

GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 7-8 (340-341) Июль-Август 2023

ТБИЛИСИ - NEW YORK



ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press.
Published since 1994. Distributed in NIS, EU and USA.

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საქურაღებოლ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დაიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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MANAGEMENT OF RISKS OF ADVERSE DRUG REACTIONS ACCORDING TO ADR REPORT FORM DATA FROM LVIV REGION HEALTHCARE FACILITIES IN 2022

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Abstract.

The study aimed to analyse the adverse drug reactions report form data received by the State Expert Center of the Ministry of Health of Ukraine from healthcare professionals in the Lviv region in 2022. Regarding specific types of medicines, the ones with proven cause-and-effect relationships that caused the highest frequency of adverse drug reactions incidents were chemotherapeutic agents (35.5%), medicines affecting the cardiovascular system (20.3%), and non-steroidal anti-inflammatory drugs (8%). Within the penicillin class, amoxicillin potentiated by clavulanate (67%) and amoxicillin (29%) were the dominant drugs showing the highest incidence rate of adverse reactions. Among cephalosporins, ceftriaxone (46%) and cefixime (15%) were found to take the lead in terms of adverse reaction frequency. The highest proportion among all adverse drug reactions caused by penicillins and cephalosporins was attributed to allergic reactions. To confirm or rule out immediate or delayed type allergies in patients, as well as in patients with a history of immediate-type allergic reactions to β -lactams and planned administration of another β -lactam, it is necessary to conduct skin testing (skin prick test, or, in the case of parenteral administration, intradermal test) with the planned β -lactam antibiotic. The second highest proportion of induced adverse drug reactions was attributed to drugs affecting the cardiovascular system (20.3%). The leading medications in the angiotensin-converting enzyme inhibitors category were enalapril (47%) and the combination of lisinopril with hydrochlorothiazide (24%). In the angiotensin II receptor blockers category of medications, valsartan (30%) and telmisartan-hydrochlorothiazide combination (20%) ranked highest. In the category of CCB drugs, amlodipine (66%) and nifedipine (20%) held the leading positions. Among angiotensin-converting enzyme inhibitors, enalapril caused the most prevalent and predicted adverse reaction, that of cough, affecting 10.5% of patients, whereas, with the combination therapy of lisinopril and hydrochlorothiazide, the cough was observed in only 5.2% of patients. Angiotensin II receptor blockers have a better safety profile, particularly concerning cough. Analysis of adverse drug reactions reports for angiotensin II receptor blockers showed no cases of cough with valsartan and telmisartan-hydrochlorothiazide combination. Among calcium channel blocker medications, amlodipine emerged to rank highest, causing one of the predicted adverse drug reactions, that of lower extremity oedema in 64% of patients. The second

position was taken by the combination of amlodipine with valsartan, which showed a statistically significant reduction of 14.3% ($p \leq 0.05$) in the incidence of oedema. Using amlodipine at a dose of 5 mg in combination with sartan medicines as angiotensin receptor blockers is an effective therapeutic alternative not only for enhancing blood pressure control in hypertensive patients but also for improving the safety profile of amlodipine. Among all the non-steroidal anti-inflammatory drugs prescribed to patients in the Lviv region in 2022, the highest number of adverse reactions was associated with the administration of diclofenac, ibuprofen, paracetamol, and nimesulide, causing adverse drug reactions in 22%, 19%, 17%, and 10% of cases, respectively. The most common systemic manifestations of adverse reactions with these non-steroidal anti-inflammatory drugs were allergic reactions (63.4%) and gastrointestinal disorders (26.8%). From an evidence-based medicine perspective, the most justified approach for primary and secondary prevention of gastrointestinal complications is the use of proton pump inhibitors.

Key words. Adverse reactions, medicinal products, report forms, antibiotics, cardiovascular drugs, non-steroidal anti-inflammatory drugs.

Introduction.

Adverse drug reactions (ADRs) rank among the primary causes of morbidity and mortality worldwide [1]. According to M. Hacker, ADRs are the fourth leading cause of death in the United States and Canada, following heart disease, cancer, and stroke, and the sixth leading cause of death globally [2]. The prevalence of adverse reactions to medications increases with the ageing of patients, due to associated multiple comorbidities, polypharmacy, changes in drug metabolism in the elderly, reduced renal function, and other factors [3,4]. Fundamental studies conducted in the late 20th and early 21st centuries in the USA and the UK revealed that adverse reactions are frequently encountered in clinical practice, often contributing to unplanned hospitalizations. The incidence of adverse drug reactions has remained relatively constant over time and is found to account for approximately 5% to 10% of cases [5].

