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Department of General and Clinical Pharmacology and Pharmacognosy

APPROVED

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METHODOLOGICAL RECOMMENDATIONS FOR LECTURES ON THE ACADEMIC DISCIPLINE

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LECTURE 1. TOPIC

"General principles of clinical pharmacology and pharmacotherapy (clinical pharmacodynamics, pharmacokinetics of drugs, types of pharmacotherapy)"

Topic relevance: Pharmacotherapy studies the basic principles and directions of drug therapy for individual diseases. It involves the use of scientifically sound principles of drug use, which will increase the effectiveness of treatment and reduce the risk associated with the complex use of drugs.

Purpose: training specialists who have knowledge of the main symptoms and syndromes, diagnostic methods and principles of drug therapy of the most common diseases of internal organs. Study of general information about the etiology, pathogenesis, symptoms, syndromes of human disease, types of pharmacotherapy.

Basic concepts (list of questions):

1. Subject and objectives of clinical pharmacology and pharmacotherapy. The relationship of pharmacotherapy with medical and biological and clinical disciplines.
2. Basic principles of medical ethics and deontology in medicine.
3. General information about the etiology, pathogenesis, symptoms, syndromes and course of human disease.
4. The concept of disease - acute and chronic, primary and concomitant disease, complications.
5. Methods of clinical examination of patients: a) questioning - complaints, anamnesis data (anamnesis of the disease, life); b) physical examination methods - examination, palpation, percussion, auscultation;
6. Laboratory methods of examination of patients (general analyzes, biochemical studies). Their practical significance.
7. Instrumental methods of examination of patients: electrophysiological (ECG), X-ray, endoscopic and cytological, ultrasound.
8. Methodology of diagnosis - preliminary, differential, final diagnosis.
9. Main types of pharmacotherapy: etiotropic, pathogenetic, symptomatic, replacement.
10. Medical documentation: a) outpatient patient's medical record; b) inpatient medical history; c) prescription list

Content of lecture material (lecture text)

Subject and objectives of clinical pharmacology and pharmacotherapy. Relationship of pharmacotherapy with medical and biological and clinical disciplines

The word pharmacology comes from the Greek word ρκαγθασοπ - medicine, poison; Ιου§ος - teaching or the Egyptian pharmaki - one who gives healing. This is the science of medicines used to provide medical care to patients. Medicines allow you to treat severe infectious diseases, diabetes, cardiovascular and other diseases. At the same time, inept handling, incorrect and irrational treatment can harm the patient.

The ancient Indian physician-philosopher Sushruta, who treated patients in the 6th century BC. e., wrote: “We live in a world of drugs. In the hands of a knowledgeable person, it is a drink of immortality, and in the hands of an ignorant person, a knife.” The study of pharmacology occupies a special place in the training of doctors. Pharmacology is based on knowledge of chemistry, biochemistry, anatomy, histology, physiology, microbiology, hygiene, pathological physiology, pathological anatomy and other theoretical and clinical disciplines.

Pharmacology is a science that studies the interaction of drugs with the body and includes three sections: theoretical (general), experimental and clinical. Theoretical pharmacology consists of two large sections: general and special pharmacology.

The section of special pharmacology is devoted to the study of pharmacokinetics and pharmacodynamics of individual groups of drugs. Pharmacokinetics studies the path of drugs in the body, that is, the processes of absorption, distribution in the body, transformation and excretion. Pharmacodynamics studies the localization of action, mechanism, and types of action of medicinal substances. The search for new effective medicinal products is carried out experimentally, the effect of biologically active substances (BAS) on the animal body under experimental conditions is studied. That is, it is necessary to study the physicochemical processes that occur as a result of the action of BAS (complexation, absorption, catalysis), the effect on biomembranes, receptors (molecular structures on the cell membrane). An analysis of functional changes in organs and systems that occur under the influence of medicinal products is carried out.

Applicants study the general rules for drawing up prescriptions and filling out prescription forms, their storage, the classification of medicinal products by main pharmacological groups, the main issues of pharmacokinetics and pharmacodynamics of the studied medicinal products, the principles of the use of medicinal products, their side effects and measures to prevent their development, the rules for accounting and safe storage of potent, poisonous substances and narcotic drugs, as well as prescription forms. Applicants learn to analyze the therapeutic efficacy and side effects of drugs, symptoms of overdose, methods for their prevention, understand issues of drug compatibility, navigate the classification of drugs, and use reference literature.

Clinical pharmacology studies the interaction of medicinal substances with the human body in pathological conditions. The task of clinical pharmacology is to study new and re-evaluate existing drugs, improve drug therapy, develop methods for the effective and safe use of drugs.

The main task when teaching the subject should be to train a specialist with a sufficient amount of theoretical knowledge and practical skills to conduct the most rational drug therapy for a particular patient, a specialist who owns the methodology for individual selection of effective and safe drugs based on pharmacokinetics, pharmacodynamics, possible manifestations of side effects, features of the course of the disease, the patient's age, optimal dosage forms, and the compilation of a rational combination of drugs in pharmacokinetic and pharmacodynamic terms.

Knowledge of clinical pharmacology is based on both experimental data and theoretical provisions of pharmacology and other biomedical sciences, as well as on the actual material of clinical disciplines. Teaching clinical pharmacology is most optimal on clinical therapeutic bases, taking into account the etiology of the disease, the main pathogenetic mechanisms of its formation, the clinical picture of its course, the corresponding drugs with their comparative analysis and the selection of the necessary one.

Clinical pharmacology as a subject considers the implementation of the most rational drug therapy in a particular patient, the methodology for choosing a treatment method taking into account the individual characteristics of the organism, the course and form of the disease, the presence of concomitant pathology, determines the most effective and safe drugs, as well as their combinations, based on evidence-based medicine data. The main tasks of clinical pharmacology include conducting clinical trials of pharmacological agents and developing methods for the effective and safe use of drugs. The main sections of clinical pharmacology are pharmacodynamics and pharmacokinetics.

It is well known among doctors that the action of drugs can vary greatly among different individuals. Drugs affect specific target molecules, which leads to the main and side pharmacological effects. The processes between the administration of the drug and the development of these effects can be divided into two 7 important components, each of which is responsible for the variability of the drug action.

