ABSTRACT

of the doctoral dissertation by Asan Ainur Asankyzy entitled «Investigation of the clinical efficacy and safety of medicinal products in chronic kidney disease», submitted for the degree of Doctor of Philosophy (PhD) in the educational programme «D141-Medicine (8D10110-Medicine)»

Relevance of the study:

Chronic kidney disease (CKD) is one of the most significant medical and social problems in the modern healthcare system. This condition is characterized by high prevalence, progressive course, and a high risk of complications and mortality. In Kazakhstan, an increase in the prevalence of CKD and in mortality associated with this disease has been observed, which in turn creates a substantial burden on the healthcare system and society as a whole. Since the clearance of many medicinal products worsens as kidney function declines, patients on dialysis represent one of the most challenging categories in terms of selection and adjustment of drug doses.

Patients with CKD require long-term and complex pharmacotherapy, which is often associated with the concomitant use of multiple medicinal products, resulting in an increased risk of polypharmacy, adverse effects, drug–drug interactions, and nephrotoxic complications.

A key prerequisite for ensuring high-quality medical care is the rational use of pharmacotherapy. The World Health Organization (WHO) defines rational pharmacotherapy as treatment prescribed in accordance with the clinical situation, taking into account the individual needs of the patient, for an appropriate period of time and at the lowest possible cost.

In this context, the assessment of the clinical efficacy and safety of the medicinal products used, as well as the determination of the rationality of drug therapy taking into account the degree of impairment of kidney function, acquire particular importance. Inadequate assessment of the safety of medicinal products may lead to worsening of the disease course, increased frequency of hospitalizations, and higher treatment costs.

Therefore, the study of the efficacy, safety, and pharmacoeconomic justification of pharmacotherapy used in CKD represents a relevant scientific area in the context of improving clinical practice, optimizing pharmaceutical care, and enhancing the quality of life of patients.

Objective of the study:

Study of the prevalence of chronic kidney disease and assessment of the effectiveness and safety of pharmacotherapy prescribed in real clinical practice.

Research objectives:

1. To determine the prevalence, morbidity, and mortality rates among patients with CKD in the Republic of Kazakhstan based on data from the Unified National Electronic Health System for the period 2014–2020.
2. To analyze and assess the effectiveness and safety of medicinal products prescribed to patients with CKD: rationality of dosing, the level of polypharmacy, and adverse reactions caused by drug–drug interactions.
3. To conduct a pharmacoeconomic analysis of the medicinal products prescribed to patients with CKD at the outpatient and inpatient levels.

Materials and methods of the study:

The study was conducted in a systematic manner as a retrospective cohort analysis. At the planning stage, an analysis of the scientific literature was carried out and the relevant problem areas were identified. In accordance with the aim and objectives of the study, a set of epidemiological, pharmacoepidemiological, pharmacoeconomic, and statistical methods was applied.

Scientific novelty of the study:

For the first time, based on data from the Unified National Electronic Health System, the prevalence, morbidity, and mortality among patients with CKD in the Republic of Kazakhstan were studied. This reflects the epidemiological burden of CKD in the country.

The effectiveness and safety of medicinal products prescribed to patients with CKD were identified and examined in a comprehensive manner. The obtained results make it possible to

assess the characteristics of drug provision for patients with CKD and the safety of the pharmacotherapy administered, which serves as a basis for optimizing treatment.

A pharmacoeconomic analysis of the treatment prescribed to patients with CKD at the outpatient and inpatient levels was conducted, and the rationality of purchasing the medicinal products used was determined. The results of the study support the selection of the most effective medicinal products for patients with CKD.

Theoretical significance of the study:

The theoretical significance of the work lies in identifying the influence of clinical and economic factors on the pharmacotherapeutic effectiveness of medicinal products prescribed to patients with CKD.

This, in turn, makes it possible to develop effective strategies for providing these patients with rational and safe medicinal products. The obtained results may serve as a foundation for further scientific research in this area and for their implementation in clinical practice, which will ensure their broad application in the future.

The results and conclusions obtained in the work can be used in the educational process, including the preparation of lecture materials and practical assignments. This contributes to improving the qualifications of nephrologists, clinical pharmacologists, and healthcare professionals.

