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QUALIFICATION WORK

on the topic: «**ANALYSIS OF SIDE EFFECTS OF CALCIUM ANTAGONISTS AND DETERMINATION OF WAYS TO MINIMIZE THEM**»

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ANNOTATION

The qualification work is devoted to the analysis of the side effects of calcium channel blockers, the analysis of the assortment on the pharmaceutical market of Ukraine, the analysis of the evidence base and the clinical efficacy of calcium antagonists.

The master thesis analyzes the number of reports of adverse reactions and monitors adverse reactions of calcium antagonists for 2017-2021.

The work is presented on 45 pages of printed text and consists of an introduction, three chapters, general conclusions, a list of sources used. The work is illustrated with 6 tables, contains 54 sources of scientific literature.

Key words: calcium antagonists, side effects, notification cards, evidence base.

АННОТАЦІЯ

Кваліфікаційна робота присвячена аналізу побічних ефектів блокаторів кальцієвих каналів, аналізу асортименту на фармацевтичному ринку України, аналізу доказової бази та клінічної ефективності антагоністів кальцію.

У роботі проведено аналіз кількості повідомлень побічних реакцій та моніторинг побічних реакцій антагоністів кальцію за 2017-2021 рік.

Робота викладена на 45 сторінках друкованого тексту та складається із вступу, трьох розділів, загальних висновків, списку використаних джерел. Робота ілюстрована 6 таблицями, містить 54 джерела наукової літератури.

Ключові слова: антагоністи кальцію, побічні реакції, карти-повідомлення, доказова база.

LIST OF CONTENTS

ABBREVIATION LIST

ACE – angiotensin-converting enzyme

ACEi – angiotensin-converting enzyme inhibitors

AH – arterial hypertension

ARA II – angiotensin receptor antagonists II

CA – calcium antagonists

CVD – cardiovascular diseases

CVS – cardiovascular system

GIT – gastrointestinal tract

HDLP – high density lipoproteins

IHD – ischemic heart disease

LDLP – low density lipoproteins

MOH – Ministry of Health

MI – myocardial infarction

NUPh – National University of Pharmacy

RAAS – 4nnerv-angiotensine-aldosterone system

SED – side effects of drugs

TRPV – total resistance of peripheral vessels

WHO – World Health Organization

INTRODUCTION

Relevance of the topic. Cardiovascular diseases are the main cause of death worldwide. Since 2000, the number of deaths from cardiovascular diseases has increased by more than 2 million, and in 2019 it reached almost 9 million. Today, cardiovascular diseases account for 16% of all deaths in the world.

Arterial hypertension, ischemic heart disease, tachyarrhythmias, and cerebrovascular disorders are the most common diseases of the cardiovascular system.

Calcium antagonists (CA) or blockers of slow calcium channels are one of the groups of drugs of first choice for the treatment of arterial hypertension, ischemic heart disease, and tachyarrhythmias. These drugs began to be used in cardiology from the mid-70s, they quickly gained so much popularity that in most developed countries they began to occupy one of the first places in terms of frequency of prescription among drugs used for the treatment of cardiovascular diseases. This is due, on the one hand, to the high clinical effectiveness of calcium antagonists, on the other hand, to the relatively small number of contraindications to their use and the relatively small number of side effects caused by them.

CA have a broad range of pharmacological effects, have been used in therapeutic practice for a long time and are well known to practical doctors. The basis for the widespread use of CA was their ability to relax the smooth muscles of the walls of muscular-type arteries and arterioles and thus reduce the overall peripheral resistance

On the other hand, the development of side effects of drug (SED) is one of the most serious medical problems. The relevance of this problem is proven by numerous statistical data obtained in different countries of the world. SED are an integral part of the spectrum of pharmacological action of any, even the most selective drug. Prevention of SED is one of the most important tasks of practical medicine, which allows improving the quality of medical care for the population.

The above made it necessary to conduct an analysis of side effects of CA, study the assortment of CA on the pharmaceutical market of Ukraine, analyze the evidence base, clinical effectiveness of drugs and determine ways to minimize their side effects.

The aim of the study. To analyze the side effects of CA in Kharkiv and Kharkiv region for the period 2017-2021 and to provide recommendations for their reduction, to conduct an analysis of the assortment on the pharmaceutical market of Ukraine, an analysis of the evidence base and clinical effectiveness of CA.

The objectives of the study:

1. To characterize the market of modern drugs for the treatment of cardiovascular diseases and to determine the place and role of calcium antagonists in the therapy of cardiovascular diseases.

2. To conduct an analysis of the assortment of calcium antagonists on the pharmaceutical market of Ukraine.

3. To conduct an analysis of side effects of calcium channel blockers in Kharkiv and Kharkiv region for the period 2017-2021.

4. Based on the analysis of the evidence base of clinical effectiveness, determine the conditions of rational use and ways to minimize the side effects of calcium antagonists.

The study object. Optimization of cardiovascular diseases.

The study subject. Side effects of calcium channel blockers, calcium antagonists, presented on the pharmaceutical market of Ukraine at the beginning of March 2023.

The research methods. Method of passive pharmacovigilance, method of spontaneous reports, method of system approach and system analysis, methods of marketing analysis.

Practical significance of the obtained results. According to the results of the work, it was established that 65 trade names of calcium channel blockers are represented on the Ukrainian market. 59 of them are dihydropyridine derivatives. Amlodipine containing drugs predominate in terms of the number of trade names.

Analysis of report cards with cases of adverse reactions for 5 years showed that the majority of SE in the form of swelling of the legs, redness and rash on the skin, itching, tachyarrhythmia, nausea, diarrhea, constipation develop when using amlodipine drugs.

Three main directions for increasing the level of safety of calcium antagonists have been established. The first is related to the use of stereoisomers. The second direction of increasing the effectiveness and safety of calcium antagonists is the use of modern drugs of the latest generation. A promising direction for optimizing the use of calcium antagonists is also their combination with antihypertensive drugs of other pharmacological groups.

The results of the obtained studies can be used by practicing doctors and health care organizers to optimize the pharmacotherapy of cardiovascular diseases.

Elements of scientific research. For the first time, the systematization of data was carried out and the cases of adverse reactions of CA in Kharkiv and Kharkiv region for the period 2017-2021 were analyzed.

An analysis of the evidence base of the clinical effectiveness of CA based on the data of international clinical guidelines, systematic reviews and clinical studies was carried out. Three main directions for increasing the level of security have been established and the conditions for the rational use of CA have been determined. The first is associated with the use of the S-enantiomer of amlodipine. The second direction of increasing the effectiveness and safety of calcium antagonists is the use of felodipine or lercanidipine, which are the most effective drugs, active in smaller doses, and also have additional pharmacological properties. A promising direction for optimizing the use of calcium antagonists is also the complex use of calcium antagonists with ACE inhibitors or thiazide/thiazide-like diuretics.

Approbation of research results and publication. The results of the work were tested at the All-Ukrainian scientific and practical Internet conference with international participation, dedicated to the 30th anniversary of the establishment of the Department of Clinical Pharmacology and Clinical Pharmacy of the National

Academy of Sciences «Клінічна фармація в Україні та світі» (16-17 March 2023, Rharkiv) and 1 theses published.

Structure and volume. The work consists of an introduction, the main part (literature review, research methods, own research and their discussion), conclusions, a list of used sources and contains 45 pages, 6 tables, 54 references to literature sources.

CHAPTER 1
ACHIEVEMENTS AND PROBLEMS OF MODERN PHARMACOTHERAPY OF CARDIOVASCULAR DISEASES
(literature review)

1.4. Epidemiology and medico-social significance of cardiovascular diseases

Cardiovascular diseases (CVD), caused by atherosclerotic lesions of main arteries (coronary, brain), are the main cause of death worldwide. In the 21st century, these diseases are the main cause of death and disability worldwide [1].

CVD remain the leading cause of death worldwide for 20 years. However, they have never claimed so many lives as today. Since 2000, the number of deaths from CVD has increased by more than 2 million and in 2019 reached almost 9 million. Today, CVD account for 16% of all deaths in the world [2].

CVD are the most common pathology in all economically developed countries of the world. Almost 4% of the world's population, and up to 20% in older age groups, suffer from cardiovascular diseases, which lead to frequent temporary loss of work capacity, disability and high mortality [3].

According to WHO estimates, 17.9 million people died from CVD in 2016, which accounted for 31% of all deaths in the world. 85% of these deaths occurred as a result of myocardial infarction and stroke, more than 75% of deaths from CVD occur in low- and middle-income countries, almost equally among men and women. Out of 17 million cases of death from non-infectious diseases under the age of 70, 82% of cases occur in low- and middle-income countries, and the cause of 37% of them is CVD [2, 3].

Arterial hypertension, ischemic heart disease (IHD), tachyarrhythmias, and cerebrovascular disorders are the most common cardiovascular diseases.

Arterial hypertension (AH) – an increase in blood pressure up to 140/90 mm Hg. And higher primary essential arterial hypertension (also known as hypertensive disease) is not associated with the presence of pathological processes in which the increase in blood pressure is caused by known causes that can be eliminated in

modern conditions. This is the most common cardiovascular pathology. With symptomatic or secondary hypertension, an increase in blood pressure is a consequence of diseases of the heart or blood vessels, pathology of the endocrine system, or other conditions [4, 5].

IHD, including stable angina, unstable angina, myocardial infarction (MI). The most common cause of coronary artery disease is atherosclerosis of the coronary arteries against the background of dyslipidemia. In our country, coronary artery disease is the most common cause of adult hospitalization among all cardiovascular diseases. One of the most dangerous forms of IHD and one of the main causes of death is MI – necrosis (death) of a section of the myocardium due to a sharp deterioration in coronary blood flow [6, 7].

Cerebrovascular diseases or vascular diseases of the brain are a group of diseases that are manifested by damage to the vessels that supply blood to the brain, which leads to damage to the substance of the brain. Among acute cerebrovascular diseases, the most dangerous is a stroke, which is the second most frequent cause of death and one of the main causes of disability in the world. There are two forms of stroke: ischemic stroke (cerebral infarction) – a clinical syndrome caused by acute focal cerebral ischemia, leading to a heart attack (zone of ischemic necrosis) of the brain; a hemorrhagic stroke is characterized by the outflow of blood from the cavity of the cerebral vessels and its pathological accumulation in the subdural, subarachnoid spaces and/or parenchyma of the brain, as well as in some cases in the cavities of the ventricles of the brain [6].