Research Aim. The study aimed to analyse and evaluate adverse reactions to medicinal products prescribed by the Lviv region healthcare professionals in 2022 and to develop solutions as well as determine the measures to reduce the risks of their further occurrence.

Research Materials and Methods.

The study focused on the analysis of data from ADR report forms, recorded by healthcare professionals in the Lviv region and submitted to the State Expert Center of the Ministry of Health of Ukraine throughout the year 2022. The analysis of case report forms on adverse drug reactions was conducted from February to April 2023. The analysis employed systemic, clinical pharmacological, and statistical approaches. Digital data were processed by the method of variational statistics using the Student's t-test on a computer using the MS Excel 2007 program. Changes at a probability level of 95% ($P \leq 0.05$) were considered reliable.

Results and Discussion.

In 2022, the State Expert Center of the Ministry of Health of Ukraine received a total of 420 case report forms (CRFs) on adverse drug reactions (ADRs) and adverse events following immunization (AEFI) from all healthcare facilities in the Lviv region. It was found that out of all 420 reported cases of adverse reactions, 394 (94%) were attributed to medicines used in medical treatments, and 26 (6%) were associated with adverse events following immunization. This study focuses solely on the analysis of adverse reactions to medicines taken by patients while they received their pharmacotherapeutic treatment.

The analysis showed that ADRs most commonly occurred in women, accounting for 55% of the cases. The age distribution of patients experiencing ADRs indicated that the highest ADR occurrence was among middle-aged individuals (30%) and elderly patients (25%).

Regarding specific types of medicines, the ones with proven cause-and-effect relationships that caused the highest frequency of ADR incidents were chemotherapeutic agents (35.5%), medicines affecting the cardiovascular system (20.3%), and non-steroidal anti-inflammatory drugs (NSAIDs) (8%).

In terms of chemotherapeutic drugs, ADRs were most commonly seen with antibiotic usage (48%), with penicillins (31%) and cephalosporins (19%) being the predominant agents, aligning closely with the findings reported in the literature [6,7].

Within the penicillin class, amoxicillin potentiated by clavulanate (67%) and amoxicillin (29%) were the dominant drugs showing the highest incidence rate of adverse reactions. Among cephalosporins, ceftriaxone (46%) and cefixime (15%) were found to take the lead in terms of adverse reaction frequency. The distribution is primarily representative of the significant frequency of prescriptions by healthcare professionals for β -lactam antibiotics to treat various bacterial infections in healthcare facilities of the Lviv region in 2022.

The highest proportion among all ADRs caused by penicillins and cephalosporins was attributed to allergic reactions. For instance, urticaria (hives) was observed in 5.9% of patients on amoxicillin potentiated by clavulanate, while only 1.5% of patients on amoxicillin experienced it, which showed a statistically significant difference ($p \leq 0.05$) between protected and non-protected penicillins. Additionally, maculopapular exanthema, a manifestation of a delayed-type hypersensitivity reaction, occurred in 10.3% and 4.4% of patients on amoxicillin potentiated by clavulanate and amoxicillin, respectively.

Regarding the use of cephalosporins, urticaria was reported in 5.9% and 2.9% of patients on ceftriaxone and cefixime, respectively. In most cases, other ADRs associated with β -lactam antibiotics were related to gastrointestinal disorders.

Beta-lactam allergies are widely recognized to pose a prevalent and significant issue in routine medical practice. These conditions can have severe consequences, including patient mortality, compromised quality of life, extended treatment periods, suboptimal use of alternative medications, unnecessary diagnostic procedures, and other related concerns [6,8,9]. All β -lactam antibiotics can cause hypersensitivity reactions. However, in recent years, researchers have focused on the occurrence of cross-reactivity among β -lactams [7,10]. Unfortunately, some healthcare professionals still lack knowledge about the safe use of alternative β -lactams in penicillin-allergic patients [11]. The analysis of previous studies reveals that the risk of hypersensitive responses in patients with penicillin allergies is only observed with the use of first-generation cephalosporins, while cephalosporins of other generations can be safely administered to them. Laboratory studies confirm that if hypersensitivity is triggered by the presence of the R1 side chain in the β -lactam ring, it manifests in all antibiotics having a similar structure. It is this structural feature that causes cross-allergic reactions between amoxicillin, ampicillin, and certain cephalosporins such as cefaclor, cefalexin, cefadroxil, cefatrizine, as they share the same R1 side chain [7,9,12]. Additionally, researchers emphasize that penicillin G and first-generation cephalosporins, such as cefalotin, exhibit cross-reactivity despite having different side chains due to their identical three-dimensional structure [6].