Practical significance of the study:

1. The results of the study make it possible to optimize the selection of medicinal products for physicians in multidisciplinary hospitals, as well as to prevent the occurrence of adverse reactions.
2. Timely prescription of effective and safe treatment for patients with CKD contributes to preventing or slowing the progression of renal failure, reducing the risk of transitioning to dialysis, and increasing patients' life expectancy.
3. The obtained results serve as a basis for assessing the compliance of CKD patient management with national clinical protocols and international recommendations, strengthening the justification of medicinal prescriptions, and including effective and safe drugs in the formularies of healthcare organizations.

Publications related to the dissertation:

Articles in international scientific journals indexed in Scopus and Web of Science:

1. Assan A. et al. A retrospective analysis of pharmacotherapy in Kazakhstan: Assessment of the rational prescription and use of antibiotics in the nephrology department of a multidisciplinary hospital //Electronic Journal of General Medicine. – 2022. – T. 19. – №. 6.
2. Assan A. et al. Medication Prescribing Patterns for Chronic Kidney Diseases: Analysis of Drug-Dose Adjustments, Polypharmacy, and Drug Interactions //Turkish Journal of Nephrology. – 2024. – T. 33. – №. 4. – C. 324-332.
3. Zhakhina G. et al. Analysis of chronic kidney disease epidemiology in Kazakhstan using nationwide data for 2014–2020 and forecasting future trends of prevalence and mortality for 2030 //Renal failure. – 2024. – T. 46. – №. 1. – C. 2326312.
4. Kim V. et al. Late diagnosis of CKD and associated survival after initiation of renal replacement therapy in Kazakhstan: analysis of nationwide electronic healthcare registry 2014–2019 //Renal Failure. – 2024. – T. 46. – №. 2. – C. 2398182.

Articles in scientific journals recommended by the Committee for Quality Assurance in the Field of Science and Higher Education of the Republic of Kazakhstan:

1. Assan A. et al. Epidemiology of glomerular diseases in Kazakhstan during the period of 2014–2019: data from the Unified National Electronic Healthcare System // Journal of Clinical Medicine of Kazakhstan. – 2024. – Vol. 21. – No. 1. – P. 55–60.

2. Analysis of adverse drug reactions in the pharmacotherapy of glomerular kidney disease. Journal: Pharmacy of Kazakhstan, February, No. 1 (252), 2024. Section: Clinical Medicine and Pharmacology. ISSN 2310–6115. Online ISSN 3006-0818.

3. Analysis of drug supply expenditures on patients on monitoring with glomerular disease in Shymkent. Journal: "Pharmacy of Kazakhstan," February, No. 1, 2025. Section: Clinical Medicine and Pharmacology. ISSN 2310–6115. Online ISSN 3006-0818.

Scientific reports presented at international scientific and practical conferences:

7 – Kuala Lumpur/Malaysia, Bangkok/Thailand, Sakarya/Turkey, Dushanbe/Tajikistan, Bali/Indonesia, Tashkent/Uzbekistan, Shymkent/Kazakhstan.

Recommendation of the dissertation for defense:

1. During the period 2014–2020, the epidemiological burden of CKD in the Republic of Kazakhstan increased significantly. The prevalence of CKD rose fourfold, and the mortality rate increased approximately threefold. A similar trend was observed for glomerular diseases: their prevalence and mortality also increased several times. The obtained data indicate a rise in the epidemiological burden of CKD and glomerular diseases during the study period.

2. The analysis of the effectiveness and safety of pharmacotherapy in patients with CKD revealed substantial deviations related to the rationality of treatment. In more than 80% of prescriptions, dose adjustment was not performed in accordance with the stage of CKD; 23.4% of the medications used were nephrotoxic; the average number of medicinal products per patient reached 9.5, indicating pronounced polypharmacy. Frequent cases of incorrect dosing and a high prevalence of potentially dangerous drug–drug interactions were identified. The obtained results indicate the presence of significant clinical risks associated with non-adherence to the principles of safe and rational pharmacotherapy in CKD.

3. The pharmacoeconomic analysis of medicinal products prescribed to patients with CKD showed that a significant proportion of them were not included in the State General Formulary, which creates an additional financial burden for medical organizations. It was also found that the structure of antibiotic use does not fully correspond to the AWaRe classification recommended by WHO: the main share of expenditures was associated with drugs from the Watch group, whereas the proportion of the Access group was considerably lower. The obtained data demonstrate pronounced deviations of real prescribing practices from the pharmacoeconomic principles of rational therapy.