The totality of the effects of a pharmacological agent and its mechanism of action are referred to as pharmacodynamic processes. These properties of drugs determine the group to

which the drug belongs and often play an important role in determining whether this group is an adequate therapy for a particular symptom or disease. Pharmacokinetic processes determine the effect of the organism on the drug and include the release of the drug from the dosage form, absorption, distribution, biotransformation and excretion.

In addition, clinical pharmacology studies side effects, features of the action of drugs depending on various conditions (age, disease, pregnancy), drug interactions when used together, the influence of food and pharmacological effects, etc. A relatively new section of clinical pharmacology is pharmacogenetics, the subject of which is the determination of the genetic basis of the organism's reaction to a drug.

As a result of studying the academic discipline, the student must: know:

- modern classifications of drugs;
- pharmacological characteristics of drugs;
- indications for the use of drugs according to knowledge of their pharmacodynamics;
- side effects when using drugs and contraindications to use;
- features of the use of drugs according to pharmacological properties;
- features of the interaction of drugs of the main groups.

The applicant acquires the skills to:

- conduct patient surveys to collect medical history and predict the possibility of complications of pharmacotherapy;
- select the necessary medications, adequate dosage form and administration regimen when prescribing to patients with major pathological syndromes;
- determine the main methods of clinical examination of patients to assess the effectiveness and safety of prescribing medications and analyze their results;
- predict the consequences of drug interactions when used in combination and have skills in prevention and correction of undesirable effects of medications;
- explain the dependence of the action of medications on the features of pharmacokinetics in patients of different ages, concomitant diseases and concomitant therapy;
- assess the benefit/risk ratio when using medications.

The term pharmacotherapy comes from the Greek word pharmacon— drug, poison, potion and терарεиа—treatment. Pharmacotherapy studies the justified use of drugs for the treatment of a specific disease, taking into account the features of its course, duration, form and stage, pathogenetic mechanisms of development, as well as concomitant diseases. The study of pharmacotherapy is closely related to toxicology (Greek toxisops—poison; lodos—science), which studies the mechanism of toxic action of drugs, symptoms of overdose, develops methods for the prevention of poisoning with drugs and other drugs, principles of treatment in cases of poisoning and complications of pharmacotherapy.

Pharmacotherapy is based on the provisions of pharmacology, medical and biological sciences and clinical disciplines. During the training, applicants master the basic methods of clinical examination of patients, general symptoms and syndromes of the most common diseases, get acquainted with the general principles of diagnosis, master scientifically based principles of pharmacotherapy, which will increase the effectiveness of treatment and reduce the risk associated with the complex use of drugs.

The goal of pharmacotherapy is to master the knowledge of applicants about the main symptoms and syndromes, diagnostic methods and principles of drug therapy of the most common diseases of internal organs. In the process of studying pharmacotherapy, applicants must master:

- basics of deontology, ethics of relations with medical personnel, patients;
- basic clinical symptoms and syndromes of the most common diseases;
- general principles of diagnosing diseases of internal organs;
- general principles of interpreting the results of a patient's examination;
- types of pharmacotherapy (etiological, pathogenetic, symptomatic, replacement);
- basic pharmacokinetic parameters of drugs, their changes in various pathologies;

 main types of drug interactions;
 main side effects when prescribing the most common drugs;
 main principles and directions of drug therapy of diseases.

The applicant acquires the skills:

o to adhere to the rules of medical ethics and deontology;

o to solve problems related to the relationship between the doctor and the patient, the patient and the doctor;

o to determine a rational treatment regimen for the patient based on the diagnosis and data on the main clinical and laboratory indicators;

o to determine the groups of drugs that are used in the treatment of a certain disease, based on the mechanism of action of the drug and the state of the body's functions;

o to determine the optimal regimen for the administration and dosage of drugs;

o to explain to patients the method and time of taking drugs or their combinations;

o to provide first aid in emergencies and acute poisonings

Basic principles of medical ethics and deontology in medicine.

The fundamental principles of medical ethics and deontology are:

1. Humane attitude towards the patient;
2. Not to participate in actions against the patient's health;
3. Providing assistance to everyone who needs it, regardless of racial, political and religious affiliation;
4. Solidarity of all doctors in respecting the dignity of people, their struggle for peace;
5. Preservation of medical/medical secrecy;
6. Participation in protecting people's lives from certain excesses that threaten them (for example, from environmental pollution);
7. Prevention of experiments on people;
8. Refraining from actions that may degrade the dignity of the medical profession

Medical ethics defines relationships in the following areas:

• medical worker - patient;
• medical worker - healthy person (relatives);
• medical worker - medical worker.

Medical ethics includes provisions on medical confidentiality, medical errors, iatrogenics, and the duties of the doctor and the patient.

Deontology is a component of medical ethics, about moral issues, it is a set of ethical norms and principles of behavior of a medical professional in the performance of their professional duties.

Medical ethics is closely related to bioethics, but these are not identical concepts. Since the science of bioethics arose through an evolutionary path in the continuation of the development of medical ethics, and covers a wider range of issues.

Medical ethics is also related to the law. But ethics and law are not identical concepts. More often, ethics implies higher standards of behavior than the law indicates.

Over the years, medical ethics has relied on the teachings of ancient times: Hippocrates, Galen, etc. To date, international documents have been adopted that establish and regulate relationships in medical ethics: the Geneva Declaration of the WMA (World Medical Association); The International Code of Medical Ethics, adopted by the General Assembly of the World Medical Association, which contains provisions according to which, if the examination or treatment requires certain knowledge that exceeds the capabilities of the doctor, he must invite other doctors with appropriate qualifications; Helsinki Declaration of Human Rights; Helsinki-Tokyo Declaration; International Declaration of Human Rights; Declaration on the Independence and Professional Freedom of the Physician, Declaration on the Rights of the Patient of the World

Medical Association.

The norm of healthy relationships between medical professionals is a caring attitude towards authority - their own and that of their colleagues. It is a fair opinion that the patient and his relatives often build their relationship to medicine on the basis of observations of relationships between medical professionals.

Approaches to ethical issues according to the World Medical Association are conventionally divided into two groups:

• rational

• irrational

Rational approaches: deontology (the study of morals and ethics, a section of ethics), virtue ethics, principledness.

Non-rational approaches: intuition, imitation, habit, feeling (desire), obedience.

General information about the etiology, pathogenesis, symptoms, syndromes and course of human disease.

Disease - a state of the body, which is characterized by functional and / or morphological changes due to the influence of certain pathogenetic factors, leads to the appearance of protective reactions. The disease is accompanied by a limitation of the body's adaptation to environmental conditions, a decrease or loss of working capacity.