To confirm or rule out immediate or delayed type allergies in patients, as well as in patients with a history of immediate-type allergic reactions to β -lactams and planned administration of another β -lactam, it is necessary to conduct skin testing (skin prick test, or, in the case of parenteral administration, intradermal test) with the planned β -lactam antibiotic. If necessary, stepwise drug provocation with the planned β -lactam should also be carried out [13]. Consequently, the range of β -lactam antibiotics to be avoided should be minimized [6].

The second highest proportion of induced ADRs was attributed to drugs affecting the cardiovascular system (20.3%). Their distribution by pharmacotherapeutic groups was as follows: angiotensin-converting enzyme inhibitors (ACEIs) - 21%, angiotensin II receptor blockers (ARBs) - 19%, and calcium channel blockers (CCBs) - 17.5%. The leading medications in the ACE inhibitor category were enalapril (47%) and the combination of lisinopril with hydrochlorothiazide (24%). In the ARB category of medications, valsartan (30%) and telmisartan-hydrochlorothiazide combination (20%) ranked highest. In the category of CCB drugs, amlodipine (66%) and nifedipine (20%) held the leading positions. These findings indicate the high frequency of prescriptions of these drug classes in the treatment of patients with cardiovascular diseases in the Lviv region.

Therefore, among ACE inhibitors, enalapril caused the most prevalent and predicted adverse reaction, that of cough, affecting 10.5% of patients, whereas, with the combination therapy of lisinopril and hydrochlorothiazide, the cough was observed in only 5.2% of patients.

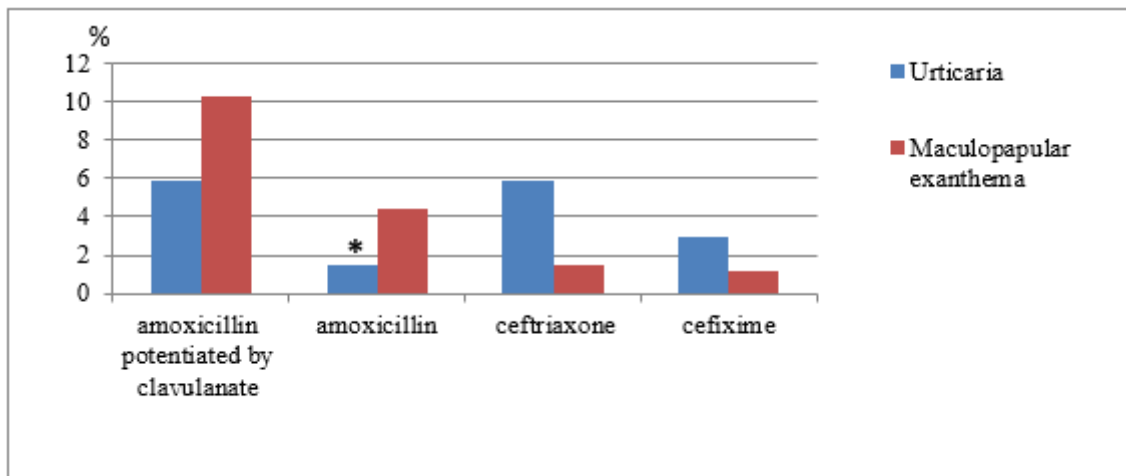


Figure 1. Comparative analysis of ADRs of β -lactam antibiotics in patients of Lviv region in 2022.

*- $p \leq 0,05$ is relevant for the amoxicillin potentiated by clavulanate.