Violations of the rhythm and conduction of the heart combine a number of conditions, which are characterized by changes in the frequency, regularity and source of generation of electrical impulses of the heart, which is a consequence of the violation of the process of their occurrence and/or conduction. According to the definition of the working group of WHO experts, heart rhythm disorders are any deviations from the normal sinus rhythm. Tachyarrhythmias are a widespread clinical phenomenon that can be caused by almost any type of cardiac pathology. Tachycardia is an increase in the heart rate of an adult over 90 beats per minute. At

the same time, the heart rate, as a rule, does not change – the heart contracts at the same intervals. Normally, the pulse is 60-80 beats per minute, and with tachycardia it can reach 200 or more [6, 8].

1.2. General approaches to diseases of the cardiovascular system

For a long time, the improvement of drug therapy for diseases of the heart and blood vessels remains the main direction of development of modern medical science. The arsenal of drugs used in cardiology is quite large and is constantly replenished. Over the past decade, not only several dozen new drugs have entered broad clinical practice, but fundamentally new pharmacological groups of drugs have been created. At the same time, due to conducting a large number of clinical and pharmacological studies based on the principles of evidence-based medicine, ideas about already well-known pharmacotherapeutic groups and individual drugs have changed significantly. Various pathological conditions of the cardiovascular system, on the one hand, and the variety of drugs used for their treatment, on the other hand, dictate the need for detailed clarification of the causes of the development, symptoms, and nature of the course of these diseases, which forms the basis for the rational choice of drugs and optimization of therapy as a whole [9].

ACE inhibitors (iACE inhibitors); angiotensin II receptor antagonists (ARA II); long-acting calcium antagonists (CA); β-adrenoblockers; diuretics (thiazide and thiazide-like) are recommended as first-line antihypertensive drugs, i.e., the drugs of choice for the treatment of patients with hypertension. All other known drugs that have a hypotensive effect (α_1-adrenoblockers, agonists of α_2-adrenoreceptors of central action, agonists of imidazoline receptors, direct vasodilators, rauwolfia alkaloids, etc.) are second-line antihypertensive drugs [6, 10].

Ishemic heart disease (IHD) combines angina pectoris (“chest frog” – angina pectoris, from angere – to strangle) and MI. The essence of IHD is a discrepancy between the myocardial oxygen demand and its delivery through the coronary vessels to the heart cells, which is accompanied by the development of myocardial hypoxia

and the accumulation of deoxidized metabolic products that irritate cardiomyocyte receptors and cause pain. The oxygen demand of the heart muscle is very high, because oxygen is necessary for intensive exchange in the myocardium. A decrease in coronary blood flow can lead not only to functional but also to morphological changes in the myocardium. The pathological basis of IHD is atherosclerosis, which is often accompanied by thrombosis. According to WHO data, over the past 30 years, the frequency of IHD has increased more than tenfold and has a tendency to increase. Antianginal drugs are mainly used to treat this disease [11].

In IHD therapy, reducing the myocardial oxygen demand is achieved in different ways: firstly, by reducing the load on the myocardium, and secondly, by reducing the work of the heart. It is possible to reduce the load on the heart by expanding the venous and arterial vessels, which leads to a decrease in the venous return of blood to the heart (reduction of “preload” on the heart), a drop in the total peripheral resistance of arteries to blood flow (reduction of “afterload” on the heart). Reduction of preload and afterload reduces myocardial oxygen demand. The work of the heart (frequency and strength of heart contractions) decreases with a decrease in adrenergic 12nnervations (β-adrenoblockers) or inhibition of the transport of calcium ions into myocardial cells (blockers of Ca^{2+}channels). As a result of the decrease in contractility of the myocardium, its need for oxygen decreases. An increase in the delivery of oxygen to the myocardium, that is, an increase in coronary blood flow and an improvement in myocardial oxygenation, is achieved by dilating the coronary vessels. Also important in the therapy of coronary artery disease is the improvement of myocardial trophism and metabolism, normalization of the rheological properties of blood [6, 11].

Treatment of patients with IHD the use of ьувшсштуі to stop an attack of angina (improvement of oxygen delivery to the myocardium) and for its prevention (reduction of myocardial oxygen demand). Organic nitrates (nitroglycerin and nitrates of prolonged action) and nitrate-like preparations (molsidomine) belong to the antianginal drugs that are included in the complex therapy of IBS. B-adrenoblockers (β-AB); calcium antagonists (CA), antiaggregants (acetylsalicylic

acid, ticlopidine, clopidogrel); hypolipidemic agents (statins, fibrates, ezetimibe, omega-3 PUFAs); metabolic drugs (trimetazidine, riboxin, meldonium, drugs containing potassium, magnesium) [12].

Heart rhythm disturbances are possible in diseases such as coronary heart disease (in 90% of cases), atherosclerosis of coronary vessels, GC, myocarditis, rheumatism, heart failure, scars after operations on the heart and blood vessels, heart defects, as well as in extracardiac diseases (neurocirculatory dystonia , disturbances in electrolyte metabolism, hypoxia, exposure to toxic substances). In patients with arrhythmia, heterotopic foci often appear in the conduction system of the myocardium, which have greater automatism than the sinus node [6, 8].

Since heart rhythm disturbances occur in diseases of various etiologies, antiarrhythmic drugs are divided into two groups:

1. true antiarrhythmics (affecting automatism, excitability and conduction of the heart's conduction system);

2. etiotropic agents (eliminate the cause of heart rhythm disturbance). These include drugs that normalize the electrolyte and energy metabolism of the heart muscle (salts of potassium, magnesium, calcitonin, sodium citrate, preparations of vitamins B1, B6, E, SG, etc.), steroidal and nonsteroidal anti-inflammatory drugs, anxiolytics, sedative drugs.

There are two main mechanisms of action of classic antiarrhythmic drugs:

- direct action on the myocardium (blockade of sodium, calcium and potassium channels, prolongation of repolarization);

- indirected action on the autonomic innervation of the heart (β-adrenomimetics, β-adrenoblockers, M-cholinoblockers).

The classification of antiarrhythmics into classes I-IV is based on the Vaughan Williams classification, which is based on the effect on the electrophysiological parameters of the myocardium. Blockers of slow calcium channels (calcium antagonists) belong to the IV class. They prolong spontaneous depolarization (phase 4) in pacemaker cells, prolong depolarization dependent on calcium current (CA and AV nodes). Due to the blockade of slow calcium channels, LPs reduce the action

potential and lengthen the refractory period, which leads to a decrease in automaticity of the sinus node and a slowing of conduction. For tachyarrhythmias, a group of derivatives of phenylalkylamine (verapamil) and benzothiazepine (diltiazem) are used. Indications: supraventricular rhythm disturbances [6].

1.5. The role and place of calcium antagonists in cardiovascular diseases treatment

Calcium antagonists (CA) are a group of drugs that combine the ability to selectively block the flow of calcium through the so-called slow calcium channels. These drugs began to be used in cardiology from the mid-70s, they quickly gained so much popularity that in most developed countries they began to occupy one of the first places in terms of frequency of prescription among drugs used for the treatment of IVD. This is due, on the one hand, to the high clinical effectiveness of CA, on the other hand, to the relatively small number of contraindications to their use and the relatively small number of SE caused by them [13].

Calcium cation is an important component of electrophysiological processes in myocytes. Calcium current is of primary importance in the implementation of positive chronotropic and inotropic effects, i.e. in maintaining the duration of the action potential, in the generation of pacemaker activity, in the stimulation of shortened myocardial and smooth muscle cells, and the violation of the regulation of its intracellular content leads to damage to cell structures, arrhythmias , extrasystoles. The passage of calcium through the cell membrane does not occur diffusely, but through special structures – ion channels, which are proteins embedded in the membrane. By changing the spatial structure, depending on the electrophase, proteins regulate the movement of Ca^{2+} ions into and out of the cell. Calcium channels are divided into three types: L, T and N. L-channels are characterized by slow kinetics. They regulate the entry of Ca^{2+} through the membrane into the “plateau” phase, their activation occurs at an electric potential of the cell membrane -50 mV, inactivation – at -40 mV. L-channels are located in cell membranes of contractile cardiomyocytes,

cells of the conducting system of the heart, and smooth muscle cells of blood vessels. This type of channels is blocked by drugs from the group of calcium antagonists. T-channels have faster kinetics. They regulate the activity of the pacemaker and the generation of action potentials in cells that are conductors. N-channels are located in nerve endings and are blocked by cadmium. The speed of the calcium current can also be influenced by neurotransmitters: adrenaline increases it, acetylcholine decreases it. Calcium antagonists affect the functional properties of channels by reversible binding to receptor molecules. Moreover, these receptors are different for derivatives of different chemical groups, and the density of receptors is a non-constant value. With hypertension, hyperthyroidism, alcohol consumption, lead poisoning, it increases, with myocardial ischemia, hypothyroidism decreases. The density of receptors also decreases as a result of the use of reserpine and long-term use of dihydropyridine derivatives. The beneficial effect of CA on the myocardium is realized in several ways: inhibition of calcium-dependent automatism, including in ectopic foci, reduction of Ca^{2+} influx into myocytes, leading to a decrease in the activity of Ca^{2+}-activated ATPase. As a result, the contractile capacity of the myocardium decreases (negative inotropic effect), energy expenditure and oxygen consumption by the myocardium decrease; decrease in heart rate (negative chronotropic effect); cardioprotective action, protection of myocytes from the consequences of overloading with calcium ions, which cause membranes and death of cardiomyocytes; elimination of endothelial dysfunction by increasing the production of vasorelaxing factor (NO) and inhibiting the synthesis of vasoconstrictor – endothelin-1; decrease in vascular smooth muscle tone (arterial vasodilatation), decrease in total resistance of peripheral vessels (TRPV) and afterload; strengthening of coronary blood circulation; a decrease in the tone of myocytes, a decrease in the tonicity of the myocardium, which is accompanied by an increase in its perfusion in diastole. Additional effects of CA: inhibition of platelet aggregation by suppression of thromboxane synthesis; hypolipidemic effect: decrease in the content of atherogenic LDL and increase in the level of antiatherogenic HDL, inhibition of the proliferation of smooth muscle cells in the walls of blood vessels; slowing of

conductivity (negative dromotropic effect); inhibition of insulin and glucagon secretion; increase in renal blood flow, decrease in proteinuria [14, 15, 16, 17].

CA, currently used in the treatment of coronary heart disease and hypertension, belong to the three main chemical groups shown in the table 1.1.