Etiology - the study of the causes and conditions of the disease.

Pathogenesis – a list of processes that determine the mechanism of occurrence, course and consequences of the identified disease

A symptom is a manifestation of the disease, detected using clinical research methods and is the basis for diagnosing and/or predicting the disease

Symptoms are divided into:

subjective (the patient himself indicates them) – headache, nausea, vomiting, constipation, etc.;

objective (detected using instrumental, laboratory and other research methods) – high blood pressure, proteinuria, changes in ECG, leukocytosis, etc.

By the time of appearance, symptoms are:

early;

late;

by diagnostic value:

– nonspecific (fever, general weakness, etc.),

– specific (heart pain, epigastric pain)

– pathognomonic - are detected in a specific disease (quail rhythm - in mitral stenosis).

Syndrome - a stable set of a number of symptoms with a single pathogenesis.

Syndrome unites a group of symptoms that characterizes a particular disease (shortness of breath + pain in the heart + tachycardia + edema = heart failure syndrome).

The concept of a disease - acute and chronic, primary and concomitant disease, complications.

In medicine, a disease is called acute if it has arisen recently. Sometimes this means a short duration of the disease.

Quite often these are respiratory viral or bacterial infections (ARI, ARVI, acute pneumonia, etc.)..

The term "acute" is also included in the definition of several diseases, such as severe acute respiratory syndrome, acute leukemia, acute myocardial infarction and acute hepatitis. This allows us to distinguish diseases from their chronic forms, such as chronic leukemia, or to emphasize the sudden onset of the disease (acute myocardial infarction).

A chronic disease (also known as a chronic illness or chronic condition) is a health condition or illness that is persistent or otherwise long-lasting in its effects, or an illness that develops over time.

The term chronic is often used when the course of a disease lasts more than three months. Common chronic diseases include diabetes, dermatitis, arthritis, bronchial asthma, chronic obstructive pulmonary disease, autoimmune diseases, and genetic diseases.

In medicine, chronic diseases are distinguished from acute diseases. Acute diseases usually affect one part of the body and respond to treatment. On the other hand, chronic diseases usually affect several parts of the body, do not fully respond to treatment, and persist for a long period of time.

Chronic diseases can have periods of remission or relapse, when the disease temporarily disappears or later reappears. Remission and relapse are commonly referred to in the context of substance abuse, which some consider to fall under the category of chronic diseases.

Chronic diseases are often non-communicable, meaning they have non-communicable causes. However, some chronic diseases are caused by communicable diseases such as HIV/AIDS.

The following terminology is used, depending on the condition of the patient and the manifestations of the disease.

Peracute - very acute or severe. It means fulminant, while "acute" only sometimes means fulminant. Per acute ("very") should not be confused with pre acute ("before", the opposite of post-acute).

Recurrent - "that which happens again" - the concept is often one of several acute episodes. Recurrent can mean the same as recurrent, although relapse is usually used to describe the return of manifestations of chronic diseases that go into remission and then relapse.

Exacerbation - a pronounced manifestation of a chronic disease. The term is used for a variety of conditions, including hepatic failure, subdural hematoma, renal failure, respiratory failure, bronchitis.

Subacute - A vaguely defined condition that is not clearly acute, but rather lies between acute and chronic (e.g., subacute endocarditis or subacute sclerosing panencephalitis).

The underlying condition is considered to be a disease that, by itself or through its complications, is the cause of seeking medical attention, the cause of hospitalization, or death.

The term "comorbidity" describes two or more disorders or diseases that occur in the same person. They may occur simultaneously or one after the other. Comorbidity also refers to the interaction between diseases that can worsen the course of both. Comorbidity is a pre-existing disease that is not related to the underlying disease etiologically, pathogenetically, and that has a different nomenclature rubric.

The main disease (the main cause of death) is a nosological form/nosological forms defined by the international classification, which by itself or through a number of complications leads to functional disorders that determine the clinical course of the disease and are the cause of death.

A combined main disease is several nosological units, each of which can lead to death

Background diseases are diseases or pathological processes that have no etiological connection with the main disease, but create conditions for its occurrence or aggravate its course. Such diseases have a direct pathogenetic connection with the main disease and play an important role in its pathogenesis.

Complications (main, secondary) – pathological processes and conditions, pathogenetically connected with the main disease (or with medical manipulations), which are not its manifestations, arising as a result of the main disease directly or due to other existing complications

They are pathogenetically connected with the main disease and arise during its course or after the main symptoms of the disease have subsided, becoming the direct cause of death.

Methods of clinical examination of patients: a) questioning – complaints, anamnesis data (anamnesis of the disease, life); b) physical examination methods – examination, palpation, percussion, auscultation.

Physical examination (also Medical examination, Clinical examination English: physicalexamination, medicalexamination, clinicalexamination; comes from Latin physician - doctor) - examination of a patient by a doctor for the presence of any medical signs or symptoms of a disease. This is the process of evaluating objective findings by using various examination methods. The information obtained must be carefully integrated with the patient's history and pathophysiology. This process is such that both the patient and the doctor understand that their interaction is diagnostic and therapeutic in nature. A carefully conducted physical examination should provide 20% of the data necessary for the diagnosis and treatment of the patient.

Diagnosis - determination of the nature of the disease and the patient's condition on the basis of his comprehensive medical examination.

Before proceeding with the diagnosis, it is necessary to:

 collect the patient's complaints;

 find out the history of the disease;

 assess the objective manifestations of the disease (examine the patient and evaluate the data of instrumental and laboratory studies)

Complaints are subjective sensations (symptoms) that disturb the patient and, in his opinion, are associated with the disease. Complaints are collected by actively questioning the patient.

The history of the disease (anamnesis - memory, history) describes its onset and development. The history of the disease is clarified by actively questioning the patient.

The history of life and allergic history are clarified by actively questioning the patient.

Examination of the patient allows you to identify objective manifestations of the disease (change in the shape of the joints, swelling, etc.).

Carrying out an adequate physical examination of the patient is extremely important in clinical practice and requires, under modern conditions, clarification of the algorithm of its clinical understanding in order to conduct successful diagnostics and study the dynamics of the clinical course of diseases. Standardization of diagnostic programs ensures understanding between doctors around the world. In such programs, the implementation of all diagnostic measures is consistently determined.