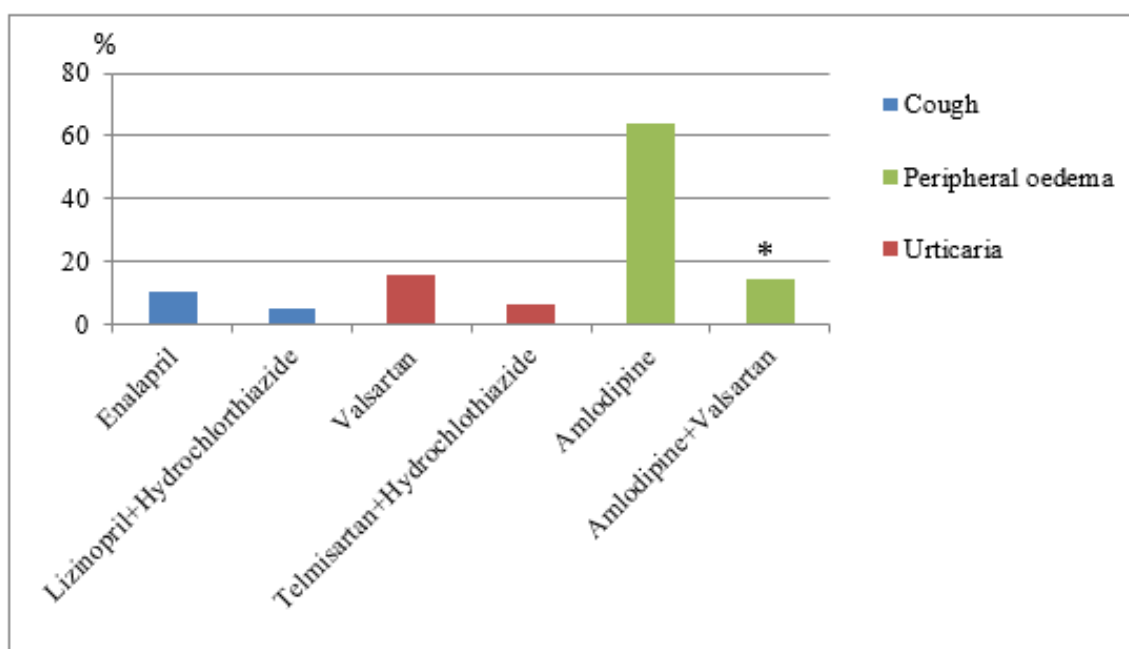


Figure 2. Comparative analysis of ADRs of drugs affecting the cardiovascular system in patients of Lviv region in 2022.

*- $p \leq 0,05$ is relevant for the amlodipine.

ARBs and ACEIs are known to have comparable efficacy, and ARBs have a better safety profile, particularly concerning cough [14,15]. Thus, the analysis of ADR reports for ARBs showed no cases of cough with valsartan and telmisartan-hydrochlorothiazide combination. However, the pharmacotherapy with these medications led to the occurrence of urticaria in 15.4% of patients on valsartan and 6% of patients on telmisartan with hydrochlorothiazide.

Cough associated with ACE inhibitors typically occurs in the first weeks of treatment with these drugs but can also develop later (several months into treatment). For the reason of determining whether the cough is caused by ACE inhibitor use, it is recommended to withdraw the medication for at least 4 days. In most cases, the cough subsides within 1-2 weeks. It is not advisable to change from one ACE inhibitor medication to a different one as the cough is a class-related ADR. Instead,

patients receiving ACE inhibitors for the treatment of arterial hypertension may be switched to taking ARBs. Moreover, clinical studies have shown that adding calcium channel blockers to ACE inhibitors reduces the cough reflex through two mechanisms: firstly, by inhibiting prostaglandin synthesis, and secondly, by inhibiting Ca^{2+} -dependent glutamate release [16]. Thus, study findings reveal that a lower incidence of coughing has been reported in the treatments with ACE inhibitors being used in combination with calcium channel blockers or diuretics [17].

Among calcium channel blocker (CCB) medications, amlodipine emerged to rank highest, causing one of the predicted ADRs, that of lower extremity oedema in 64% of patients. The second position was taken by the combination of amlodipine with valsartan, which showed a statistically significant reduction of 14.3% ($p \leq 0.05$) in the incidence of oedema. Peripheral

oedema is a common dose-dependent adverse reaction to CCBs, particularly when target blood pressure levels cannot be achieved, necessitating a drug dose increase of up to 10 mg. Therefore, using amlodipine at a dose of 5 mg in combination with sartan medicines as angiotensin receptor blockers (ARBs) is an effective therapeutic alternative not only for enhancing blood pressure control in hypertensive patients but also for improving the safety profile of amlodipine [18].