Table 1.1

Classification of calcium antagonists (T. Toyo-Oka, W. Nayler, 1996) [6, 8]

Chemical structure	The first generation	The second generation Iia	The second generation Iib	The third generation
Dihydropyridines	Nifedipine	Nifedipine GITS Felodipine SR Nicardipine SR	Felodipine Nisoldipine Isradipine Nimodipine Nitrendipine	Amlodipine Lacidipine Lercanidipine
Phenylalkylamines	Verapamil	Verapamil SR	Halopamine Anipamyl Thiapamil	-
Benzothiazepines	Diltiazem	Diltiazem SR	Clentiazem	-

When the chemical structure of CA I generation was changed, new compounds were synthesized that differed from their predecessors in greater efficiency, selectivity and duration of action. They were called CA II generation. The derivative of phenylalkylamine verapamil, along with a vasodilating effect and a decrease in heart rate, has a significant inhibitory effect on AV conduction and automaticity of the sinus node. The drug is indicated for patients with angina pectoris in combination with supraventricular rhythm disorders, tachycardia. Verapamil is well absorbed in the gastrointestinal tract (up to 95%). Bioavailability is low (10–20%) due to binding to plasma proteins and rapid metabolism in the liver. After peroral administration, the effect occurs after 1 hour, reaching a maximum after 2 hours, duration of action – up to 6 hours. With intravenous administration, the duration of action of verapamil is

10–20 minutes. The benzothiazepine derivative diltiazem causes dilatation of arterioles, increases collateral blood flow and thereby improves blood supply to the myocardium as a whole; inhibits platelet aggregation; reduces elevated blood pressure (both systolic and diastolic) and does not affect normal blood pressure. When taken orally, diltiazem is absorbed almost completely, its bioavailability is about 45%. Pharmacokinetic parameters approximately correspond to verapamil [6, 18, 19, 20].

Dihydropyridine derivative nifedipine slightly reduces the strength of heart contractions, does not affect the conductivity and excitability of the myocardium. Compared to verapamil, it has a more pronounced vasodilating effect, including on coronary vessels. It shows disaggregating properties. When taken orally, it is completely absorbed, begins to work after 30-40 minutes, the effect lasts about 6 hours. Bioavailability – 60%. Other dihydropyridine derivatives: amlodipine (Norvask), isradipine (Lomir), nicardipine (Carden), nimodipine (Nimotop), nisoldipine (Siscor), nitrendipine (Nitrepine), riodipine (Foridon), felodipine (Plendil) differ from nifedipine by a significantly longer duration of vasodilation action (amlodipine, nitrendipine) and greater vasoselectivity (felodipine, amlodipine). Nisoldipine differs in high selectivity for coronary arteries, and nimodipine for cerebral arteries. Currently, prolonged forms of verapamil, diltiazem, and nifedipine are widely used, which can be prescribed 1–2 times a day [6, 21, 22, 23, 24].

1.6. **General complications and side effects of calcium channel blockers**

According to the WHO, the development of side effects of drugs (SED) is one of the most serious medical problems. For example, in the USA, 106,000 people die from various types of them every year – this is the fourth most common cause of death in the population. According to the data of the American authors, SED is noted in 10.9% of cases in hospital patients. In 2.1% of cases, they are severe, and in 0.2%, they are fatal. In 4.7% of cases, SED become the reason for hospitalization. The economic costs associated with stopping complications from taking medical preparations exceed 177 billion dollars per hour. According to WHO experts, in some

countries up to 20% of the state budget is spent on the fight against the consequences of adverse drug reactions. The relevance of this problem is proven by numerous statistical data obtained in different countries of the world [25, 26, 27].

Adverse drug reactions or side effects are an integral part of the spectrum of pharmacological action of any, even the most selective, drug. The prevention or minimization of SED is one of the most important tasks of practical medicine, which allows improving the quality of medical care for the population, and the wide application of the analysis of satisfaction with the availability and quality of medical care gives health authorities the most important additional tool necessary for the assessment of health care technologies in order to make management decisions about priority areas financing [25, 28, 29, 30].

CA have a wide range of pharmacological effects, have been used in therapeutic practice for a long time and are well known to practicing doctors [31, 32]. The basis for the widespread use of CA was their ability to relax the smooth muscles of the walls of muscular-type arteries and arterioles and thus reduce the overall peripheral resistance [33, 34, 35].

Adverse reactions observed when taking CA are mainly associated with peripheral vasodilation – arterial hypotension, hyperemia of the face and neck, headache, hot flashes [36]. Nifedipine, in addition, can cause tachycardia, swelling of the lower extremities [37, 38, 39]. Verapamil, by suppressing the automatism of the sinus node, contributes to the development of bradycardia, and its influence on AV-conduction can lead to blockade [40]. Reception of CA of the first generation, especially verapamil, may be accompanied by constipation. Contraindications to the appointment of AK: severe arterial hypotension, sinus node weakness syndrome, pregnancy. Verapamil is contraindicated in CA conduction disorders [37, 40].

Conclusions for chapter 1

According to the results of the literature review and analysis of epidemiological and pharmacoepidemiological studies, the frequency of CA use is 18–28%. In practice, the doctor often has to choose which drug should be preferred

when prescribing therapy. In this regard, it is relevant to study and analyze of SE when using CA in patients with cardiovascular diseases in real clinical practice, with the aim of improving the quality of medical and preventive care for the population.

CHAPTER 2
MATERIALS AND METHODS

The object of the study was the assortment of CA on the pharmaceutical market of Ukraine. To analyze the assortment of CA and determine the place of CA among all drugs affecting the cardiovascular system, the state register of medicinal products in Ukraine for 2022 was used [41].

The object of the study were also cases of adverse reactions to drugs (SED) of the pharmacological group «Calcium antagonists», which according to the international ATC classification are presented under the code C08 Calcium antagonists, and to which adverse reaction notification cards were sent in health care institutions in the city of Kharkiv and of the Kharkiv region for 2017-2021.

During this period, 9.512 notification cards were sent to the Pharmacovigilance Department of the State Expert Center of the Ministry of Health of Ukraine (hereinafter referred to as the State Expert Center of the Ministry of Health of Ukraine) on all cases of adverse drug reactions from medical institutions in Kharkiv and Kharkiv region.

Information about adverse reactions was collected by means of passive pharmacovigilance using the method of spontaneous reports from card-messages about the adverse reaction of the drug during its medical use from the data provided by doctors, paramedics, midwives, pharmacists, nurses (hereinafter – workers with medical and /or pharmaceutical education) of all health care institutions, regardless of ownership.

Card-notification of adverse reaction and/or lack of effectiveness of a drugs during its medical use is a form by which employees with medical and/or pharmaceutical education and applicants report any cases of adverse reactions and/or lack of effectiveness of medicines.

The method of spontaneous messages allows you to attract the public; to carry out control of adverse reactions of all medicines that are allowed for medical use in Ukraine.

Known databases of evidence-based medicine were used to analyze the clinical efficacy and safety of calcium antagonists: Cochrane Library, Trip Database, PubMed [42].

CHAPTER 3
STUDY RESULTS

3.1. Determining the place of calcium channel blockers in the range of drugs affecting the cardiovascular system in Ukraine

The first stage of our research was devoted to determining the place of calcium antagonists (CA) among all drugs affecting the cardiovascular system available on the pharmaceutical market of Ukraine during 2022. To conduct the research, we used the state register of medicines of Ukraine [41].

As of March 20, 2023, 11 522 trade names of drugs were registered in Ukraine. Of them, 3854 are of domestic medicines, 7 668 are foreign. 743 trade names of drugs of various groups affecting the cardiovascular system are registered. Of these, 58 names are β-adrenoblockers, 228 monocomponent and combined drugs affecting the renin-angiotensine-aldosterone system (RAAS), 23 antiarrhythmics, 83 – hypolipidemic, 23 names of peripheral vasodilators, 23 – nitrovasodilators, 9 – α_1-adrenoblockers, 93 – diuretics, etc. As of March 20, 2023, 65 trade names of CA were registered in Ukraine. This is 8.7% of all cardiac drugs.

CA are also part of a number of combined antihypertensive drugs. On the pharmaceutical market, there are 23 drugs containing CA + an ACE inhibitor (for example, equator, liram, tarka, etc.), 15 drugs containing CA + an angiotensin II receptor antagonist (for example, combisart, sevikar, teldipine), 1 combination with β-adrenoblocker (alotendin), 1 combination with a diuretic (arifam). That is, single-component and combined drugs containing CA make up 14% of the assortment of drugs that affect the cardiovascular system.

3.2. Analysis of the assortment of calcium antagonists in Ukraine

At the second stage of our research, we analyzed the assortment of CA in Ukraine.

As of March 2023, 9 international non-proprietary names (INNs) of CA were registered on the pharmaceutical market of Ukraine, of which 7 INNs are

dihydropyridine derivatives, 1 each is a phenylalkylamine and benzothiazepine derivative. There are 65 trade names of calcium channel blockers on the Ukrainian market, 59 of them are dihydropyridine derivatives. In terms of the number of trade names, amlodipine drugs prevail – 38. 8 nifedipine drugs, lercanidipine – 6, nimodipine – 5, nitrendipine – 1, felodipine – 1 are registered. 4 verapamil trade names are registered, 2 – diltiazem. Among the registered calcium antagonists, 61.5% are drugs of Ukrainian manufacturers, 38.5% are foreign drugs. The drugs are presented on the market in the form of 4 dosage forms: tablets, capsules, drops for oral administration, solution for injections.

Thus, the assortment of calcium channel blockers on the modern pharmaceutical market of Ukraine is quite wide. Among the registered drugs of this group, dihydropyridine derivatives predominate, namely amlodipine drugs. However, only 6 drugs derived from phenylalkylamine and benzothiazepine are registered. Tablets (coated tablets, prolonged-release tablets, modified-release tablets) are the most common form of calcium antagonists. Only some drugs are released in other dosage forms (capsules, drops for oral administration, solution for injections).

3.3. Analysis of the side effects of calcium antagonists in the Kharkiv region

The next stage of our research was devoted to the analysis of reports of adverse reactions of calcium channel blockers from the total number of reports received in 2017-2021, 9 512 from 145 health care facilities in the city of Kharkiv and the Kharkiv region.

The obtained results showed that during 2017-2021, 195 notification cards with cases of adverse reactions to calcium antagonists were received from health care institutions of Kharkiv region and Kharkiv, of which 59 and 61 notification cards were received in 2017 and 2018, in 2019 – 53 notification cards, in 2020 – 12 notification cards, in 2021 – 10 notification cards (табл. 3.1).

Table 3.1

The number of adverse reactions of calcium antagonists during 2017-2021 in health care institutions of Kharkiv and Kharkiv region

Number of cards-notifications				
2017	2018	2019	2020	2021
59	61	53	12	10

From the analysis of the received cards-notifications, it can be seen that 49 (25.1%) of them report side effects of calcium channel blockers in men, 146 – in women (74.9%). According to the age of the patients, the recorded side effects of CA are distributed as follows. 45 cards-notifications belong to patients under 60 years of age, which is 23% of the total amount of information. 60 cards-notifications belong to patients aged 61 to 70 years. This is equal to 30.8% of the total number of cards. 68 cards-notifications came from patients aged 71 to 80 years, 34.9%. 22 cards-notifications from patients over 80 years old (11,3%).

