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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, valsartan (30%) and telmisartan-hydrochlorothiazide combination (20%) ranked highest. In the category of CCB drugs, amiodipine (66%) and nifedipine (20%) held 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, amiodipine 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 amiodipine with valsartan, which showed a statistically significant reduction of 14.3% (p≤0.05) in the incidence of oedema. Using amiodipine 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 amiodipine. 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≤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≤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, 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 (52%) 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.
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\textsuperscript{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≤0.05) in the incidence of oedema. Peripheral 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,
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 amiodpine 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 amiodpine [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, phenacitin, 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 de 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), amiodpine (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 amiodpine+valsartan combined therapy, oedema was observed in 14.3% of cases.

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

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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