сокращений: РГЗТ – реакция гиперчувствительности замедленного типа, РПГА – реакция прямой гемагглютинации, ФИ – фагоцитарный индекс, ФЧ – фагоцитарное число

INTRODUCTION

Drug-related problems are defined as “any circumstance related to the patient’s use of a drug that actually or potentially prevents the patient from gaining the intended benefit of the drug” [1, 2]. Such undesirable consequences due to the use of medicinal products (MPs) are common in medical institutions both at the stage of primary medical care (in hospitals) and at the stage of outpatient (ambulatory) treatment of patients. Most of these problems are revealed at the stage of prescribing,

dosing or intake of drugs by patients. Potential causes of DRPs are: the simultaneous prescription of five or more drugs (polypharmacy), complex regimens for the use of medicinal products, as well as the use of new MPs in clinical practice, which is associated with a high risk of adverse drug reactions (ADRs) during their use [3, 4]. Another important reason for the development of DRPs in patients is the lack of clear recommendations from doctors about the use of concomitant medications or alternative methods of treatment [5].

The medical conditions resulting from DRPs, are serious issues for patients and society, as the suffering of patients and the costs of corrections caused by these problems are significant [6–8]. The economic consequences of DRPs in the United States of America (USA) are estimated at more than \$ 150 billion annually [9]. Moreover, the estimate of the costs associated with medical errors when using drugs ambulatory varies from 30.1 to 136.8 billion US dollars [10, 11].

Among the main causes of DRPs, the following ones are distinguished: off-label prescription and use of drugs, discrepancies between the doctor-prescribed and real regimes of the use of MPs, irrational choice of drugs, poor patients' compliance to treatment, drug interactions, as well as interactions with the food components, adverse reactions, overdose, the use of subtherapeutic doses and the need for additional drug therapy [12–15]. According to the systematic review published by Krähenbühl Melcher et al., about 8% of hospitalized patients have adverse drug reactions and 5–10% of prescriptions in these patients are erroneous [16]. Forster A.J. and colleagues studied the frequency of ADRs and revealed that those reactions occurred in 15% of patients at the hospitalization stage, and in 12–17% of patients after their discharge from a medical institution [17–19].

The identification and study of drug-related problems, as well as the identification of the main groups and individual representatives of the drugs with a high risk of developing DRPs, are important stages in the treatment of patients. They can reduce morbidity, mortality and increase compliance of patients to treatment [20].

According to our search in Russian medical literature, the DRPs methodology is practically not used in domestic practice, and the number of such studies is occasional [21, 22].

The aim of the current study is to analyze the cases of ADRs caused by non-steroidal anti-inflammatory drugs (NSAIDs) using the DRP PCNE V5.01 qualification system.

MATERIALS AND METHODS

The objects of this study were the cases of ADRs development after the use of NSAIDs described in official notification forms and recorded in the regional database of spontaneous reports called "ARCADs (Adverse Reactions in Crimea, Autonomic Database)" for the period of January 2009 – December 2018. For the covered period, 415 forms containing information about the ADRs of varying severity in the patients treated in medical institutions, in outpatient settings and the cases of self-treatment were found.

The detection of ADRs was carried out by the codes

of the Anatomical Therapeutic Chemical (ATC) classification of medicines of the World Health Organization [23], the data from the instructions for medical use (analogue of Short Medical Product Characteristics) found in the State Drug Registers of the Russian Federation and Ukraine (for the cases registered before the incorporation of the Republic of Crimea into the Russian Federation).