The analysis of cards-notifications revealed that among calcium antagonists in 2017, the maximum number of adverse reactions was registered for such drugs as Amlodipine-Astrapharm, Amlodipine-KV, Amlodipine-Pharmak, Amlodipine-Zdorovya. In 2018, Amlodipine-Astrapharm, Amlodipine-KV, Amlodipine-Pharmak were also the leaders in terms of the number of notification cards, in 2019 - Amlodipine-Farmak, Aladin and Amlodipine-KV, in 2020 - Amlodipine, Technolog, in 2021 - Amlodipine-KV and Amlodipine-Health (табл. 3.2).

Table 3.2

Analysis of adverse reactions of calcium antagonists during 2017-2021 in health care institutions of Kharkiv and Kharkiv region

Names of drug, manufacturing company	Number of cards-notifications				
	2017	2018	2019	2020	2021
Amlodipine-Zdorovya	7	-	3	1	2
Amlodipine-Farmak	10	13	10	-	-

Amlodipine-KV, Kyivmedpreparat	11	14	6	1	2
Aladine, Farmak	5	7	8	1	1
Amlodipine-Astrapharm	16	17	2	-	-
Amlodipine, Technolog	2	1	4	3	1
Phenigidine-Zdorovya	1	-	1	-	-
Alotendine-Eric	2	-	1	-	-
Amlong, Microlabs Limited	1	-	-	-	-
Farmadipine, Pharmac	-	-	2	-	-
Amlodipine-Sandoz	-	3	3	-	1
Semlodipine, Kusum Pharm	-	2	1	-	-
Lerkamen, Berlin Chemie	-	-	1	-	-
Verapamil h/ch, Borshchagivsky factory	-	-	2	-	-
Verapamil-Darnytsia	-	-	1	-	-
Valodip, KRKA	-	-	2	1	-
Amlodipine, Teva	-	-	2	1	1
Triplixam, Servier Lab	2	-	4	-	1
Amlessa, KRKA	1	-	-	-	1
Nifedipine, Technolog	-	2	-	1	-
Kombisart N, Kyiv vitamine factory	-	-	-	1	-
Equator, Gideon Richter		-	-	1	-
Phelodip, Teva	-	-	-	1	-
Nifedipine, Darnytsia	-	1	-		-
Amlodipine, Darnytsia	-	1	-	-	-
Gipril-A plus, Micro Labs	1	-	-	-	-

The next stage of our research was the monitoring of adverse reactions of CA for the period 2017-2021 (table. 3.3).

Recorded adverse reactions are most often manifested in the form of edemas of the lower extremities, face, tachyarrhythmia, hypotension, allergic reactions, such as rash and reddening of the skin, itching, angioedema, headache, dizziness, insomnia, tinnitus, paresthesias, dry cough, nausea, nocturia, facial redness. No serious adverse reactions with fatal consequences were registered.

Table 3.3

Monitoring of the frequency of adverse reactions of calcium chanel blockers during 2017-2021 in health care institutions of Kharkiv and Kharkiv region

Side effects	The number of registered adverse reactions				
	2017	2018	2019	2020	2021
Edemas of the lower extremities	48	45	37	8	6
Edemas of face	2		1		
Tachyarrhythmia		5	8	1	
Hypotension		3			
Rash on the skin	3	6	4	1	1
Itching of skin	3	1		1	1
Angioedema	1		1		
Headache	3		2	1	1
Dizziness			1	2	
Insomnia		1	1		
Tinnitus			2		
Paresthesias				1	
Dry cough	1		5		1
Nausea	1	3			
Nocturia	1				
Redness of the face, feeling of heat	1	2	1		1
Total number of adverse reaction	64	66	63	15	12

Therefore, the monitoring of SE to CA for the period 2017-2021 showed that the largest number of reports of adverse reactions was recorded in the form of

swelling of the lower extremities in the area of the ankle joints (65.5%). The following side reactions were also recorded: allergic skin reactions (9.5%), tachyarrhythmia (6.4%), nausea (1.8%), headache (3.2%), dry cough (3.2%), redness of the face, feeling of heat (2.3%), hypotension (1.4%) and others. These adverse reactions did not require additional hospitalization and did not cause disability of the patients.

Table 3.4

Distribution of the number of adverse reactions on the most popular calcium antagonists for the period 2017-2021

Side effects	The number of registered SED for 5 years					
	Amlodipine-Astra-pharm	Amlodipine-KV	Amlodipine-Pharmak	Amlodipine-Zdo-rovya	Amlodipine, Tech-nolog	Aladine
Edemas of the lower extremities	23	25	29	13	4	18
Edemas of face	1		1			1
Tachyarrhythmia	1	4			3	3
Hypotension		1			2	
Rash on the skin	4	4	1	2	2	2
Itching of skin		2	1		1	
Angioedema	1	1	1	1		1
Headache	1	2				
Dizziness					1	
Insomnia		1				1
Tinnitus					1	
Paresthesias	1	1				2
Total number	32	41	33	16	14	28

In the course of the analysis of adverse reactions to calcium channel blockers, it was found that the maximum number was noted in the drugs Amlodipine-KV (41), Amlodipine-Farmak (33) and Amlodipine-Astrafarm (32). When using Amlodipine-KV was recorded:

- ✓ 25 SE – «edemas of the lower extremities», which is 70%;

- ✓ 6 SE – «allergic reactions in the form of redness and rash on the skin, itching of the skin», which is 14,6%;
- ✓ 4 SE – «tachyarrhythmia», which is 9,8%.

When taking Amlodipine-Farmak:

- ✓ 29 SE – «edemas of the lower extremities», which is 87,8%;
- ✓ 1 SE – «allergic reactions in the form of redness and rash on the skin, itching of the skin», which is 3%;
- ✓ 1 SE – «headache», which is 3%.
- ✓ По 1 SE – «face edemas», which is 3%.

When using Amlodipine-Astrafarm:

- ✓ 23 SE – «edemas of the lower extremities», which is 71,9%;
- ✓ 4 SE – «allergic reactions in the form of redness and rash on the skin, itching of the skin», which is 12,5%;
- ✓ 1 SE – «tachyarrhythmia», «headache», «dizziness», «face edemas», «feeling of heat» which is 15,6%.

Therefore, Amlodipine-KV, Amlodipine-Pharmak and Amlodipine-Astrafarm are the leaders in the number of adverse reactions. The drugs are prescribed to patients for the treatment of such diseases as hypertension, chronic stable angina, vasospastic angina (Prinzmetal's angina).

According to the literature, amlodipine drugs can cause the development of the following side effects, such as drowsiness, dizziness, headache, palpitation, flushing, abdominal pain, nausea, leg swelling, swelling and fatigue; leukocytopenia, thrombocytopenia; hyperglycemia; insomnia, mood changes (including anxiety), depression; confusion of consciousness; tremor, dysgeusia, syncope, hypoesthesia, paresthesia; hypertension, peripheral neuropathy; visual impairment (including diplopia); tingle; increased heartbeat; MI, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation); tides; arterial hypotension; vasculitis; dyspnea, rhinitis; cough; stomach pain, nausea; vomiting, dyspepsia, intestinal motility disorders (including constipation and diarrhea), dry mouth; pancreatitis, gastritis, gum hyperplasia; hepatitis, jaundice, increased level of liver enzymes

(which was most often associated with cholestasis); alopecia, purpura, skin discoloration, increased sweating, itching, rash, exanthema; angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Mr. Stevens Johnson, Quincke's edema, photosensitivity; swelling of the lower legs; arthralgia, myalgia, muscle spasms, back pain; impaired urination, nocturia, increased frequency of urination; impotence, gynecomastia; edema, fatigue; pain behind the sternum, asthenia, pain, malaise; increase or decrease in body weight; cases of extrapyramidal syndrome development [https://compendium.com.ua/uk/akt/65/3319/amlodipinum/#toc-1].

Side effects to calcium antagonist drugs, which were recorded during the analysis of cards-notifications, coincide with the literature data [40].

As for amlodipine drugs, which received the largest number of reports of adverse reactions, one of the explanations may be that amlodipine drugs are the leaders of the Ukrainian pharmaceutical market. In addition, these drugs are the most demanded and popular among doctors and consumers.

3.4. Determining the conditions for the rational use of slow calcium channel blockers in order to prevent / minimize their side effects

To analyze the clinical effectiveness and conditions of rational use of CA, well-known databases were used: Cochrane Library, Trip Database, and PubMed. These databases contain systematized primary or secondary information on a specific clinical issue: the effectiveness and safety of various medical technologies [42].

The results of the analysis of the evidence base of calcium channel blockers are shown in the table 3.5.

Table 3.5

Results of analysis of the evidence base of clinical efficacy and safety of calcium channel blockers based on data from systematic reviews

№	Name of the study, year of publication	The obtained results of clinical studies are presented in systematic reviews
1	Systematic review:	*Aim.* Calcium channel blockers are a heterogeneous

	benefits and safety of long-acting calcium antagonists in coronary artery disease: the Action trial**.** 2005 [43]	class of drugs, including dihydropyridine and non-dihydropyridine subgroups, commonly used in the treatment of hypertension. A systematic review of the 24-hour time course of the blood pressure-lowering effect has not been published. To assess how much variation there is in hourly systolic and diastolic blood pressure lowering by dihydropyridine calcium channel blockers over a 24-hour period in people with hypertension aged 18 years or over, with baseline systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg, or both. *Results.* We included 16 randomized controlled trials of dihydropyridine calcium channel blockers in this systematic review, with 2768 randomized participants. Drugs studied included amlodipine, lercanidipine, mandipine, nifedipine, and felodipine (all administered once daily) and nicardipine (administered twice daily). We analyzed and presented data by hour post dose. The blood pressure-lowering effect was stable over time; there were no clinically important differences in blood pressure-lowering effect of calcium channel blockers between each hour for either systolic blood pressure (estimated mean hourly differences ranged between 9.45 mmHg and 13.2 mmHg) or diastolic blood pressure (estimated mean hourly differences ranged between 5.85 mmHg and 8.5 mmHg). However, there was a moderate risk of