With the help of the examination, it is possible not only to form a general idea of the condition of the patient's body as a whole, but also to make the correct diagnosis "at first glance" (acromegaly, thyrotoxic goiter, etc.). Pathological signs detected during the examination of the patient provide significant assistance in collecting anamnesis and conducting further research.

In order to fully use all the possibilities of the examination, it is necessary to adhere to the rules listed below:

• lighting in which the examination is performed;

• examination technique;

• examination plan.

The examination is best performed in daylight or under fluorescent lamps. In addition to

direct lighting, which reveals the entire contour of the body and its components, it is worth using side lighting, which allows you to detect various pulsations on the surface of the body (apical impulse of the heart), respiratory movements of the chest, peristalsis of the stomach and intestines.

Examination technique: the patient, completely or sometimes partially naked, can be sequentially examined in direct and side lighting. Examination of the torso and chest is best done in an upright position, the abdomen should be examined in both a vertical and horizontal position.

A general and detailed examination are distinguished. During a general examination, attention is paid to the patient's general condition, his position, body structure, etc. A detailed (local) examination is understood as an examination of parts and areas of the body - the head, face, neck, chest, abdomen, limbs.

First, a general examination is performed, which includes:

1) the patient's general condition;
2) the patient's state of consciousness and mental state;
3) the patient's body position;
4) the patient's posture and gait;
5) body structure;
6) the state of nutrition;
7) the condition of the skin and visible mucous membranes;
8) the condition of the muscular system;
9) the condition of the bones and joints;
10) the condition of the lymph nodes.

General condition of the patient. From the very beginning of the examination, the doctor must assess the general condition of the patient. When determining the general condition, a number of the following data should be taken into account: the patient's physical activity, his behavior, consciousness, body position. The following general conditions of the patient are distinguished: 1) satisfactory, 2) moderate, 3) severe, 4) extremely severe.

State of consciousness and mental state of the patient. In addition to clear consciousness, when the patient reasonably answers all questions and is well oriented in the environment, there are various disorders of consciousness.

Stupor - a state of stupor. The patient is poorly oriented in the environment, answers questions with a delay.

Sopor, or hibernation, from which the patient emerges for a short period of time with a loud exclamation or disturbance. Reflexes are preserved.

Coma is a state of unconsciousness characterized by a complete lack of reaction to external stimuli, lack of reflexes and a disorder of vital functions. The most common comas are:

- alcoholic coma (occurs with alcohol intoxication);
- apoplexy coma (occurs with cerebral hemorrhage);
- hypoglycemic coma can occur with an overdose of insulin;
- diabetic coma (ketoacidotic, hyperlactatemic, hyperosmolar) is observed in diabetes mellitus;
- hepatic coma develops in acute hepatocellular insufficiency;
- uremic coma occurs in acute toxic lesions and in the terminal period of chronic kidney diseases;
- epileptic coma is observed in epilepsy.

From the above-mentioned disorders of consciousness, one should distinguish a state of short-term loss of consciousness caused by temporary ischemia of the brain, which is called fainting, or fainting (syncope).

During the examination, the patient's mental state can be assessed: agitation, excitement, apathy, depression. In some patients, during the development of infectious diseases (typhoid fever and typhus), pneumonia, as well as in patients with alcoholism, delusions and

hallucinations may appear.

Patient position.

The following patient positions are distinguished: active, passive and forced.

Active position - the patient easily changes his position depending on the circumstances.

Passive position is observed in the unconscious state of the patient and, less often, in cases of extreme weakness. Patients are motionless, the head and limbs hang down due to their weight.

The patient takes a forced position to stop or reduce the painful sensations he has (pain, cough, shortness of breath).

Posture and gait. Posture is the general appearance of a person in a standing position. If the patient walks, not confined to bed, during the examination, attention is paid to his posture and gait, which depend on the general condition of the patient, the development and tone of muscles, static organs, central nervous system, profession. A straight posture is characteristic of a healthy person. It is found in those patients whose general condition is satisfactory. The presence of a flabby posture, when the torso is tilted forward, the head is lowered, and the arms hang down, indicates significant physical weakness or mental depression, which may be a consequence of a certain disease. In patients with spinal lesions, the posture becomes stooped. The posture of a patient with ankylosing spondylitis (Bechterew's disease) in the late stage is very typical. There is a pronounced stoop (hunchback), a neck stretched forward (the “beggar’s pose”). In the case of a significant accumulation of free fluid in the abdominal cavity, the upper half of the patient’s body is tilted back, and the stomach protrudes forward (“proud” posture).

The gait of a healthy person is characterized by confidence, appropriate speed and rhythm; moreover, the movements of the legs, torso and arms are fully coordinated. The presence of a slow, difficult gait, when the patient moves with difficulty, slowly rearranging his legs, may indicate significant general weakness caused by the underlying disease. A patient with hemiparesis (incomplete paralysis of the muscles of one half of the body, as a result of a stroke) while walking performs a semicircular movement with the affected lower limb, without lifting the heel off the ground. In the presence of diseases of the lower limbs (dislocation, ankylosis), the patient limps, leaning on a stick. In case of damage to the hip joint or sciatic nerve, the patient protects the affected leg and while walking moves it forward by turning the entire pelvis without bending the leg in the ball joint and makes a bow-like movement with the torso. A wobbly, uncertain gait is observed during alcohol intoxication, as well as in patients with lesions of the labyrinth, cerebellum, with impaired cerebral circulation and in patients with multiple sclerosis. Spastic gait is a characteristic feature of patients who have suffered inflammation of the brain. A “duck” gait with small steps occurs in patients with softening of the bones (osteomalacia). Patients with spinal tuberculosis (tabesdorsalis) have an ataxic (disorderly) gait, caused by disorders of coordination of voluntary movements of the lower extremities. The gait of such patients is uncertain. While walking, they excessively raise their legs and throw them forward (“cock” gait). To make it easier to maintain balance, they spread their legs wide and walk with their heads down, constantly visually controlling the path under their feet. In the presence of Parkinson's syndrome, the patient's gait is stiff, the arms do not perform normal movements while walking, often half bent at the elbow joints; the patient takes the first step with some difficulty. He moves in small, fairly fast steps, and in the case of stopping and turning, significant difficulties arise. The patient's head is tilted forward, the torso is bent, there is trembling of the fingers and often the head.

The patient's body structure (habitus) includes the constitution, body weight, height, and muscle development.