The study of the frequency and severity of DRPs and their further analysis were carried out using the DRP PCNE V5.01 (Pharmaceutical Care Network Europe) 2006 qualification system in the modification of Andriy B. Zimenkovsky [24]. This system is based on the coding in 4 main categories: P – problems, C – causes, I – interventions and O – consequences. According to the "P" code, DRPs are divided into the following groups: manifestations of ADRs (allergic/non-allergic), the rationality of the choice of a suspect and concomitant drugs, their dosage regimen and dosage form, the errors that occur during the drug intake, the possibility of drug interactions and some others problems. The causes of DRPs standardized by code "C" are classified as follows:

- ✓ DRP associated with the choice of the suspected drug, and its dose;
- ✓ DRP caused by the use of concomitant drugs and the possibility of drug interactions;
- ✓ patient-oriented psychological factors (i.e. a patient's inability to take a suspected and/or concomitant drug);
- ✓ DRPs resulting from the low awareness of doctors and patients about a rational use of drugs (lack of knowledge of the instructions for medical use and/or patients' treatment protocols);
- ✓ DRP related to pharmaceutical logistics (drug availability).

The interventions of a doctor or a clinical pharmacist, indicated by the code "I", are divided into 3 subgroups: the first one is the level of the specialist who prescribed the medicine, the second subgroup is the level of the patient and the third subgroup is the level of the medicine itself. Among such interventions, the cancellation of a suspected drug, the withdrawal of concomitant MPs, as well as the administration of a new drug to correct the consequences caused by ADRs have been distinguished. Among the outcomes of DRPs (code "O"), there are 2 main options: the drug-related problem is completely solved and the drug-related problem is not solved [24–27].

RESULTS AND DISCUSSION

To study the drug-related problems, in the regional database of spontaneous reports about adverse reac-

tions, an automatic search was performed and 415 notification forms corresponding to the M01 ATC classification code were selected. They amounted to 5.96% of the total number of ADRs for the period from 1 January 2009 till 31 December 2018 (the total number of records was 6960).

The first stage of the work was devoted to identifying the frequency of ADRs for each representative of the NSAIDs group. Ibuprofen and Diclofenac became

the “leaders” by the incidence of reactions. The occurrence of cases for Ibuprofen was 142 cases (34.22% of the total number of records for NSAIDs), and for Diclofenac it was 90 cases (21.69%). Much less frequently, ADRs occurred when patients took Nimesulide (45 cases, 10.84%), Ketorolac (44 records, 10.6%) and Meloxicam (23 cases, 5.54%). The frequency of ADRs for other active substances from M01 group is presented in Table 1.

Table 1 – Frequency of adverse reactions associated with prescription of NSAIDs and registered in the Republic of Crimea for the period of 2009–2018

NSAIDs	ATC code	Quantity of reports (absolute)	Quantity of reports (% of total NSAIDs ADRs)
Ibuprofen	M01AE01	142	34.22
Diclofenac	M01AB05	90	21.69
Nimesulide	M01AX17	45	10.84
Ketorolac	M01AB15	44	10.60
Meloxicam	M01AC06	23	5.54
Dexketoprofen	M01AE17	14	3.37
Diclofenac combinations	M01AB55	14	3.37
Lornoxicam	M01AC05	9	2.17
Nimesulide combinations	M01AX67	5	1.20
Etoricoxib	M01AH05	5	1.20
Aceclofenac	M01AB16	5	1.20
Celecoxib	M01AH01	3	0.72
Rofecoxib	M01AH02	3	0.72
Naproxen	M01AE02	2	0.48
Parecoxib	M01AH04	2	0.48
Other NSAIDs combinations	M01BX	2	0.48
Ibuprofen combinations	M01AE51	1	0.24
Mefenamic acid	M01AG01	1	0.24
Glucosamine	M01AX05	1	0.24
Chondroitin sulfate	M01AX25	1	0.24
The combination of Glucosamine and Chondroitin sulfate	M09AX	1	0.24
Ketoprofen	M01AE03	1	0.24
Indomethacin	M01AB01	1	0.24

The calculation of DRPs values for each of the recorded cases made it possible to determine the following: in 81 (19.51%) and 91 (21.9%) cases, the DRPs value was 6 and 7, respectively. The DRPs values in the range of 8–10 were found in 92 cases (8 DRPs – 38 records (9.16%), 9 DRP – 20 records (4.8%) and 10 DRP – 34 reports (8.2%)). Special attention was paid to forms, in which the DRPs values amounted to more than 10 problems per case (124 reports, 29.9%).