		bias for this finding. Once-daily dihydropyridine calcium channel blockers appeared to lower blood pressure by a relatively constant amount throughout the 24-hour dosing interval. *Conclusions.* Six dihydropyridine calcium channel blockers studied in this review lowered blood pressure by a relatively similar amount each hour over the course of 24 hours. The benefits and harms of this pattern of blood pressure lowering are unknown. Further trials are needed with accurate recording of time of drug intake and with reporting of standard deviation of blood pressure at each hour. We did not attempt to assess adverse effects in this review due to the lack of reporting and the short duration of follow-up.
2	Calcium antagonists, is there a real concern about safety? 1998 [44]	Calcium antagonists are widely used in the treatment of arterial hypertension and, or in ischemic heart disease. During the last 3 years, controversial articles and editorials have been published concerning the potential risk of calcium antagonists in regard to mortality, cancer and haemorrhage. The information has been mainly derived from case-control studies. The major concern about such observational studies of treatment outcome is the large potential for systematic error to affect the results. However, overviews of controlled trials with calcium antagonists do not provide clear evidence of an effect of calcium antagonists on mortality, risk of

		cancer and risk of bleeding.
3	Clinical implications of the World Health Organization-International Society of Hypertension statement on calcium antagonists. 1997 [45]	The controversy over the efficacy and safety of calcium antagonists is over 2 years old. Since millions of patients worldwide are currently using calcium antagonists for the treatment of high blood pressure and angina, a systematic review of their potential risks and benefits is much needed. In response to this need, the World Health Organization (WHO) and the International Society of Hypertension (ISH) recently convened an ad-hoc subcommittee to review the available evidence (J Hypertens 1997, 15:105-115). Importantly, the WHO-ISH statement does take a strong stand in favor of large long-term trials that compare antihypertensive agents, and we all agree that these comparative trials are urgently needed. However, the WHO-ISH statement is marred in part by errors of omission, by the selective use of evidence and epidemiologic principles, and by a narrow application of the viewpoint of those who believe that evidence can come only from the results of megatrials. As a result, practicing clinicians will find more useful information in existing hypertension and postmyocardial infarction guidelines
4	Comparative efficacy and tolerability of two long-acting calcium antagonists, mibefradil and	In a previous forced-titration trial, mibefradil 100 mg QD was as effective as amlodipine 10 mg QD in reducing sitting diastolic blood pressure (SDBP), and it produced significantly less leg edema than

	amlodipine, in essential hypertension. 1997 [46]	did amlodipine 10 mg QD. The present multicenter, double-masked, randomized, parallel-design trial was performed to assess the reproducibility of these results using a flexible-titration design. Following a 4-week, single-masked, placebo run-in period, 296 patients with a trough SDBP of between 95 and 114 mm Hg (21 to 27 hours postdose) were randomized to receive once-daily treatment with mibefradil 50 mg (n = 146) or amlodipine 5 mg (n = 150). In patients whose trough SDBP was greater than 90 mm Hg after 4 or 8 weeks of double-masked therapy, the dosage was titrated upward to mibefradil 100 mg or amlodipine 10 mg for the remainder of the 12-week active treatment period. A greater proportion of amlodipine-treated patients (65%) than of mibefradil-treated patients (54%) required titration to the higher dose. Despite this difference, statistically equivalent reductions in trough SDBP were observed after 12 weeks of treatment with 50 to 100 mg of mibefradil QD (-11.7 +/- 6.4 mm Hg) and 5 to 10 mg of amlodipine QD (-11.9 +/- 6.9 mm Hg). SDBP was normalized to < or = 90 mm Hg at week 12 in 66% of patients treated with mibefradil and 65% of those receiving amlodipine. The tolerability profile of mibefradil was superior to that of amlodipine, with significantly fewer patients (P = 0.009) reporting leg edema after mibefradil treatment (7%) than after amlodipine treatment (17%). The results of

		this study confirm those of the previous trial. Once-daily treatment with mibefradil 50 to 100 mg for 12 weeks was as effective as 12 weeks of once-daily treatment with amlodipine 5 to 10 mg in reducing SDBP and was associated with a significantly lower incidence of leg edema.
5	Angiotensin Receptor Blocker Combined With Calcium Antagonist Evaluation of Safety and Lowering of Systolic Blood Pressure Study. 2018 [47]	*Aim.*This study is looking to evaluate which drug combination, olmesartan/amlodipine or perindopril/amlodipine, is better at lowering blood pressure in people with mild to moderate hypertension. The investigators will be enrolling people who are either currently taking medication to lower their blood pressure or who have been recently diagnosed with high blood pressure and are not yet on medication. Patients on medication for their blood pressure will be asked to stop taking this medication for 2 to 4 weeks. If their blood pressure is suitable (not too high or low) they will be randomised to one of their treatment arm: *Results.*Seven RCTs were included and had sample sizes ranging from 185 to 1,183 subjects (total: 3,909 subjects). The pooled analysis showed that the on-target rate of hypertension treatment was significantly higher in the amlodipine + ARB group than in the amlodipine monotherapy group (RR =1.59; 95% CI, 1.31–1.91; P<0.01). The response rate of systolic blood pressure (SBP) (RR =1.28; 95% CI, 1.04–1.58; P<0.01) and diastolic blood

		pressure (DBP) (RR =1.27; 95% CI, 1.12–1.44; P=0.04) were significantly higher in the amlodipine + ARB group than in the amlodipine monotherapy group. The change in SBP (RR =−3.56; 95% CI, −7.76–0.63; P=0.10) and DBP (RR =−3.03; 95% CI, −6.51–0.45; P=0.09) were higher in hypertensive patients receiving amlodipine + ARB but the difference did not reach statistical significance. ARB + amlodipine treatment carried a lower risk of adverse events relative to amlodipine monotherapy (RR =0.88; 95% CI, 0.80-0.96; P<0.01).
6	Comparative effects of felodipine ER, amlodi-pine and nifedipine GITS on 24 h blood pressure control and trough to peak ratios in mild to moderate ambulatory hypertension: a forced titration study. 1998 []	*Aim:* To evaluate the 24 h antihypertensive efficacy and duration of action of felodipine extended release (ER) in comparison with two other long acting dihydropyridine calcium antagonists, amlodipine and nifedipine gastrointestinal therapeutic system (GITS), in patients with mild to moderate essential hypertension substantiated by ambulatory blood pressure (BP) monitoring. Design: Randomized, forced titration, parallel group study. Clinic BP was measured at every patient's visit, and 24 h ambulatory BP was monitored at baseline and at the end of each dose-titration period. Setting: Single centre: hypertension research unit in Quebec City, Quebec. Patients: There were 89 patients enrolled into the study. Eighty-four eligible patients were randomized, and 83 completed the

		study and were included in the final efficacy analysis. *Interventions:* Following a two-to four-week washout period (baseline), patients were randomly allocated to receive felodipine ER 5 mg, amlodipine 5 mg or nifedipine GITS 30 mg for four weeks (low dose). All study patients had their daily dose doubled to felodipine ER 10 mg, amlodipine 10 mg or nifedipine GITS 60 mg for a further four weeks (high dose). *Main results:* Significant ($P < 0.001$) and similar changes from baseline in clinic BP were observed in all treatment groups for low and high doses. Ambulatory BP profiles showed comparable blood pressure reductions with felodipine ER and amlodipine, and a trend towards a lesser reduction with nifedipine GITS during 24 h, daytime and night-time periods. BP loads were similarly reduced with the three treatments. Trough to peak ratios (T:Ps) were calculated from 24 h ambulatory BP curves according to two different approaches: for diastolic and systolic BP, respectively, the global approach produced T:Ps of 0.49 and 0.50 with felodipine ER 5 mg; 0.50 and 0.34 with felodipine ER 10 mg; 0.70 and 0.60 with amlodipine 5 mg; 0.88 and 0.82 with amlodipine 10 mg; 0.65 and 0.55 with nifedipine GITS 30 mg; 0.68 and 0.53 with nifedipine GITS 60 mg. T:Ps in the individual approach were 0.07 and 0.10 with felodipine ER 5

		mg; 0.23 and 0.31 with felodipine ER 10 mg; 0.22 and 0.31 with amlodipine 5 mg; 0.45 and 0.58 with amlodipine 10 mg; 0.27 and 0.31 with nifedipine GITS 30 mg; and 0.24 and 0.40 with nifedipine GITS 60 mg. *Conclusion:* There was no evidence in this study of a difference among felodipine ER, amlodipine and nifedipine GITS in lowering ambulatory or clinic BP. Treatment based on ambulatory BP may be preferable to treatment guided by T:Ps because ambulatory BP is firmly established as a predictor of cardiovascular risk. Furthermore, there is no consensus on how to calculate T:Ps, and different methods of calculation may give divergent results.
7	Lercanidipine : a review of its efficacy in the management of hypertension. 2003 [49]	Lercanidipine (Zanidip) is a vasoselective dihydropyridine calcium channel antagonist that causes systemic vasodilation by blocking the influx of calcium ions through L-type calcium channels in cell membranes. It is a highly lipophilic drug that exhibits a slower onset and longer duration of action than other calcium channel antagonists. Furthermore, lercanidipine may have antiatherogenic activity unrelated to its antihypertensive effect. In two large, nonblind, noncomparative studies involving approximately 16 000 patients with mild-to-moderate hypertension, systolic blood pressure (BP) and diastolic BP (DBP) were significantly reduced after 12 weeks' treatment with lercanidipine 10-20 mg/day.

		Furthermore, in the largest study, 64% of patients were responders (DBP <90 mm Hg) after 12 weeks of treatment and an additional 32% had their BP normalised (BP <140/90 mm Hg). In comparative trials, lercanidipine 10-20 mg/day was as effective as nifedipine slow release (SR) 20-40 mg twice daily, amlodipine 10 mg/day, felodipine 10-20 mg/day, nifedipine gastrointestinal therapeutic system (GITS) 30-60 mg once daily or verapamil SR 240 mg/day at reducing SBP and DBP in patients with mild-to-moderate hypertension after 2-16 weeks of therapy. In addition, 4 weeks of lercanidipine therapy (10 mg/day) was as effective as captopril 25mg twice daily, atenolol 50 mg/day or hydrochlorothiazide 12.5 mg/day. Lercanidipine 5-30 mg/day effectively decreased BP in elderly patients (aged >60 years) with mild-to-moderate hypertension or isolated systolic hypertension to the same extent as amlodipine 5-10 mg/day, nifedipine GITS 30-60 mg/day or lacidipine 2-4 mg/day after 24-26 weeks of therapy. In addition, a limited number of studies suggest that lercanidipine may have antihypertensive efficacy in patients with severe or resistant hypertension, in hypertensive patients with type 2 diabetes mellitus and in postmenopausal women with mild-to-moderate essential hypertension. Lercanidipine is well tolerated, with most treatment-emergent events related to vasodilation. Common adverse events