Constitution - a set of functional and morphological features of the organism, formed on the basis of inherited and acquired properties that characterize its reactions to the influence of exo- and endogenous factors. According to the classification of M. V. Chernorutsky, three constitutional types are distinguished: asthenic, hypersthenic and normosthenic.

The normosthenic type is characterized by the proportional development of all parts of

the body. The skull of normostenics is elongated, the neck is of medium length, the chest is wide, the epigastric angle is almost straight, the abdomen is oval in shape, elastic, slightly protruding, the shoulders are broad, the limbs are long; thick, the palms and feet are wide, the subcutaneous tissue is moderately developed, the muscles of the body are well developed, elastic.

The asthenic type is characterized by a significant predominance of the longitudinal dimensions of the body over the transverse, of the lower extremities over the upper, of the chest over the abdomen. The skull is elongated, the face is narrow, the neck is long and thin, the chest is flat and narrow, the epigastric angle is less than 90° (acute), the abdomen is sunken, the shoulders are narrow, the pelvis is narrow, the limbs are long, thin, the fingers are long, delicate, the shoulder blades lag behind the chest, protrude like bird wings (scapulaealatae), the subcutaneous tissue is poorly developed, the skin is thin, dry, the muscles are poorly developed, flabby. Hypersthenic type is characterized by the relative superiority of the transverse dimensions of the body. The abdomen prevails over the chest, the upper limbs over the lower ones, the diaphragm stands high. Hypersthenics have a broad, rounded face, a short and thick neck, broad shoulders and pelvis, a wide, short, protruding chest, narrow intercostal spaces, a supra-abdominal angle of more than 90°, a round, large, protruding abdomen, short, thick limbs, wide palms and feet, well-developed subcutaneous tissue, often excessively, dense, elastic skin, moderately developed muscles. In general, the figure of hypersthenics is stocky.

Constitutional features should not be interpreted as those that predetermine certain diseases, that is, lead to their development. At the same time, it is known that people of the asthenic type have a tendency to lower blood pressure, splanchnoptosis (prolapse of the abdominal organs), and gastric and duodenal ulcers are more common. On the other hand, hypersthenics are more likely to have high blood pressure, obesity, gout, diabetes, atherosclerosis, and gallstone disease than normo- and asthenics.

Height. A person's height is determined using a height meter. In adult men, height ranges on average from 165 to 180 cm, and in women - from 155 to 170 cm. The body length of tall men is 173-190 cm, in women - 161 cm and higher. The average height of men is 167-172, in women - 155-160 cm. Short height for men is less than 165 cm, in women - less than 155 cm. Height for men is less than 130 cm, and in women - less than 120 cm is considered dwarfism. Height over 190 cm is considered gigantic. Excessive secretion of growth hormone (somatotropin) by the anterior pituitary gland at a young age (before and during puberty) leads to the development of gigantism, which is characterized by a proportional acceleration of the growth of all bones of the skeleton, especially the limbs, and a significant lengthening of the whole body (more than 190 cm). In the case of hypersecretion of somatotropin after the end of the period of physiological growth, people develop acromegaly, in the presence of which an increase in the superciliary arches, nasal bones, lower jaw, hands, feet, internal organs is noted. In 90% of cases, acromegaly develops in patients with pituitary adenoma, most often eosinophilic, which secretes an excessive amount of somatotropin. Abnormally high growth is also observed in the case of a decrease in the function of the gonads - hypogenitalism, or eunuchoidism. Men who have been castrated before puberty are characterized by very tall stature, long lower limbs, a wide pelvis, and underdeveloped genitalia. Castrates (eunuchs) have a small head, no Adam's apple, noticeable fat deposits on the buttocks and chest, wrinkled facial skin, and no facial hair (beard, mustache), body, pubic hair, and perineum. In women, early castration (complete removal of the ovaries) performed before puberty results in tall stature, significant development of the subcutaneous tissue, underdevelopment of the mammary glands, and secondary sexual characteristics. Dwarfism is most often observed as a result of endocrine gland dysfunction, particularly the anterior pituitary and thyroid gland. Pituitary dwarfism (pituitary nanism, pituitary microsomia), associated with insufficient secretion of somatotropin, is characterized by normal proportions of body parts ("miniature" person, midget). The skin of such dwarfs is tender and thin, the subcutaneous tissue and skeletal muscles are poorly developed, the genitals are underdeveloped, the internal organs are small in size, proportional to height. Their mental development is normal. Decreased thyroid function and insufficiency of

thyroid hormones that occur in childhood lead to a delay in physical and mental development. Such individuals have dwarf growth, disproportionately short limbs in relation to the trunk and head, wide and short-fingered hands, a wide face with a low forehead, deep eye sockets, swollen eyelids, a thick tongue that does not fit in the mouth, underdeveloped genitals; Their skin is thickened, elastic (myxedematous), movements are slowed down, and there are profound mental disorders, which are primarily expressed in dementia (cretinism).

Body weight. Body weight is determined by weighing using medical scales. When determining normal body weight, height, chest circumference, age, gender, constitution, etc. are taken into account. The simplest and most common is the Broca formula for determining normal body weight. According to this formula, the normal body weight of a person is: height (in cm) - 100. When determining body weight according to the Broca formula, fluctuations within ±10% are assumed. An increase in body weight is most often observed in cases of obesity of various genesis and the appearance of edema. Weight loss can be caused by a number of reasons: malnutrition, digestive system disorders (vomiting, diarrhea), endocrine and metabolic disorders (thyrotoxicosis, diabetes mellitus and insipidus), malignant tumors, severe intoxications and infections, and some neuropsychiatric disorders.

State of fatness. Fatness depends on the degree of development of the subcutaneous tissue. There are average, excessive (increased) and reduced degrees of fatness. The assessment of the degree of fatness is carried out by means of a routine examination, measuring the skin fold captured with fingers or weighing. The skin together with the subcutaneous tissue is best on the abdomen near the navel or in the left hypochondrium, captured between two fingers, the formed fold is lifted and its thickness is measured. In case of average fatness, the thickness of the fold is about 2 cm, in case of reduced fatness - less than this figure, and in case of increased fatness - more than 2 cm. Excessive accumulation of fat in the body, which leads to an increase in body weight by 20% or more from the average normal values, is called obesity (adipositas, obesitas).