Such high rates most likely indicate an irrational choice of the NSAIDs, incorrect dosing or possible drug interactions. The frequency of DRPs values for NSAIDs

is shown in Fig. 1. The total number of DRPs for all the cases was 3785 (therefore, the average value was 9 DRPs / a patient).

At the next stage of the work, the DRPs values for each NSAID were calculated. Our analysis of the ADRs records revealed that the highest DRPs values were observed for Parecoxib (13 problems) though the only case for this substance was found in the database. The results also included Dexketoprofen with an average amount of 12.5 DRPs / a case (95% CI: 7–17) and Diclofenac combinations with 10 DRPs / a case (95% CI: 5–17 DRP).

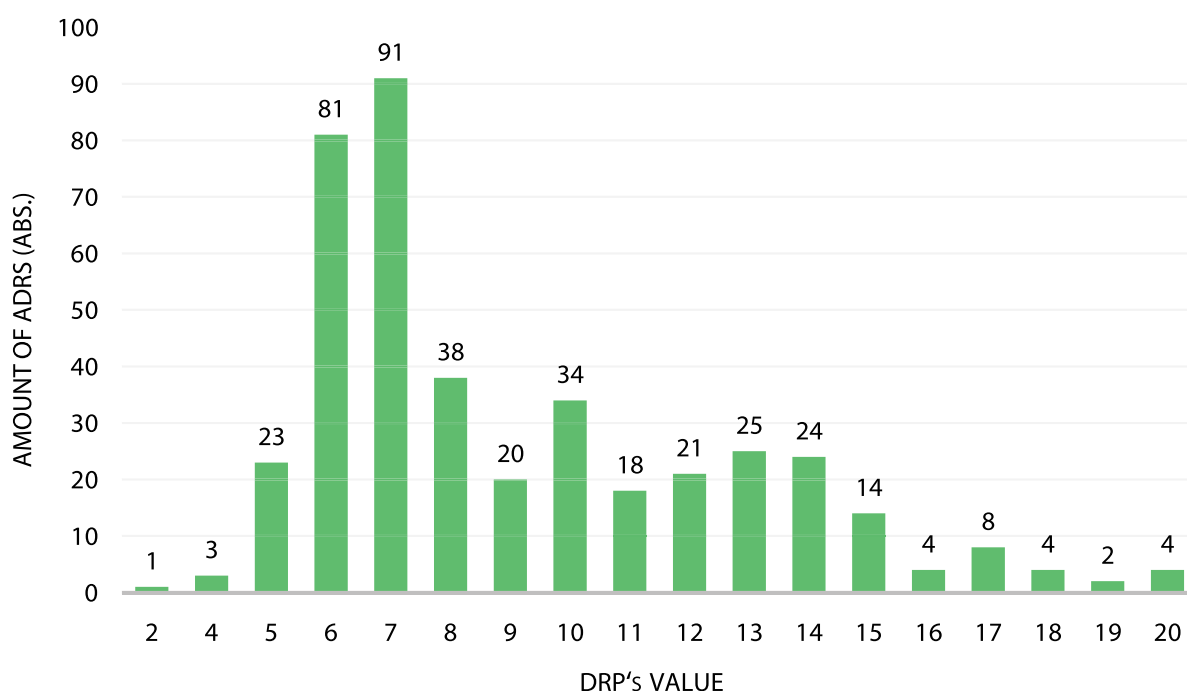


Figure 1 – Frequency of DRP's Values in NSAIDs ADRs records

The average values of DRPs / a case in the range of 9-9.5 were observed in the records for Ketorolac, Meloxicam and Aceclofenac. High maximum DRPs values for Ketorolac and Meloxicam (20 and 19 DRP, respectively) are noteworthy, as

they indicate the irrational prescription of MPs and a high risk of serious ADRs developing during their use. The distribution of the NSAIDs according to the median, maximum and minimum DRPs values is presented in Table 2.