Conclusion

The clinical effectiveness and safety of drug therapy in patients with CKD is one of the relevant areas of modern medicine. This is due to the fact that in such patients, the pharmacokinetics and pharmacodynamics of medicinal products change, which leads to reduced therapeutic efficacy and a simultaneous increase in the risk of toxic effects. Therefore, a comprehensive assessment of the clinical effectiveness, safety, and economic justification of medicinal products used in patients with kidney diseases in the context of Kazakhstan is a crucial condition for ensuring rational pharmacotherapy.

Within the framework of this study, epidemiological indicators of chronic kidney diseases, including glomerular diseases, as well as the characteristics of pharmacotherapy and drug safety in the Republic of Kazakhstan, were comprehensively analyzed. The obtained results provided valuable data on the prevalence of CKD. The goals and objectives of the dissertation were fully achieved.

According to epidemiological data, during the period from 2014 to 2020, the prevalence of CKD in Kazakhstan increased significantly: while in 2014 there were 10,346 cases per one million population, in 2020 this indicator reached 38,287. The rate amounted to 6,365 people per one million population versus 4,040 people, and the all-cause mortality rate increased nearly threefold—from 279 to 916 cases per one million population. In 2020, the number of registered CKD cases reached 713,348. A similar trend was observed in mortality associated with CKD: in 2020, 17,068 deaths were recorded. The dynamics of glomerular disease prevalence were also unfavorable: while 7,756 cases were registered in 2014, the number increased to 30,686 in 2019. All-cause mortality rose from 254 to 1,025 per one million population. The number of new cases also increased—from 4,875 in 2014 to 6,320 in 2019. The most common comorbidities associated

with glomerular diseases were diabetes mellitus, cardiovascular diseases, and arterial hypertension. The obtained data showed that during the study period, the prevalence of glomerular diseases increased fourfold, while mortality rose threefold. This study is one of the first works in Central Asia, particularly in Kazakhstan, devoted to assessing the burden of chronic kidney disease. Despite identifying 211,655 patients, it was found that the level of CKD detection remains insufficient. These data confirm the growing socioeconomic burden of CKD and glomerular diseases.

During the analysis of the effectiveness and safety of pharmacotherapy in patients with CKD, it was found that polypharmacy, inconsistencies in drug combinations, and the risk of nephrotoxicity occurred quite frequently. A total of 98 medicinal products prescribed to patients with CKD were included in the study and analyzed according to the ATC classification. The most commonly prescribed were drugs affecting the cardiovascular system (group C), which is explained by the high prevalence of hypertension and cardiovascular complications; drugs affecting hematopoiesis (group B), including iron preparations, anti-anemia agents, and anticoagulants; as well as drugs for the treatment of gastrointestinal diseases and metabolic disorders (group A)—antidiabetic agents, vitamins, and mineral supplements. Although rarely prescribed, clinically justified drugs included systemic antimicrobial agents (group J) and immunomodulatory or antineoplastic agents (group L), predominantly used in post-transplant patients. The most frequently prescribed medicinal products were amlodipine, metformin, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), and vitamins.

The prevalence of polypharmacy in the study population was high: mild—12.2%, moderate—48.2%, and severe—39.6%. On average, each patient received 8 medicinal products. Among all prescriptions, 23.4% of the medicinal products were nephrotoxic, 53.0% were safe, and the safety of 23.4% of them was insufficiently proven. Six drugs (acyclovir, ketoprofen, nitrofurantoin, simvastatin, cyclophosphamide, and enoxaparin) were often prescribed in doses that did not correspond to the level of renal function.

In addition, a number of potentially hazardous drug combinations were identified, including:

1. Pentoxifylline + spironolactone — risk of hyperkalemia and disturbances of arterial blood pressure;
2. Ketoprofen + pentoxifylline — risk of gastrointestinal and renal toxicity;
3. Pentoxifylline + enoxaparin — increased risk of bleeding;
4. Nitrofurantoin + simvastatin — risk of hepatotoxicity and myopathy;
5. Ketoprofen + spironolactone — risk of hyperkalemia and decreased kidney function;
6. Ketoprofen + enoxaparin — high risk of severe bleeding.