Sharp weight loss, in which the subcutaneous fat layer disappears and the muscles atrophy, is called wasting, or cachexia. A patient with cachexia resembles a skeleton covered with skin. In addition, in the presence of cachexia, the skin color becomes earthy-gray, and a sharp general weakness develops. Cachexia can be observed in the case of the development of malignant tumors, especially those that affect the digestive organs, and in patients with Simmonds' disease (hypothalamic-pituitary cachexia).

Examination of the skin and visible mucous membranes. The color of the skin depends on the degree of blood supply to the skin vessels, the quantity and quality of the pigment, the thickness and transparency of the skin. Pale skin color is observed in anemia, bleeding, aortic heart disease, and kidney diseases. Earthy skin tone - in malignant neoplasms, brown - in malaria, and the color of "coffee with milk" - in subacute septic (bacterial) endocarditis. Red skin color can be transient in fever, overheating of the body or permanent - in people who have been exposed to both high and low external temperatures for a long time, in patients with erythremia, hypertension, diabetes mellitus. Bluish skin color - cyanosis. In case of circulatory disorders, cyanosis is expressed in the areas of the body most distant from the heart, namely on the fingers and toes, the tip of the nose, lips, and auricles - acrocyanosis. Its occurrence depends on an increase in the content of reduced hemoglobin in venous blood as a result of excessive absorption of blood oxygen by tissues when blood flow slows down. In other cases, cyanosis becomes widespread - central cyanosis. Its cause is oxygen starvation as a result of insufficient arterialization of blood in the small circle of blood circulation. Jaundice (icterus) is characterized by yellow color of the skin, mucous membranes and sclera due to the accumulation of the bile pigment bilirubin in the tissues. It develops in diseases of the liver, bile ducts, blood, heart, pancreas. The causes of dark skin color, or pigmentation, are diverse. Of the pathological forms, the most pronounced is skin pigmentation in adrenal gland damage (Addison's disease), in malaria (melanosis).

Skin moisture: profuse sweating is observed in febrile patients with a decrease in temperature, as well as in tuberculosis, thyrotoxic goiter, malaria, purulent processes, etc. Dry

skin can be caused by large losses of body fluid, for example, in diarrhea, prolonged vomiting (toxicosis of pregnancy, organic pyloric stenosis).

Skin elasticity, its turgor is determined by taking the skin (usually the abdominal wall or the extensor surface of the hand) in a fold with two fingers. In a normal state, the skin fold quickly disappears after removing the fingers, but with reduced turgor it does not straighten for a long time.

Edema. Edema develops due to increased fluid leakage from the vascular bed through the capillary walls and its accumulation in the tissues. The accumulated fluid may be of stagnant (transudate) or inflammatory (exudate) origin. Local edema depends on local disorders of blood and lymph circulation and is observed when veins are blocked by a thrombus, compressed from the outside by a tumor or an enlarged lymph node. General edema, associated with diseases of the heart, kidneys and other organs, is characterized by spreading throughout the body (anasarca) or localization in symmetrical, limited areas on both sides of the body. With widespread and significant edema, transudate can also accumulate in body cavities: abdominal (ascites), pleural (hydrothorax) and in the pericardial cavity (hydropericardium).

There are edema of cardiac and renal origin. Cardiac edema is localized in the early stages of the disease on the lower extremities, occurs in the evening, has a dense consistency, is cold, the skin over them has a bluish color. Edema of renal genesis is localized on the face, on the eyelids, occurs in the morning, has a soft consistency, is warm, the skin over them is pale.

Skin rashes (eruptio). When examining the skin, scars after wounds, abscesses and operations may be detected, rashes: roseola, papules, erythema, urticaria, vesicles, hemorrhages, nodules, nodules, pustules, furuncles, ulcers, bedsores.

Skin derivatives. Diagnostic value is represented by the assessment of the condition of hair and nails. Hair growth disorders are more often observed in endocrine diseases. Excessive hair growth of the whole body (hirsutism, hypertrichosis) can be congenital, but is more common in tumors of the adrenal cortex (Itsenko-Cushing syndrome), gonadal glands. Reduced hair growth is observed in myxedema, cirrhosis of the liver, eunuchoidism and infantilism. Hair is also affected in some skin diseases.

Increased brittleness of nails is observed in myxedema, anemia, hypovitaminosis; damage is possible in some fungal diseases. Wide, thickened, dense nails are found in acromegaly. In bronchiectasis, congenital heart defects, the nails become rounded, becoming similar to an hourglass.

Muscular system. When examining the muscular system, the degree of its development is determined, which depends on the nature of the patient's work, sports, etc. Local atrophy of the muscles, especially of the limbs, is of diagnostic importance, which is detected by measuring their circumference and comparing it with the data of the symmetrical location of the other limb. The determination of muscle strength and the detection of muscle function disorders (convulsions) also have a diagnostic role. Local (limited) atrophy of individual muscle groups is observed in patients with diseases of the central nervous system (CNS), for example, atrophy of the muscles of a paralyzed limb that developed after a cerebral stroke, damage to peripheral nerves that arose as a result of muscle inactivity, trophic disorders. The development of this pathology is led by dermatomyositis, periarteritis nodosa (on the lower extremities). Sometimes in the case of damage to the CNS (cerebral hemorrhage), excessive tension of certain muscles develops with the formation of their contractures. In the presence of muscle inflammation (myositis), dermatomyositis, trichinosis, palpation of skeletal muscles reveals their soreness and often swelling.

Examination of the musculoskeletal system. When examining joints, attention is paid to their configuration, limitation and soreness during active and passive movements, swelling, hyperemia of adjacent tissues. A centimeter tape is used to measure the contour of the joints and the length of the bones. In some cases, a special goniometer is used to determine the volume of movements in the joints and a number of instrumental and laboratory studies are performed (radiography, joint puncture, arthroscopy, bacteriological, biochemical analyses, serological

tests, etc.). Multiple lesions, mainly of large joints, are characteristic of acute rheumatic fever. Rheumatoid arthritis causes lesions primarily of small joints of the hands with their subsequent deformation. In deforming osteoarthritis, there is a thickening of the last phalanges of the fingers and toes (Heberden's nodes). Monoarthritis (infection of one joint) occurs more often with tuberculosis or gonorrhea. Along with the examination, palpation of the joints is performed, with the help of which it is possible to determine the temperature of the skin over the joint (in case of inflammation it becomes "hot"), to detect edema and infiltrate of periarticular tissues, fluid in the joint cavity, and tenderness. To determine the presence of intra-articular effusion, a jolting or rolling palpation is used: 3 or 4 fingers pressed together are placed on the joint area (for example, on the knee joint cup) and several short and strong jolts are performed with them towards the middle of the joint cavity. If there is fluid in the joint cavity, oscillations (fluctuation) are felt.