		included headache, flushing and peripheral oedema. Importantly, the incidence of vasodilatory oedema was significantly lower in patients receiving lercanidipine than in those receiving some other calcium channel antagonists.
8	Synthesis of Dihydro-pyrimidines: Isosteres of Nifedipine and Evalu-ation of Their Calcium Channel Blocking Efficiency. 2023 [50]	Hypertension and cardiovascular diseases related to it remain the leading medical challenges globally. Several drugs have been synthesized and commercialized to manage hypertension. Some of these drugs have a dihydropyrimidine skeleton structure, act as efficient calcium channel blockers, and affect the calcium ions' intake in vascular smooth muscle, hence managing hypertension. The synthesis of such moieties is crucial, and documenting their structure-activity relationship, their evolved and advanced synthetic procedures, and future opportunities in this area is currently a priority. Tremendous efforts have been made after the discovery of the Biginelli condensation reaction in the synthesis of dihydropyrimidines. From the specific selection of Biginelli adducts to the variation in the formed intermediates to achieve target compounds containing heterocylic rings, aldehydes, a variety of ketones, halogens, and many other desired functionalities, extensive studies have been carried out. Several substitutions at the C3, C4, and C5 positions of dihydropyrimidines have been explored, aiming to produce feasible derivatives with acceptable yields as well as

		antihypertensive activity. The current review aims to cover this requirement in detail.
9	Anti-hypertensive efficacy of amlodipine dosing during morning versus evening: A meta-analysis. 2019 [51]	A meta-analysis was performed to compare the antihypertensive efficacy of morning and evening dosing. Database of Pubmed, Embase, Cochrane, Web of Science CNKI, VIP, and Wanfang were searched up to December 2018. A total of 19 randomized control trials and 1215 participants were included in this meta-analysis. Administration time of amlodipine did not affect the office blood pressure (RR = -0.03, 95% CI -0.93-0.88, P = 0.96), daytime blood pressure (RR = -0.30, 95% CI -1.05-0.46, P = 0.44), 24 h mean blood pressure (RR = 1.15, 95% CI -0.39-2.70, P = 0.14), or heart rate (RR = 0.11, 95% CI -1.22-1.45, P = 0.87). Administration of amlodipine in the evening could significantly reduce the nighttime blood pressure (RR = 2.04, 95% CI 1.27-2.81, P < 0.00001), increased non-dipper alteration (RR = 0.51, 95% CI 0.41-0.63, P < 0.00001), and contained better anti-hypertension efficacy (RR = 0.64, 95% CI 0.55-0.74, P < 0.00001). For patients with hypertension, especially for non-dipper hypertension, taking amlodipine in the evening will be more beneficial. Better quality trials conducted in different regions and with larger sample size are necessary to verify the conclusion of this study.
10	Benefits and safety of long-acting calcium	Calcium antagonists have been used in patients with cardiovascular diseases for about 2 decades.

	antagonists in coronary artery disease: the Action Trial. 2005 [52]	As a class, they are among the most widely used drugs for treatment of cardiovascular conditions. Numerous randomized placebo-controlled studies have demonstrated the value of these agents for relieving symptoms in patients with angina, an action generally associated with increased exercise tolerance in formal exercise testing. However, data accumulated from clinical trials conducted over the last decade have raised concerns as to whether some or all of the calcium antagonists increase morbidity (eg, worsen unstable angina, increase heart failure, or increase the risk of infarction[3]) and mortality. These data on the potential adverse effects of calcium antagonists have been obtained from patients who have a variety of clinical manifestations of coronary artery disease, including stable angina pectoris, unstable angina, and acute myocardial infarction (MI), during long-term use after MI, and heart failure. Unfavorable effects of calcium antagonists also have been seen in several previous trials of MI and unstable angina patients; in particular, agents of the dihydropyridine class have been associated with an increased risk of death and nonfatal MI. In this issue of *Circulation*, Furberg et al demonstrate increasing mortality with increasing doses of nifedipine (an adverse dose-response relation). This provides further evidence that the excess mortality with nifedipine is likely to be causal. Trends toward

		increased cardiovascular morbidity or mortality also have been observed with other dihydropyridines, such as nicardipine or isradipine, albeit only small or moderate-sized studies are available. If a calcium antagonist is used, it would be prudent to use a nondihydropyridine agent such as diltiazem or verapamil. If a patient with angina also has CHF or poor left ventricular function, amlodipine may be a relatively safe alternative. Although the long-acting preparation may have some theoretical advantages, there is no good evidence of a reduction in major vascular events to support their use. Widespread use of calcium antagonists should await the results of the ongoing trials. In patients with hypertension, diuretics or β-blockers initially should be considered the drugs of choice. Such a position is consistent with the guidelines of the Fifth Joint National Committee and the Canadian Hypertension Society. In such circumstances, diltiazem or verapamil may be preferred over a dihydropyridine calcium antagonist. Large trials currently are under way that compare the new calcium antagonists with diuretics. Until such trials demonstrate the clear superiority of calcium antagonists, diuretics should remain the first line of therapy in hypertension.

Thus, according to the data of 10 systematic reviews, it was established that CA are effective and safe drugs for the treatment of cardiovascular diseases. They are

especially effective in the elderly with isolated systolic hypertension, a combination of hypertension and IHD (tension angina, vasospastic angina), hypertrophy of the left ventricle, and damage to peripheral arteries. The most common side effects of CA are leg swelling and reflex tachyarrhythmia. One of the ways to minimize the side effects of amlodipine is to use its S-enantiomer. To achieve the optimal therapeutic effect of S-amlodipine, doses of the drug are two times smaller, which leads to fewer side effects. The longer effect of S-amlodipine compared to racemate amlodipine due to its longer half-life also helps to reduce the likelihood of reflex tachycardia. That is, S-amlodipine is a safer and longer-acting alternative to the racemate. The use of isolated S-amlodipine instead of the racemic mixture has many advantages because the required dose and side effects can be reduced [51]. Another way to improve the effectiveness and safety of CA is the use of modern drugs of the latest generation. So, for example, one of the most effective antihypertensive agents in the treatment of hypertension is felodipine [42]. Its pharmacodynamics is characterized by a highly selective effect on precapillary resistance vessels, and the effect on vascular tissue is one hundred times stronger than on the myocardium. An important place in the therapy of hypertension is occupied by the 3rd generation dihydropyridine derivative lercanidipine, which has a unique pharmacokinetics, is characterized by high lipophilicity and maximum vascular selectivity. It has been proven that lercanidipine also exhibits nephroprotective properties [49], since, unlike other CA, the drug expands not only afferent but also efferent arterioles. Lercanidipine has high hypotensive activity in patients with chronic renal failure.

The next direction of increasing the safety of CA is complex pharmacotherapy. The use of combined drugs, which include components with different mechanisms of action, pharmacokinetics and pharmacodynamics, is one of the promising directions for the prevention of various complications in patients with hypertension [53, 54]. So, for example, in the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm) study, the combination of amlodipine and perindopril proved to be particularly effective in patients with IHD in combination with hypertension. In addition, both drugs are metabolically neutral. The effect of the

combination on central aortic pressure indicates its particular effectiveness in situations with increased pulse pressure, for example, in the elderly. Also popular is the combination of calcium antagonists with diuretics (for example, with hydrochlorothiazide, indapamide), which allows not only to avoid leg swelling, but also potentiates the antihypertensive effect of CA.

Conclusions for chapter 3

1. In the pharmaceutical market of Ukraine, 9 international non-proprietary names of calcium antagonists are registered, of which 7 INNs are dihydropyridine derivatives, 1 each is phenylalkylamine and benzothiazepine derivatives. There are 65 trade names of calcium channel blockers on the Ukrainian market. 59 of them are dihydropyridine derivatives. In terms of the number of trade names, amlodipine drugs prevail - 38.
2. The obtained results showed that during 2017-2021, 195 notification cards with cases of adverse reactions to calcium antagonists were received from health care institutions of the Kharkiv region and the city of Kharkiv.
3. Analysis of cards-notifications with cases of adverse reactions for 5 years showed that the majority of adverse reactions in the form of leg edemasg, redness and rash on the skin, itching, tachyarrhythmias, nausea, diarrhea, constipation develop when using Amlodipine-KV, Amlodipine-Farmak and Amlodipine-Astrapharm. These adverse reactions did not require additional hospitalization and did not cause disability of the patients.
4. According to the data of 10 systematic reviews, it was established that calcium antagonists are effective and safe drugs for the treatment of cardiovascular diseases.
5. Three main directions for reducing the side effects of calcium antagonists have been established, such as the use of S-amlodipine, the choice of felodipine or lercanidipine, and the combination of calcium antagonists with ACE inhibitors and diuretics.

CONCLUSIONS

1. It was established that there are 65 trade names of calcium channel blockers on the Ukrainian market. 59 of them are dihydropyridine derivatives. Amlodipine drugs predominate in terms of the number of trade names (38).
2. Analysis of cards-notifications with cases of adverse reactions for 5 years showed that the majority of side effects in the form of edemas of the legs, redness and rash on the skin, itching, tachyarrhythmias, nausea, diarrhea, constipation develop when using Amlodipine-KV, Amlodipine-Farmak and Amlodipine-Astrafarm. These adverse reactions did not require additional hospitalization and did not cause disability of the patients.
3. Based on the data of 10 systematic reviews, it was established that calcium antagonists are effective and safe drugs for the treatment of cardiovascular diseases.
4. Three main directions for increasing the safety level of calcium antagonists have been established. The first is associated with the use of the S-enantiomer of amlodipine - S-amlodipine. This allows you to reduce the dose of the drug by two times, which leads to fewer side effects. The longer effect of S-amlodipine compared to amlodipine-racemate also helps to reduce the likelihood of reflex tachycardia.
5. 5. The second direction of improving the effectiveness and safety of calcium antagonists is the use of modern drugs of the latest generation, such as felodipine or lercanidipine, which are the most effective drugs, active in smaller doses, and also have additional pharmacological properties.
6. A promising direction of optimizing the use of calcium antagonists is also their combination with antihypertensive drugs of other pharmacological groups. This allows you to reduce the dosage of drugs and reduce or prevent their side effects. The most effective is the complex use of calcium antagonists with ACE inhibitors or thiazide/thiazide-like diuretics.

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APPLICATIONS

APPLICATION A

ANALYSIS OF THE RANGE OF CALCIUM ANTAGONISTS ON THE PHARMACEUTICAL MARKET OF UKRAINE

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Introduction. Arterial hypertension (AH) is one of the most common diseases. More than 1.5 billion people worldwide suffer from this disease. Arterial hypertension is a risk for the appearance in patients of coronary disease, myocardial infarction, development of heart failure, disorders of blood circulation in the brain. 50% of all mortality from cardiovascular diseases is caused by arterial hypertension.

The generally accepted point of view regarding hypertension is the recognition of the central role of calcium ions, the level of which in vascular smooth muscles increases significantly in this disease. This not only directly affects electromechanical coupling in these muscles, but also damages other cell membrane transport systems. One of the achievements of pharmacology and cardiology is the introduction into clinical practice in the 80s of the last century of calcium antagonists, which became the first choice in the treatment of hypertension.