Table 2 – Median, maximum and minimum of NSAIDs-related problems

NSAID	Maximum	Minimum	Median	Range
Dexketoprofen	17	7	12.5	10
Diclofenac combinations	17	5	10	12
Ketorolac	20	5	9.5	15
Meloxicam	19	5	9	10
Aceclofenac	12	5	9	7
Diclofenac	19	6	8	13
Ibuprofen	16	4	7	12
Lornoxicam	10	6	7	4
Nimesulide	17	2	7	15
Celecoxib	13	6	7	7
Nimesulide combinations	14	4	7	10
Naproxen	7	5	6	2
Rofecoxib	8	6	6	2
Etoricoxib	11	6	6	5

The results presented above, indicate that Naproxen (a non-selective inhibitor of cyclooxygenase-2 (COX-2)), Rofecoxib and Etoricoxib (highly selective COX-2 inhibitors) have a better safety profile compared to other NSAIDs [28]. When administrated, the amount of this drug-related problems was lower than that of the other representatives of the group.

The fourth stage of the analysis was devoted to the

study of NSAIDs' administration routes (local, rectal, intravenous, intramuscular and per os) and their association with DRPs values. The results of the analysis showed that most often ADRs occurred when NSAIDs were taken per os. The frequency of such cases was 270 (65%). Less often, adverse reactions were observed after intramuscular (125 cases, 30.1%), intravenous (9 cases, 2.2%), rectal (9 cases, 2.2%) and local (2 cases, 0.5%) administration routes (Fig. 2).

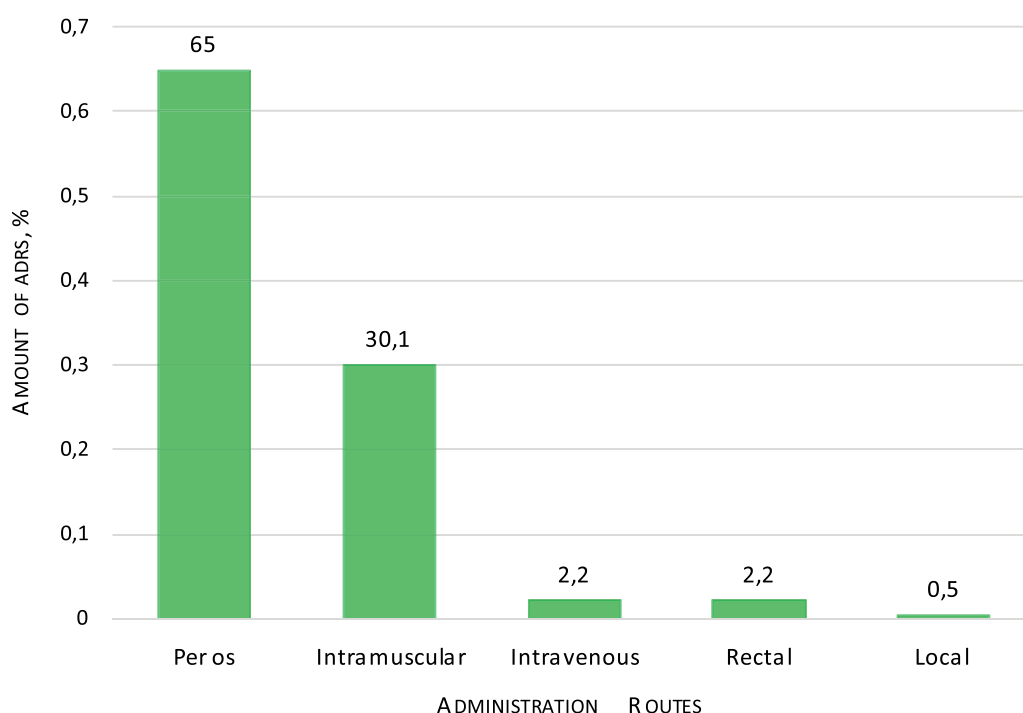


Figure 2 – Distribution of ADR according to administration routes

The analysis of DRPs values for each of the presented routes revealed that high DRPs values were observed in case of rectal (4 records with DRPs values of more than 11, which amounted to 44.4% of all the cases for this administration route) and intramuscular routes (50 cases with DRPs values of more than 11 cases, which