Pain in the joints and periarticular areas (muscles, tendons) is determined by palpation and pressure. In case of joint damage, in addition to the patient's complaints of pain that appears spontaneously and during movements, pain of varying degrees of severity can be detected when pressing on these joints or on neighboring areas. Pain when pressing on bones and joints sometimes has a certain diagnostic value. Thus, pain when pressing on the spinous processes of the vertebrae may indicate the development of pathological changes, for example, tuberculous spondylitis.

The presence of pain when pressing on the front surface of the shoulder joint usually indicates the development of shoulder-scapular periarthritis.

Next, the active and passive function of the joints is examined. In order to determine the active mobility of the joints, the patient is asked to independently perform various movements of the limbs and spine (flexion, extension, rotation to the right and left). To study the passive function, the doctor himself performs various movements in the joints of the patient who is lying freely in bed or on a couch. The study of the function of the joints should be carried out carefully so that the patient does not experience pain and other unpleasant sensations. During the performance of active and passive movements, you can sometimes hear a crunch or crack in the joints or feel friction or slight tremor with your palm placed on their surface. These sound phenomena occur during the friction of the articular ends, the surface of which becomes uneven due to significant bone and cartilage changes. In the presence of joint diseases, in addition to soreness, changes in configuration and varying degrees of restriction of their mobility are detected. In later stages of the disease, especially in the case of rheumatoid arthritis, contractures occur, i.e. significant restrictions of mobility in the joints, which are caused by pathological processes in the joints themselves and the surrounding soft tissues. Complete immobility of the joint is called ankylosis (from the Greek ankylos - crooked). Ankylosis can be functional (temporary), for example, caused by pain, and organic (permanent), for example, caused by the development of rheumatoid arthritis, after injuries.

Examination of lymph nodes. The following peripheral lymph nodes are examined by inspection and palpation: cervical, submandibular, supra- and subclavian, axillary, ulnar, inguinal and popliteal. Normal, unchanged lymph nodes are not visible and are not determined by palpation. Enlarged peripheral lymph nodes are palpated without much effort. In case of significant enlargement, they become visible during examination. During examination, attention is paid to the skin over the lymph nodes. To judge the condition of the lymph nodes, in addition to examination, it is necessary to use the palpation method. Lymph nodes are felt with the palmar surface of the fingers, and deeper palpation is carried out with the fingertips. It is worth paying attention to the size of the lymph nodes, their soreness, mobility, consistency, adhesion to the skin. With lymphadenitis, the lymph nodes are enlarged, slightly compacted, mobile, painful on palpation, the skin over the lymph nodes is reddened. With tuberculosis, cervical lymph nodes are more often enlarged, they become dense in consistency, they are fused with the skin and among themselves, there are fistulous passages. Lymphogranulomatosis is characterized by a systemic increase, more often in the cervical and axillary, less often inguinal lymph nodes, of

moderate density, which are fused into packages with well-mobile skin above them. In case of tumor metastases, the lymph nodes are of stony density, not fused with the skin and among themselves.

Local enlargement of peripheral lymph nodes occurs in the presence of cancer metastases in these nodes. The origin of some distant metastases is presented as follows (according to V. A. Pechatnikova, 1967). For example, at the beginning of the disease of stomach cancer, an orthograde path of metastasis usually occurs, i.e. cancer cells spread along the lymph flow. As the lymph nodes are blocked by cancer metastases, retrograde lymph flow and retrograde metastases appear (through the retroperitoneal lymphatic pathways - Krukenberg metastases to the ovaries, Schnitzler metastases to the pararectal cell, metastases to the navel through the round ligament of the liver - Sister Mary Joseph's node, Irish metastasis to the inguinal lymph node). When parasternal lymph nodes are blocked by metastases, the lymph flowing to the upper nodes of this chain from the lower deep nodes of the neck encounters an obstacle, and in the supraclavicular lymph nodes appear retrograde-lymphogenic Virchow metastasis. Virchow's "gland" - a dense enlarged lymph node on the neck, palpated between the legs of the sternocleidomastoid muscle and the upper edge of the clavicle, is characteristic of gastric cancer metastasis. The origin of Virchow's metastases can also be due to other ways of spreading cancer cells.

Enlargement of the mediastinal lymph nodes is detected by X-ray examination, mesenteric - by ultrasound. In some cases, for diagnostic purposes, puncture or biopsy of the peripheral lymph node is resorted to.

After a general examination, attention is paid to individual parts of the body, in particular, the head (skull), face, oral cavity, neck, chest, abdomen, limbs are examined.

Head (skull). During the examination of the head, its shape and size are assessed. Usually, the size of the head (skull) is normally proportional to the face and other parts of the body. This is a mesocephalic type of head. An excessively small head (microcephaly) is observed in children with congenital idiocy, and an abnormally large head (macrocephaly) is observed in patients with hydrocephalus (hydrocephaly). Children with hydrocephalus have wide fontanelles and a large skull that does not correspond to a small face. A rachitic skull (after rickets) has a square shape, with the occipital bone flattened, almost vertically inclined, and the frontal tubercles noticeably protrude. The Mongoloid skull is characterized by a spherical shape with a rounded top. It occurs in children with congenital idiocy. A tower-shaped head (tower head) is often noted in the presence of congenital hemolytic anemia.

Characteristic signs of the development of acromegaly, in addition to noticeably enlarged feet and hands, are an overdeveloped lower jaw, a thick long nose, which generally leads to the formation of a certain pathological shape of the head.

Attention should be paid to the position of the head. Thus, patients with meningitis throw their heads back. Head tremors can be observed in elderly people who have developed atherosclerosis of the arteries of the subcortical part of the brain (atherosclerotic parkinsonism). In case of aortic valve insufficiency, head shaking synchronous with heart contractions is often observed.

Attention is paid to the hair on the head. Changes in scalp hair, such as baldness in young people, may be the result of seborrhea - a disease characterized by increased sebum secretion, which is caused by disorders of the nervous, endocrine systems and other factors. Alopecia areata is seen in patients with syphilis. In some unkempt, dirty individuals, head lice can be detected during examination of the scalp.