Aim of the study: analyze the range of calcium antagonists registered in Ukraine as of March 2023.

Materials and methods. To analyze the assortment of calcium channel blockers registered in Ukraine, as of March 2023, the state register of medicinal products of Ukraine was used.

Results and discussion. The obtained results showed that the studied drugs registered in Ukraine according to the ATC classification belong to group C08 Calcium antagonists. As of March 2023, 9 international non-proprietary names (INNs) of calcium antagonists were registered on the pharmaceutical market of Ukraine, of which 7 INNs are dihydropyridine derivatives, 1 each is phenylalkylamine and benzothiazepine derivatives. There are 65 trade names of calcium channel blockers on the Ukrainian market. 59 of them are dihydropyridine derivatives. By the number of trade names, amlodipine drugs prevail – 38. 8 nifedipine drugs, lercanidipine – 6, nimodipine – 5, nitrendipine – 1, felodipine – 1 are registered. 4 verapamil trade names are registered, 2 - diltiazem. Among the registered calcium antagonists, 61.5% are drugs of Ukranian manufacturers, 38.5% are foreign drugs. The drugs are presented on the market in the form of 4 dosage forms: tablets, capsules, oral drops, solution for injections.

Conclusions. The range of calcium channel blockers on the modern pharmaceutical market of Ukraine is quite wide. Dihydropyridine derivatives predominate, namely, amlodipine drugs, predominate among the registered medicines of this group. However, there are only 6 drugs of phenylalkylamine and benzothiazepine derivatives. Tablets (tablets, coated tablets, prolonged-release tablets, modified-release tablets) are the most common medicinal form of calcium antagonists. Other medicinal forms are available only in certain drugs.

APPLICATION B

КЛІНІЧНА ФАРМАЦІЯ В УКРАЇНІ ТА СВІТІ

2023

Міністерство охорони здоров'я України
Національний фармацевтичний університет
Кафедра клінічної фармакології
та клінічної фармації

The Ministry of HealthCare of Ukraine
National University of Pharmacy
Department of Clinical Pharmacology
and Clinical Pharmacy

СЕРТИФІКАТ
CERTIFICATE

№ 341

Цим засвідчується, що

This is to certify that

Zhudat Ikram

брав(ла) участь у роботі Всеукраїнської науково-практичної Internet-конференції з міжнародною участю **"Клінічна фармація в Україні та світі"**, присвяченої 30-річчю заснування кафедри клінічної фармакології та клінічної фармації Національного фармацевтичного університету

16-17 березня 2023 р., м. Харків

participated in the All-Ukrainian scientific and practical Internet-conference with international participation **"Clinical pharmacy in Ukraine and the World"**, dedicated to the 30th anniversary of the Department of Clinical Pharmacology and Clinical Pharmacy of the National University of Pharmacy founding

March 16-17, 2023, Kharkiv

В.о. ректора НФаУ, проф. **Алла КОТВІЦЬКА**

Проректор з науково-педагогічної роботи НФаУ, проф. **Інна ВЛАДИМИРОВА**

Завідувачка кафедри клінічної фармакології та клінічної фармації, проф. **Катерина ЗУПАНЕЦЬ**

APPLICATION C

Shchokina K.G., Joudat Ikram, Belik H.V.

National University of Pharmacy, Kharkiv

Analysis of side effects of calcium antagonists and determination of ways to minimize them

Introduction. Diseases of the cardiovascular system, such as arterial hypertension, coronary heart disease, tachyarrhythmias, occupy a leading place in the structure of morbidity. Therefore, optimization of therapy for cardiovascular diseases is one of the urgent problems of medicine and pharmacology. Calcium antagonists (CA) are one of the first choice drug groups for the treatment of diseases of the cardiovascular system. However, we must not forget that any drug has not only pharmacological, but also side effects. The problem of side effects of drugs today is very important. In this regard, the analysis of the side effects of calcium antagonists and the search for ways to minimize them are relevant.

Aim of the study. To analyze the side effects of CA in Kharkiv and Kharkiv region for the period 2017-2021 and to provide recommendations for their reduction, an analysis of the evidence base and clinical effectiveness of CA.

Materials and methods. We conduct an analysis of side effects of calcium channel blockers in Kharkiv and Kharkiv region for the period 2017-2021. Based on the analysis of the evidence base of clinical effectiveness, we determined the conditions of rational use and ways to minimize the side effects of CA. We used methodы of passive pharmacovigilance, method of spontaneous reports, method of system approach and system analysis in our work. To analyze the clinical effectiveness and conditions of rational use of CA, well-known databases were used: Cochrane Library, Trip Database, and PubMed. These databases contain systematized primary or secondary information on a specific clinical issue: the effectiveness and safety of various medical technologies.

Results. Analysis of cards-notifications with cases of adverse reactions for 5 years showed that the majority of side effects in the form of edemas of the legs, redness and rash on the skin, itching, tachyarrhythmias, nausea, diarrhea, constipation

develop when using Amlodipine-KV, Amlodipine-Farmak and Amlodipine-Astrafarm. These adverse reactions did not require additional hospitalization and did not cause disability of the patients.

Thus, according to the data of 10 systematic reviews, the most common side effects of CA are leg swelling and reflex tachyarrhythmia. One of the ways to minimize the side effects of amlodipine is to use its S-enantiomer. To achieve the optimal therapeutic effect of S-amlodipine, doses of the drug are two times smaller, which leads to fewer side effects. The use of isolated S-amlodipine instead of the racemic mixture has many advantages because the required dose and side effects can be reduced. Another way to improve the effectiveness and safety of CA is the use of modern drugs of the latest generation. So, for example, felodipine one of the most effective antihypertensive agents in the treatment of hypertension. Its pharmacodynamics is characterize is d by a highly selective effect on precapillary resistance vessels, and the effect on vascular tissue is one hundred times stronger than on the myocardium. An important place in the therapy of hypertension is occupied by the 3rd generation dihydropyridine derivative lercanidipine, which has a unique pharmacokinetics, is characterized by high lipophilicity and maximum vascular selectivity. The next direction of increasing the safety of CA is complex pharmacotherapy. The use of combined drugs, which include components with different mechanisms of action, pharmacokinetics and pharmacodynamics, is one of the promising directions for the prevention of various complications in patients with hypertension.

Conclusions. Thus, the most common side effects of CA are leg swelling and reflex tachyarrhythmia. Three main directions for increasing the level of safety of CA have been established. The first is related to the use of stereoisomers. The second direction is the use of drugs of the latest generation. A promising direction is also CA combination with antihypertensive drugs of other pharmacological groups. The results of the obtained studies can be used by practicing doctors and health care organizers to optimize the pharmacotherapy of cardiovascular diseases.

APPLICATION D

Національний фармацевтичний університет

Кафедра управління та забезпечення якості у фармації

СЕРТИФІКАТ № 50

Жудат Ікрам

учасника І Науково-практичної internet-конференції з міжнародною участю «Актуальні проблеми якості, менеджменту і економіки у фармації і охороні здоров'я»

19 травня 2023 року, м. Харків

Оргкомітет засвідчує, що отримувач (ка) прийняв (ла) активну участь в обговоренні актуальних питань за темою конференції (обсяг 15 годин – 0,5 кредита ECTS) і набув (ла) відповідних компетентностей:

- **здатність опанувати сучасні підходи управління якістю та соціально-економічними процесами в закладах охорони здоров'я та фармацевтичних організаціях;**
- **здатність діяти на основі етичних міркувань та мотивів;**
- **здатність до саморозвитку, навчання впродовж життя та ефективного самоменеджменту.**

В.о. Ректора Національного фармацевтичного університету **Алла КОТВІЦЬКА**

Ф А 2.2.1-32-366

National University of Pharmacy

Faculty for foreign citizens' education
Department of Pharmacology and Pharmacotherapy
Level of higher education master
Specialty 226 Pharmacy, industrial pharmacy
Educational program Pharmacy

APPROVED
The Head of Department
of Pharmacology and
Pharmacotherapy

_____
Sergey SHTRYGOL'
«21» of September 2022

ASSIGNMENT

FOR QUALIFICATION WORK
OF AN APPLICANT FOR HIGHER EDUCATION

Ikram JOUDAT

1. Topic of qualification work: «Analysis of side effects of calcium antagonists and determination of ways to minimize them», supervisor of qualification work: Kateryna SHCHOKINA, doctor of Pharmacy, prof.

approved by order of NUPh from "06" of February_2023 № 35

2. Deadline for submission of qualification work by the applicant for higher education: september 2022.

3. Outgoing data for qualification work: The qualification work is devoted to the analysis of the side effects of calcium channel blockers, the analysis of the assortment on the pharmaceutical market of Ukraine, the analysis of the evidence base and the clinical efficacy of calcium antagonists. The work consists of an introduction, the main part (literature review, materials and methods, own research), conclusions, a list of literature sources).

4. Contents of the settlement and explanatory note (list of questions that need to be developed):
The master thesis analyzes of domestic and foreign literature sources on this topic; theoretical substantiation of the relevance and expediency of optimization of pharmacotherapy of cardiovascular diseases, analyzes the number of reports of adverse reactions and monitors adverse reactions of calcium antagonists for 2017-2021 and analyzes the evidence base for the clinical efficacy of drugs.