amounted to 40% of all the cases with intramuscular administration). For oral route, high DRPs values (DRP ≥ 11) were observed in 64 records, which amounted to 23.7% of the total number of peroral intake of NSAIDs. The distribution of DRPs values for all the routes of administration is presented in Table 3.

Table 3 – Distribution of DRPs values according to administration routes

Route (total amount of records)	Range of DRPs values	Cases of ADRs (abs.)	Cases of ADR (% from total amount of cases per route)
Per os 270 records	0–5	23	8.5
	6–10	183	67.8
	11–15	55	20.4
	16–20	9	3.3
Intramuscular 125 records	0–5	3	2.4
	6–10	72	57.6
	11–15	37	29.6
	16–20	13	10.4
Intravenously 9 records	6–10	6	66.7
	11–15	3	33.3
Per rectum 9 records	0–5	1	11.1
	6–10	5	55.5
	11–15	4	44.4
Local 2 records	6–10	2	100

The obtained results indicate a higher risk of DRPs when parenteral routes of administration are used. In our opinion, it is primarily due to the peculiarities of the

pharmacokinetics of NSAIDs after intramuscular and intravenous injections.

Special attention was paid to the analysis of ADRs

records with DRPs values equal to 18–20. The total number of such reports was 10: 5 were associated with Ketorolac use, 3 and 2 cases – with Meloxicam and Diclofenac, respectively.

Such high values of DRPs in 8 cases were caused by an irrational combination of two or more NSAIDs in one patient. In 3 cases there was an excess of single and/or daily doses of the suspected drug and in 3 clinical situations, there was an excess of the course of treatment. In some cases, two or more reasons for such high rates of DRPs were found.

In our opinion, the range, i.e. the differences between the maximal and minimal DRPs values, is of special interest, as it can reflect the potential risk of a drug problem for each drug included in the analysis. As follows from the data in Table 2, the highest risk of prob-

lems determined by the range of the values is associated with Nimesulide, Ketorolac and Diclofenac prescriptions. Undoubtedly, the final and clear index should include not only the range of values but also the minimum value.

The analysis of violations of the dosing regimen (a low dose or an extended duration / an extended dose or a short duration) is also of a scientific interest. It is *a priori* a determining factor in the occurrence of DRPs. Information on a dosing regimen is presented in category "P" of the DRPs PCNE V5.01 qualification system. It made possible to obtain the data on the frequency of such mistakes for NSAIDs. The excess of the dose was found in 23 cases (5.53% of the total amount of NSAIDs ADRs), the doses below the minimum therapeutic ones were found in 16 cases (3.85%). The distribution of dosing violations is presented in Fig. 3.