Non-steroidal anti-inflammatory drugs (NSAIDs) ranked third in terms of the frequency of adverse reactions. NSAIDs are a group of symptomatic medicines that are widely used in medical practices and are known for their effectiveness in the treatment and prevention of a wide range of diseases due to their pleiotropic pharmacological properties [19,20]. Among all the NSAIDs prescribed to patients in the Lviv region in 2022, the highest number of adverse reactions was associated with the administration of diclofenac, ibuprofen, paracetamol, and nimesulide, causing ADRs in 22%, 19%, 17%, and 10% of cases, respectively. The most common systemic manifestations of adverse reactions with these NSAIDs were allergic reactions (63.4%) and gastrointestinal disorders (26.8%). Therefore, despite the over a century-long history of using NSAIDs in clinical practice, the issue of mitigating adverse reactions to non-steroidal antiphlogistic medicines, especially those affecting the gastrointestinal system, remains unresolved, significantly limiting the potential utilization of non-steroidal anti-inflammatory drugs [21,22]. Many risk factors are known to increase the likelihood of developing adverse reactions to NSAIDs, such as elderly age (>60 years), presence of comorbidities (cardiovascular, hepatic, renal diseases), concurrent use of glucocorticoids or high doses of NSAIDs, smoking, etc. [23]. Given that gastrointestinal adverse reactions ranked second in terms of frequency, it would be advisable to provide recommendations on the prevention of their development. Thus, from an evidence-based medicine perspective, the most justified approach for primary and secondary prevention of gastrointestinal complications is the use of proton pump inhibitors (PPIs) [24-27]. However, it is also known that the long-term use of PPIs is an independent risk factor for the development of enteropathy in NSAID users, therefore they should be used with caution [20,24,28]. In addition, it is essential to consider the risk of potential adverse interactions when using omeprazole and lansoprazole, to prevent NSAID-induced gastrointestinal damage in patients concurrently taking medications such as diazepam, phenytoin, warfarin, β -blockers, digoxin, phenacetin, paracetamol, clarithromycin, etc., which are also metabolized by cytochrome P-450 enzymes [29,30].

In conclusion, taking into account the findings of our study, it can be stated that improving patients' quality of life and enhancing treatment adherence through minimizing adverse drug reactions (ADRs) are crucial healthcare issues. Therefore, during pharmacotherapy, physicians should carefully evaluate the risks and benefits of prescribing medications for each patient and resort to alternative treatment methods when necessary.

It is essential to continuously implement incentivizing measures for healthcare professionals in medical institutions to encourage ADR reporting and conduct more thorough

evaluations to potentially reduce the risks associated with ADR occurrence.

Conclusion.

1. The most frequently observed adverse drug reactions (ADRs) in the Lviv region in 2022 were associated with chemotherapeutic agents (35.5%), drugs affecting the cardiovascular system (20.3%), and nonsteroidal anti-inflammatory drugs (8%).

2. Hypersensitivity reactions were the most dangerous among the adverse reactions of β -lactam antibiotics. Amoxicillin potentiated by clavulanate caused urticaria in 5.9% of patients and maculopapular exanthema in 10.3%. Similarly, amoxicillin resulted in urticaria in 1.5% of patients and maculopapular exanthema in 4.4%. For ceftriaxone, urticaria occurred in 5.9% of patients, while for cefixime, it was 2.9%.

3. Patients with a history of immediate-type allergic reactions to β -lactams and planned prescription of an alternative β -lactam are recommended to undergo skin testing (skin prick test, or if the drug is administered parenterally, intradermal test), and if necessary, stepwise drug provocation with the planned β -lactam.

4. Among the angiotensin-converting enzyme inhibitors (ACEIs), enalapril (47%) and lisinopril+hydrochlorothiazide combination (24%) were the leading drugs in terms of the number of reported ADRs. In the angiotensin II receptor blockers (ARBs) group, valsartan (30%) and the combination of telmisartan+hydrochlorothiazide (20%) were the most common drugs associated with adverse reactions. Among the calcium channel blockers (CCBs), amlodipine (66%) and nifedipine (20%) were drugs with the most frequently reported ADRs.

5. If patients experience cough within 2 weeks of using ACEIs, they should be

switched to angiotensin II receptor blockers (ARBs) or simultaneous use with calcium channel blockers.

6. Amlodipine caused lower extremity oedema in 64% of patients, while in amlodipine+valsartan combined therapy, oedema was observed in 14.3% of cases.

7. The use of amlodipine in a 5mg dose in combination with valsartan is an effective therapeutic alternative to improve the safety profile of amlodipine.

8. Nonsteroidal anti-inflammatory drugs (NSAIDs) mostly caused allergic reactions (63.4%) and gastrointestinal disorders (26.8%). Proton pump inhibitors (PPIs) are the most justified option for primary and secondary prevention of NSAID-induced gastrointestinal complications.

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