Among these combinations, the most frequently encountered was the combination of pentoxifylline and spironolactone, which, under conditions of severe polypharmacy, was prescribed more than 30 times.

Of the 98 medicinal products, 23 (23.5%) required dose adjustment depending on renal function. However, 19 of them (19.3%) were prescribed in doses that did not correspond to the specific stage of CKD. The highest frequency of dosing errors was observed for pentoxifylline (92.7%) and nitrofurantoin (37.1%); similar discrepancies were also identified for simvastatin, spironolactone, ketoprofen, and enoxaparin. Certain medications (nitrofurantoin, ketoprofen) were used despite contraindications in CKD.

Data from the national pharmacovigilance system (2017–2019) showed that the number of reports of adverse drug reactions (ADRs) increased from 1,858 to 2,229 cases (+16.7%). The number of reports submitted by pharmaceutical companies increased by 30.7%.

In 2019, the following groups of medicinal products most frequently caused ADRs: antibacterial agents (68.1%), agents affecting the central nervous system (9.9%), hematological drugs (5.3%), and medications for cardiovascular therapy (3.8%).

In patients with CKD, the most common adverse reactions were hyperkalemia, bleeding, dizziness, nausea, and acute decline in renal function. At the same time, the Naranjo algorithm for assessing the causal relationship between drug use and ADRs was not applied, which represents an important limitation of the current pharmacovigilance system.

Overall, the obtained results showed that pharmacotherapy in patients with CKD in Kazakhstan is largely based on international recommendations and is aimed at controlling arterial hypertension, correcting anemia, and maintaining metabolic balance. However, the high frequency of polypharmacy, the large number of dosing errors, and the presence of dangerous drug combinations are factors that reduce the safety of pharmacotherapy.

In this regard, strict control of prescriptions, individualized dose selection based on renal function, and active involvement of clinical pharmacologists are extremely important conditions for improving the effectiveness and safety of treatment in patients with CKD.

The results of the economic analysis revealed a number of shortcomings in Kazakhstan's medication policy. It was found that the structure of antibiotic consumption according to the AWaRe classification does not fully comply with WHO requirements. Over the entire study period, total expenditures on antibiotics belonging to the controlled group (Watch) amounted to 3,300,190.49 tenge, or 66% of the total. Antibiotics from the Access group accounted for only 1,538,907.89 tenge, or 31%. The remaining 3% corresponded to antibiotics not included in the AWaRe classification due to incomplete data.

In the global structure of antibiotic consumption, WHO sets a target of 60% for the Access group and 40% for the Watch group, which ensures rational use of key antibiotics and preserves their effectiveness. Therefore, in Kazakhstan, there is a need for systematic monitoring of antibiotic consumption patterns and strengthening of related measures.

In addition, based on the assessment of the share of expenditures on the most expensive antibiotics within the HPA framework, it was established that:

• in 2018, the top three were: ceftriaxone — 36.02%, cefazolin — 16.39%, levofloxacin — 14.49%;

• in 2019: ceftriaxone — 41.96%, amoxicillin in combination with a beta-lactamase inhibitor — 19.49%, cefazolin — 13.66%;

• in 2020: ceftriaxone — 49.22%, amoxicillin with a beta-lactamase inhibitor — 15.30%, cefazolin — 12.74%;

• in 2021: meropenem — 26.31%, amoxicillin with a beta-lactamase inhibitor — 18.06%, ceftriaxone — 17.70%.

Thus, it was confirmed that the structure of antibiotic consumption according to the AWaRe classification in Kazakhstan does not correspond to WHO target benchmarks, which necessitates systematic monitoring and strengthening of measures for the rational use of antibacterial agents.

Furthermore, the study showed that antibiotics from the Reserve group were not used, although their availability and rational use are among the key WHO requirements. These findings indicate the need for the introduction and development of a clinical pharmacy service, whose tasks include assessing the appropriateness of prescribing and using medicinal products, including antibiotics, monitoring adverse reactions, and providing counselling to patients and healthcare professionals on the safe and effective use of medicines. The implementation of such measures will help improve the quality of medical care and reduce financial costs.