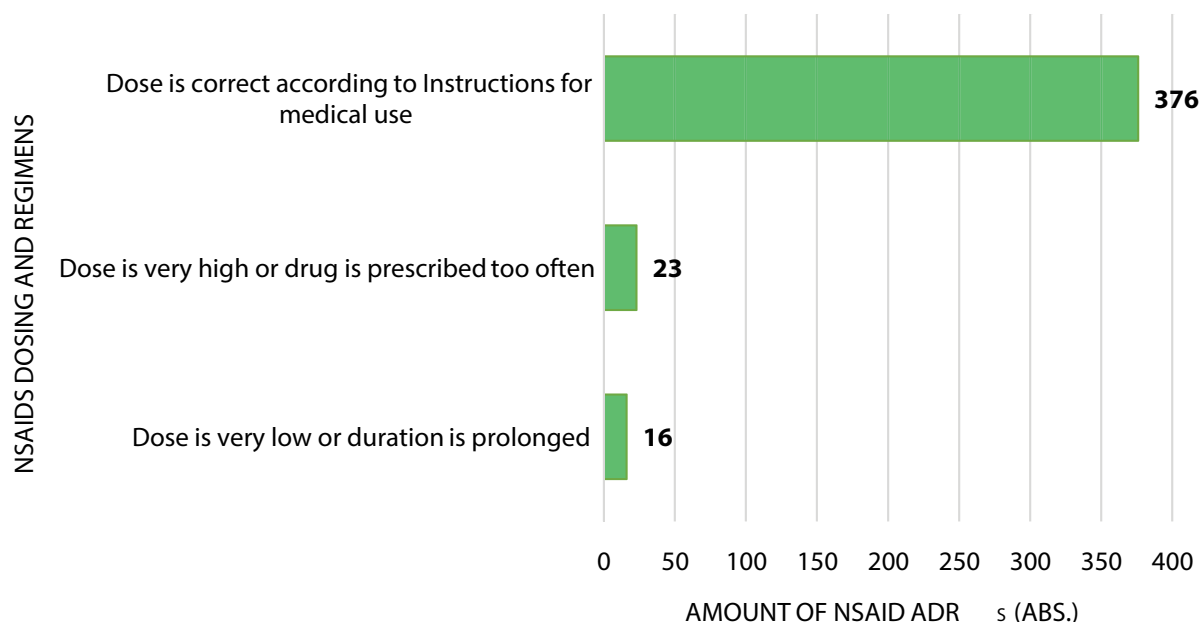


Figure 3 – Distribution of ADRs cases with violations of the dosage regimen

It is worth noting that the use of the DRPs system in the practice of doctors, clinical pharmacologists and pharmacists is an important and promising tool which makes it possible to improve the quality of pharmacotherapy and adherence to treatment. For drug safety professionals, the DRPs system makes it possible to identify priority areas in pharmacovigilance.

The results of the carried out analysis made it possible to identify NSAIDs, the prescription of which needs special attention due to the high risks of drug-related problems (Parecoxib, Dexketoprofen, Nimesulide, Diclofenac and Ketorolac).

In addition, the analysis of DRPs values using the DRP PCNE V5.01 qualification system made it possible to identify NSAIDs with a good safety profile. Among

these drugs, it is worth to note Naproxen, Rofecoxib and Etoricoxib associated with a low amount of DRPs.

CONCLUSION

Using the drug-related problems (DRPs) system in the analysis of the safety of NSAIDs made it possible to identify the representatives of this group which may have an extra risk of ADRs in real medical practice. Among NSAIDs, it is worth to note Parecoxib, Dexketoprofen and Diclofenac combinations. The prescription of the mentioned products should be carried out with strict regard to the approved indications and contraindications for use, dose and duration of treatment, as well as taking into consideration all kinds of possible drug-drug interaction.

FINANCIAL SUPPORT

This study did not have any financial support from third parties.