5. List of graphic material (with exact indication of the required drawings):
tables – 6

6. Consultants of chapters of qualification work

Chapters	Name, SURNAME, position of consultant	Signature, date	
		assignment was issued	assignment was received
1	Kateryna SHCHOKINA, professor of higher education institution of pharmacology and clinical pharmacotherapy department	Kateryna SHCHOKINA, 21.09.2022	Ikram JOUDAT, 21.09.2022
2	Kateryna SHCHOKINA, professor of higher education institution of pharmacology and clinical pharmacotherapy department	Kateryna SHCHOKINA, 21.09.2022	Ikram JOUDAT, 21.09.2022
3	Kateryna SHCHOKINA, professor of higher education institution of pharmacology and clinical pharmacotherapy department	Kateryna SHCHOKINA, 21.09.2022	Ikram JOUDAT, 21.09.2022
4	Kateryna SHCHOKINA, professor of higher education institution of pharmacology and clinical pharmacotherapy department	Kateryna SHCHOKINA, 21.09.2022	Ikram JOUDAT, 21.09.2022

7. Date of issue of the assignment: "21" of September 2022

CALENDAR PLAN

№ з/п	Name of stages of qualification work	Deadline for the stages of qualification work	Notes
1.	Conducting a literature review on the issues of the work.	December 2022	**done**
2.	Conducting of studies	January-February 2023	**done**
3.	Writing and preparation of the manuscript of the qualification work	March-April 2023	**done**
4.	Submitting the final version of the work to the academic supervisor and receiving feedback from him	April 2023	**done**
5.	Registration of the work and accompanying documents and submission to the Examination Committee of the NUPh.	April 2023	**done**

An applicant of higher education _____ Ikram JOUDAT

Supervisor of qualification work _____ Kateryna SHCHOKINA

ВИТЯГ З НАКАЗУ № 35
По Національному фармацевтичному університету
від 06 лютого 2023 року

нижченаведеним студентам 5-го курсу 2022-2023 навчального року, навчання за освітнім ступенем «магістр», галузь знань 22 охорона здоров'я, спеціальності 226 – фармація, промислова фармація, освітня програма – фармація, денна форма здобуття освіти (термін навчання 4 роки 10 місяців та 3 роки 10 місяців), які навчаються за контрактом, затвердити теми кваліфікаційних робіт:

Прізвище студента	Тема кваліфікаційної роботи		Посада, прізвище та ініціали керівника	Рецензент кваліфікаційної роботи
• **по кафедрі фармакології та фармакотерапії**				
Жудат Ікрам	Аналіз побічних ефектів антагоністів кальцію та визначення шляхів їх мінімізації	Analysis of side effects of calcium a ntagonists and determination of wa ys to minimize them	Проф. Щокіна К.Г.	Доц. Отрішко І.А.

Підстава: подання деканату, згода ректора

Ректор

Вірно. Секретар

Ф А2.8-47-110

ВИСНОВОК

Комісії з академічної доброчесності про проведену експертизу

щодо академічного плагіату у кваліфікаційній роботі

здобувача вищої освіти

№ 112576 від « 25 » квітня 2023 р.

Проаналізувавши випускну кваліфікаційну роботу за магістерським рівнем здобувача вищої освіти денної форми навчання Жудат Ікрам, 5 курсу, _____ групи, спеціальності 226 Фармація, промислова фармація, на тему: «Аналіз побічних ефектів антагоністів кальцію та визначення шляхів їх мінімізації / Analysis of side effects of calcium antagonists and determination of ways to minimize them», Комісія з академічної доброчесності дійшла висновку, що робота, представлена до Екзаменаційної комісії для захисту, виконана самостійно і не містить елементів академічного плагіату (компіляції).

Голова комісії,

професор **Інна ВЛАДИМИРОВА**

2%

31%

Ф А 2.2.1-32-353

REVIEW

of scientific supervisor for the qualification work of the master's level of higher education of the specialty 226 Pharmacy, industrial pharmacy

Ikram JOUDAT

on the topic: «Analysis of side effects of calcium antagonists and determination of ways to minimize them»

Relevance of the topic. Cardiovascular diseases are the main cause of death worldwide. Today, Arterial hypertension, ischemic heart disease, tachyarrhythmias, and cerebrovascular disorders account for 16% of all deaths in the world. Blockers of slow calcium channels are one of the groups of drugs of first choice for the treatment of arterial hypertension, ischemic heart disease and tachyarrhythmias. Calcium antagonists have a broad range of pharmacological effects, have been used in therapeutic practice for a long time and are well known to practical doctors.

On the other hand, the development of side effects of drug is one of the most serious medical problems. The relevance of this problem is proven by numerous statistical data obtained in different countries of the world. Side effects are an integral part of the spectrum of pharmacological action of any, even the most selective drug. Prevention of side effects of drugs is one of the most important tasks of practical medicine, which allows improving the quality of medical care for the population.

In this regard, it is important to monitor the side effects of calcium channel blockers and find ways to minimize them. Master student of the department Ikram Joudat in the qualification work analyzed the side effects of calcium antagonists in Kharkiv and the Kharkiv region for the period 2017-2021 and provide recommendations for their reduction, conduct an analysis of the assortment on the pharmaceutical market of Ukraine, analyzed of the evidence base and clinical effectiveness of calcium antagonists.

Practical value of conclusions, recommendations, and their validity. The conclusions and recommendations formulated in the qualifying work correspond to

the objectives of the study. The results of the obtained studies can be used by practicing doctors and health care organizers to optimize the pharmacotherapy of cardiovascular diseases. The results of the research are covered by the author in 1 theses of the scientific and practical conference.

General conclusion and recommendations on admission to defend. The work is performed in full, designed in accordance with the current requirements for the qualification works at the National University of Pharmacy, and can be recommended for submission to the SEC for further defense.

Scientific supervisor _____ Kateryna SHCHOKINA

«3» of April 2023

Ф А 2.2.1-32-356

REVIEW

for qualification work of the master's level of higher education, specialty 226 Pharmacy, industrial pharmacy

Ikram JOUDAT

on the topic: «Analysis of side effects of calcium antagonists and determination of ways to minimize them»

Relevance of the topic. Diseases of the cardiovascular system, such as arterial hypertension, coronary heart disease, tachyarrhythmias, occupy a leading place in the structure of morbidity. Therefore, optimization of therapy for cardiovascular diseases is one of the urgent problems of medicine and pharmacology. Calcium antagonists (CA) are one of the first choice drug groups for the treatment of diseases of the cardiovascular system. However, we must not forget that any drug has not only pharmacological, but also side effects. The problem of side effects of drugs today is very important. In this regard, the analysis of the side effects of calcium antagonists and the search for ways to minimize them are relevant.

Theoretical level of work. In the work submitted for review, the author has worked out a large amount of scientific sources on the relevant topics.

The systematization of data was carried out and the cases of adverse reactions of CA in Kharkiv and Kharkiv region for the period 2017-2021 were analyzed. An analysis of the evidence base of the clinical effectiveness of CA based on the data of international clinical guidelines, systematic reviews and clinical studies was carried out. Three main directions for increasing the level of security have been established and the conditions for the rational use of CA have been determined.

The results obtained made it possible to determine the conditions for the rational use of calcium antagonists in the treatment of cardiovascular diseases. The conclusions made by the author and the provisions of the qualification work are based on a sufficient number of studies.

Author's suggestions on the research topic. Based on the results obtained, the author determined the main directions for minimizing the side effects of calcium channel blockers.

Practical value of conclusions, recommendations, and their validity. The conclusions and practical recommendations proposed by the applicant are based on sufficient data obtained in the course of the conducted research, thorough analysis, and generalization of results. The results obtained can be used by pharmacists and physicians to optimize the pharmacotherapy of cardiovascular diseases.

Disadvantages of work. No significant shortcomings were identified in the work, however, it can be noted: individual grammatical, stylistic, and technical errors; Some tables are too large and it would be more expedient to place them in applications. These do not fundamentally change the assessment of the work and do not reduce its scientific and practical significance.

General conclusion and assessment of the work. The work meets the requirements for qualification work in NUPh and can be recommended for defense.

Reviewer _____ assoc. prof. Inna OTRISHKO

«7» of April 2023

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ
Витяг з протоколу № 14
від 11 квітня 2023 року
м. Харків
засідання кафедри фармакології та фармакотерапії

ПРИСУТНІ: зав. каф. проф. Штриголь С.Ю., проф. Кіреєв І.В., проф. Деримедвідь Л.В, проф. Бутко Я.О., проф. Щокіна К.Г., доц. Бєлік Г.В., доц. Рябова О.О., доц. Жаботинська Н.В., доц. Куценко Т.О., доц. Таран А.В., доц. Матвійчук А.В., доц. Савохіна М.В., доц. Степанова С.І., ас. Кононенко А.В., ас. Толмачова К.С., ас. Цеменко К.В., Адлер Б.А., Чубар`ян Ю.І., Барзак Д.Т., Краснораменська О.В., Шульга Ю.М., Рубан Я.В., Суровцева Д.О., Леонова Я.І., Заворотько Д.І., Вороніна А.О., Давидов Е.М., Шостенко К.В., Дібт Шараф Еддін, Жудат Ікрам, Алауі Абдаллауі Яссін, Буррус Ахлам, Ель Хамді Мохаммед, Меллоукі Хамза, Іфтахі Яссін, Карім Ашраф, Айнау Умайма, Елбадауі Хажар, Ель Хайель Хаджар, Толбі Ель Мехді, Беналлал Зінеб, Бенсаід Мохаммед, Ел-Жамаі Сальма, Ельбахаджі Раіхана, Бензід Ясіне, Кадді Каутар.

ПОРЯДОК ДЕННИЙ:
Розгляд кваліфікаційних робіт здобувачів вищої освіти для подання робіт до Екзаменаційної комісії.

СЛУХАЛИ:
Здобувача вищої освіти Жудат Ікрам зі звітом про проведену наукову діяльність за темою кваліфікаційної роботи: «Аналіз побічних ефектів антагоністів кальцію та визначення шляхів їх мінімізації».

УХВАЛИЛИ:
Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Жудат Ікрам допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувач кафедри фармакології
та фармакотерапії, проф. _____ Штриголь С.Ю.
Секретар кафедри фармакології
та фармакотерапії, ас. _____ Кононенко А.В.

Ф А2.2.1-32-042

НАЦІОНАЛЬНИЙ ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

ПОДАННЯ
ГОЛОВІ ЕКЗАМЕНАЦІЙНОЇ КОМІСІЇ
ЩОДО ЗАХИСТУ КВАЛІФІКАЦІЙНОЇ РОБОТИ

Направляється здобувач вищої освіти Ікрам ЖУДАТ до захисту кваліфікаційної роботи за галуззю знань 22 Охорона здоров'я
спеціальністю 226 Фармація, промислова фармація
освітньою програмою Фармація
на тему: «Аналіз побічних ефектів антагоністів кальцію та визначення шляхів їх мінімізації».

Кваліфікаційна робота і рецензія додаються.

Декан факультету _____ / Світлана КАЛАЙЧЕВА /

Висновок керівника кваліфікаційної роботи

Здобувач вищої освіти Ікрам ЖУДАТ виконала весь необхідний обсяг робіт. Магістерська робота може бути рекомендована до подачі в ЕК НФаУ для подальшого захисту кваліфікаційної роботи.

Керівник кваліфікаційної роботи

_____ Катерина ЩОКІНА

« 3 » квітня 2023 року

Висновок кафедри про кваліфікаційну роботу

Кваліфікаційну роботу розглянуто. Здобувач вищої освіти Ікрам ЖУДАТ допускається до захисту даної кваліфікаційної роботи в Екзаменаційній комісії.

Завідувач кафедри
фармакології та фармакотерапії

_____ Сергій ШТРИГОЛЬ

«11» квітня 2023 року

Qualification work was defended

of Examination commission on

« ___ » _____ 2023

with the grade _____

Head of the State Examination commission,

DPharmSc, Professor

_____ / Oleh SHPYCHAK /