The results of a physician survey demonstrated that there are a number of serious shortcomings in the prescription of drug therapy for patients with CKD. Thus, 45% of respondents do not take the glomerular filtration rate (GFR) into account, and only 36.7% recognize the need for dose adjustment. This indicates an insufficient level of safety in pharmacotherapy.

Moreover, only 32% of physicians acknowledge the need to adjust doses in the presence of liver disease, and 8% have no knowledge at all regarding the safety of medicinal products in CKD. Such trends increase the risk of polypharmacy, more frequent adverse reactions and complications, and ultimately lead to higher inpatient costs.

The results of the study clearly demonstrated the relevance of the problem of drug safety in patients with CKD and glomerular diseases (GD). Epidemiological data confirm a steady annual increase in the prevalence and mortality associated with these pathologies, while the analysis of pharmacotherapy revealed a high frequency of polypharmacy and drug–drug interactions. Under conditions of widespread use of nephrotoxic agents and potentially hazardous drug combinations, the risk of further deterioration in kidney function, an increase in the number of complications, and more frequent hospitalizations rises significantly.

In this context, strengthening the pharmacovigilance system in the treatment of patients with CKD is a key mechanism for ensuring the safety and effectiveness of drug therapy. In this area, it is necessary to carry out systematic analysis of drug prescriptions, risk factor assessment with the involvement of clinical pharmacists, and to promote a culture of reporting adverse reactions.

Integrating pharmacovigilance with the electronic health system and introducing digital tools for clinical decision support will create conditions for early identification of medication-related risks. Thus, the results obtained in this work provide compelling evidence for the need to develop and implement a comprehensive pharmacovigilance system to ensure effective and safe pharmacotherapy in patients with CKD in Kazakhstan. The data presented on the effectiveness and safety of pharmacotherapy in CKD are of high scientific and clinical significance and may serve as an important basis for the further improvement of nephrology care in the country.

Conclusions

1. **Epidemiological indicators of CKD, including glomerular diseases**

In the Republic of Kazakhstan, the prevalence of chronic kidney disease increased from 10,346 per million population in 2014 to 38,287 in 2020, rising fourfold, while its incidence decreased from 6,365 to 4,040 per million population, a 1.5-fold reduction. The all-cause mortality rate increased from 279 to 916 per million population, showing a threefold rise. When analyzing the contribution of glomerular diseases to chronic kidney disease indicators, it was observed that from 2014 to 2020 the prevalence of glomerular diseases increased fourfold, while their mortality rose threefold. Thus, the study results demonstrate a substantial increase in the epidemiological burden of chronic kidney disease and glomerular diseases in Kazakhstan.

2. **Dose rationality, polypharmacy, and drug–drug interactions in patients with CKD**

In the safety analysis of medications prescribed to CKD patients, 23.4% were identified as nephrotoxic, 53.02% were safe, and for 23.4% of the medications there was no information regarding their safety and efficacy. Additionally, six improperly dosed medications (Acyclovir, Ketoprofen, Nitrofurantoin, Simvastatin, Cyclophosphamide, Enoxaparin sodium) were identified. The average number of medications prescribed to CKD patients was 9.5. Dose adjustment according to the CKD stage was not performed for 82.6% of the medications. Low polypharmacy was observed in 12.2% of patients, moderate polypharmacy in 48.2%, and severe polypharmacy in 39.6%, with the highest proportion corresponding to CKD stage 1. This information demonstrates that clinical inconsistencies and medication-related risks are frequently encountered in the pharmacotherapy prescribed to CKD patients.

3. **Pharmacoeconomic analysis of medications prescribed at inpatient and outpatient levels for patients with** CKD

According to the pharmacoeconomic assessment of medications prescribed to CKD patients, the presence of drugs not included in the Kazakh National Formulary imposed an additional financial burden on healthcare institutions, and the use of antibiotics did not comply with the WHO-recommended AWaRe classification. Throughout the study period, total expenditures for Watch-group antibiotics amounted to 3,300,190.49 tenge, or 66%. Expenditures for Access-group antibiotics accounted for only 1,538,907.89 tenge, or 31%. The remaining 3% corresponded to medications not included in the AWaRe classification. These indicators showed that the structure of antibiotic use in Kazakhstan does not align with WHO standards and highlight the need to improve pharmacoeconomic policies.