AUTHOR CONTRIBUTIONS

All authors had equally contributed to the research work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Binu K, Nimmy NJ, Varghese GP. A survey of Drug related problems identified by community pharmacy in South India. *International Journal of Pharmaceutical, chemical and biological sciences*. 2012;2(2):368–374.
2. van Mil JW, Westerlund LO, Hersberger KE, Schaefer MA. Drug-related problem classification systems. *Ann Pharmacother*. 2004;38(5):859–67.
3. Roberts MS, Stokes JA, King MA, Lynne TA, Purdie DM, Glasziou PP, et al. Outcomes of a randomized controlled trial of a clinical pharmacy intervention in 52 nursing homes. *Br J Clin Pharmacol*. 2001;51:257–265.
4. Shareef J, Sandeep B, Shastry CS. Assessment of Drug related problems in patients with cardiovascular diseases in a Tertiary care teaching hospital. *Journal of Pharmaceutical Care*. 2014;2(2):71–76.
5. Adepu R, Adusumilli PK. Assessment of Drug related problems in patients with chronic diseases through Health Status Survey in a South Indian Rural Community setting. *Indian J Pharm Sci*. 2016;78(4):537–542.
6. Eichenberger PM, Lambert ML, Kahmann IV, van Mil JW, Hersberger KE. Classification of drug-related problems with new prescriptions using a modified PCNE classification system. *Pharmacy World & Science*. 2010;3(32):362–372.
7. Pfister B, Jonsson J, Gustafsson M. Drug-related problems and medication reviews among old people with dementia. *BMC Pharmacol Toxicol*. 2017;8:52. doi:10.1186/s40360-017-0157-2.
8. Fog AF, Kvalvaag G, Engedal K, Straand J. Drug-related problems and changes in drug utilization after medication reviews in nursing homes in Oslo, Norway. *Scand J Prim Health Care*. 2017;35(4):329–335. doi:10.1080/02813432.2017.1397246.
9. Hong K, Hong YD, Cooke CE. Medication errors in community pharmacies: The need for commitment, transparency, and research. *Res Social Adm Pharm*. 2019;15(7):823–826. doi: 10.1016/j.sapharm.2018.11.014.
10. Hammerlein A, Griesse N, Schulz M. Survey of Drug-Related Problems Identified by Community Pharmacies. *The Annals of Pharmacotherapy*. 2007;11:1852.
11. Boretska O.B. Vykorystannia systemy liko-poviazanykh problem (drug-related problems, DRP) dlia otsinky yakosti retsepturnykh pryznachenn v aptechnykh zakladakh [Use of drug-related problems (DRP) to evaluate the quality of prescription at pharmacies]. *Upravlinnia yakistiu medychnoi ta farmatsevtichnoi dopomohy*. 2012;3:31–37. Ukrainian.
12. Adusumilli PK, Adepu R. Drug related problems: An overview of various classification systems. *Asian J Pharm Clin Res*. 2014;7(4):7–10.
13. Wilmer CM, Huiskes VJB, Natsch S, Rennings AJM, van den Bemt BJJ, Bos LM. Drug-related problems in a clinical setting: a literature review and cross-sectional study evaluating factors to identify patients at risk. *European Journal of Hospital Pharmacy*. 2015;22(4):229–235. Available at: <https://ejhp.bmj.com/content/22/4/229.full>.
14. Parthasarathi G, Ramesh M, Kumar JK, Madaki S. Assessment of Drug Related Problems and Clinical Pharmacists' Interventions in an Indian teaching hospital. *J Pharm Pract Res* 2003; 33:272–274. doi:10.1002/jppr2003334272.
15. Abraham RR. Drug Related Problems and Reactive Pharmacist Interventions for Inpatients Receiving Cardiovascular Drugs. *IJBMS*. 2013; 3(2):42–48.
16. Krähenbühl MA, Schlienger R, Lampert M, Haschke M, Drewe J, Krähenbühl S. Drug-related problems in hospitals: a review of the recent literature. *Drug Saf*. 2007;30(5):379–407.
17. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. *Ann Intern Med*. 2003;138(3):161–7.
18. Schlienger RG, Luscher TF, Schoenenberger RA, Haefeli WE. Academic detailing improves identification and reporting of adverse drug events. *Pharm World Sci*. 1999;21(3):110–5.
19. Greeshma M, Lincy S, Maheswari E, Tharanath S, Viswam S. Identification of Drug-related problems by Clinical Pharmacist in Prescription with Polypharmacy: a prospective interventional study. *J Young Pharm*. 2018;10(4):460–465. doi:10.5530/jyp.2018.10.100.
20. Ayalew MB, Megersa TN, Mengistu YT. Drug-related problems in medical wards of Tikur Anbessa specialized hospital, Ethiopia. *J Res Pharm Pract*. 2015;4(4):216–21.
21. Chernov AA, Klejmenova EB, Sychev DA, Abil'mazhinova AA, Yashina LP, Otdelenov VA, Payushchik SA. Prichiny gemorragicheskikh oslozhnenij u pacientov stacionara, poluchayushchih lechebnye dozy antikoagulyantov [Causes of hemorrhagic complications in hospital patients receiving therapeutic doses of anticoagulants]. *Klinicheskaya farmakologiya i terapiya*. 2018;27(5):23–29. DOI 10.32756/0869-5490-2018-5-23-29. Russian.
22. Matveev AV, Egorova EA, Matveeva NV, Krashenninnikov AE, Dormidor AG. Adverse reactions of ACE inhibitors. Retrospective analysis of spontaneous reports in local database. *The New Armenian Medical Journal*. 2019; 13(2): 10–17.
23. ATC/DDD Index 2019. Available at: https://www.whocc.no/atc_ddd_index/.
24. Eichenberger PM, Lampert ML, Kahmann IV. Classification of drug-related problems with new prescriptions using a modified PCNE classification system. *Pharm World Sci*. 2010;32:362–372.
25. Zimenkovskiy A.B., Ryvak T.B., Khanyk N.L. Liko-poviazani problemy farmakoterapii (DRP) ta metodolohiia yikh otsinky i standartyzatsii [Pharmacotherapy-related pharmacotherapy (DRP) problems and methodology for their valuation and standardization]. *Ratsionalna farmakoterapiia*. 2011;1–2:16–22. Ukrainian.
26. Zimenkovskiy A.B., Ryvak T.B., Khanyk N.L. Kontseptsiiya DRP yak chastyna filosofii ratsionalnoi farmakoterapii, intehrovanoi z systemoiu farmatsevtichnoi opiky [The concept of DRP as part of the philosophy of rational pharmacotherapy integrated with the pharmaceutical care system]. *Ratsionalna farmakoterapiia*. 2011;1–2:23–29. Ukrainian.

27. Classification for Drug related problems. V 6.2. 14.01.2010. Pharmaceutical Care Network Europe Foundation. «The PCNE Classification V 6.2».
28. Voronkov A.V., D'yakova I.N., Ogurczov Yu.A., Zhidkova Yu.Yu., Gamzeleva O.Yu. Izuchenie vliyaniya original'ny'x mnogokomponentny'x gelej na formirovanie patologich-

eskogo rubcza s ispol'zovaniem novogo metodicheskogo podxoda [Study of the influence of original multicomponent gels on the process of pathological scar formation using new methodological approach]. Eksperimental'naya i klinicheskaya farmakologiya. 2014; 77(9): 38–42. Russian.

AUTHORS

Matveyev Alexander Vasilyevich – PhD (Medicine), docent of the Department of Internal Medicine No.1 with the course of Clinical Pharmacology of Medical Academy n.a. S.I. Georgievsky of Vernadskiy CFU; executive director of ANO “National Pharmacovigilance Research Center”. ORCID 0000-0002-6636-3950. E-mail: avmcsmu@gmail.com

Krashennnikov Anatoly Evgenievich – PhD (Pharmacy), CEO of ANO “National Pharmacovigilance Research Center”. ORCID 0000-0002-7791-6071. E-mail: anatoly.krashennnikov@drugsafety.ru.

Egorova Elena Aleksandrovna – PhD (Pharmacy), assistant of the Department of Internal Medicine No.1 with the course of Clinical Pharmacology of Medical Academy n.a. S.I. Georgievsky of Vernadskiy CFU. ORCID 0000-0003-4012-2523. E-mail: elena212007@rambler.ru

Konyaeva Elena Ivanovna – PhD (Medicine), docent of the Department of Internal Medicine No.1 with the course of Clinical Pharmacology of Medical Academy n.a. S.I. Georgievsky of Vernadskiy CFU. E-mail: konyaeva.simferopol@gmail.com