Face. Facial expression depends on various pathological mental and somatic states, age, gender.

In many diseases, the face acquires a characteristic appearance:

1. Facial edema is most often found in kidney diseases (glomerulonephritis) - a swollen, pale face, bags under the eyes, narrow eye slits, dry skin.

2. Corvisart's face - characteristic of patients with heart failure. It is swollen, yellowish-

pale with a bluish tint. The mouth is constantly half-open, the lips are cyanotic.

3. Feverish face (faciesfebris) - hyperemia of the skin, shiny eyes, excited expression. In lobar pneumonia, the purpuric blush is more pronounced on the side of the inflammatory process in the lung.

4. Facial features and expression are changed in various endocrine diseases:

a) acromegalic face – enlargement of prominent parts (nose, chin, cheekbones) occurs in acromegaly;

b) myxedematous face indicates decreased thyroid function, it is uniformly swollen, with the presence of mucosal edema, palpebral fissures are reduced, facial contours are smoothed, hair on the outer halves of the eyebrows is absent;

c) thyrotoxic face (facies basedovica) – the face of a patient suffering from thyroid hyperfunction is mobile, with dilated palpebral fissures, increased shine of the eyes, bulging eyes, which gives the face an expression of fear;

d) a moon-shaped, intensely red, shiny face with the development of a beard and mustache in women is characteristic of Itsenko-Cushing's disease.

5. Sardonic laughter (risussardonicus) – a persistent grimace, in which the mouth expands as in laughter, and the forehead forms folds, as in sadness, observed in patients with tetanus.

6. Face with mitral stenosis (faciesmitralis) – a youthful face, cyanotic blush.

7. Hippocratic face (faciesHyppocratica) – changes in facial features first described by Hippocrates, associated with collapse in severe diseases of the abdominal organs (diffuse peritonitis, perforation of a stomach ulcer, rupture of the gallbladder): sunken eyes, pointed nose, deathly pale with a bluish tint of the facial skin, covered with large drops of cold sweat.

Next, individual parts of the face are examined (eyes, eyelids, nose, lips).

Eyes. During an eye examination, attention should be paid to the size of the palpebral fissures, eyelids, conjunctiva, eyeballs, sclera, cornea and pupil. Ptosis (drooping) of one upper eyelid is a sign of oculomotor nerve paralysis, which can occur as a result of cerebral hemorrhage. A combination of symptoms such as unilateral depression of the eyeball, narrowing of the palpebral fissure, ptosis of the upper eyelid and narrowing of the pupil constitutes Horner's syndrome, indicating compression of the sympathetic nerve by a tumor, dilated aorta, etc. In case of impaired lipid metabolism, local cholesterol deposition occurs in the skin of the eyelids and under the eyelids in the form of flat, slightly raised yellowish spots - xanthomas.

Examination of the conjunctiva. During an examination of the mucous membrane of the eyelids, pallor (in case of anemia), redness (in case of inflammation), cyanosis (in case of hypoxia) can be detected. Small hemorrhages may be observed on the conjunctiva of the eyelids, vaults and eyeballs, the occurrence of which is due to arterial hypertension, whooping cough, subacute infective endocarditis.

Protrusion of both eyes (exophtalmus) is characteristic of thyrotoxicosis. Sunken eyeballs (enophthalmus) are typical of myxedema.

Pupils. Assessment of the shape and uniformity of the pupils, their reaction to light, "pulsation", as well as studies of accommodation and convergence are important in a number of diseases. Narrowing of the pupils (miosis) is observed in uremia, brain tumors and intracranial hemorrhages, poisoning with morphine drugs. Dilation of the pupils (mydriasis) occurs in comatose states, with the exception of uremic coma, as well as in atropine poisoning. Unevenness of the pupils (anisocoria) is noted in a number of lesions of the nervous system.

In patients with aortic valve insufficiency, rhythmic constriction and dilation of the pupils, synchronous with cardiac contractions, can often be observed.

The study of the pupillary reaction to light is carried out in the following way. The doctor tightly covers the eyes of the examinee with his palms (in the dark the pupils dilate), after which he takes his palms away from the eyes and monitors the reaction of the pupils. If the reaction of the pupils to light is preserved, then when light rays enter the eyes, the pupils narrow. In case of damage to the optic nerve, poisoning with morphine hydrochloride and atropine sulfate, as well as during the development of a comatose state and pathological changes in the brain, the reaction

of the pupils to light is absent. In order to study the reaction of the pupils to accommodation, the doctor suggests that the patient look at the tip of the finger, which is slowly brought closer to the patient's eyes and then moved away from them. Such movements of the fingertip are repeated several times. If the reaction to accommodation is preserved, when the tip of the finger approaches, the pupils narrow, and when it is moved away - they dilate. The pupillary reaction to accommodation is absent in case of atropine sulfate poisoning and after its introduction into the conjunctival sac, as well as in case of damage to the peripheral optic nerves. Often during the development of spinal tuberculosis, less often - in the case of the development of multiple sclerosis and brain tumors, the Argyll Robertson symptom is observed, the essence of which is that in the case of preservation of the reaction to accommodation, there is no reaction of the pupils to light (due to damage to the fibers of the oculomotor nerve).

Nose. When examining the nose, pay attention to its shape, skin color, and patency of the canals. A saddle-shaped nose is observed in the presence of congenital and tertiary syphilis. A thick nose occurs in patients with acromegaly. Redness of the nose, caused by dilation of skin vessels, is often observed in patients with alcoholism.

In the presence of rhinophyma (a peculiar chronic disease of the skin of the nose), the nose is red, enlarged, and distorted. Sharp respiratory movements of the wings of the nose - expansion of the nostrils during inhalation and narrowing during exhalation - are observed in case of severe shortness of breath. Nosebleeds (eristaxis) occur in the presence of arterial hypertension, leukemia, uremia and in case of damage and fragility of the vessels of the nasal mucosa. Mucous and mucopurulent discharge from the nose occurs during catarrhal inflammation of the nasal mucosa (rhinitis), purulent - during inflammation of the maxillary cavity and frontal sinus. Herpetic rash (herpesnasalis), which has already been mentioned, may appear on the wings of the nose and near them.

In case of curvature of the nasal septum, in the presence of polyps in it, swelling of the mucous membrane, nasal breathing is difficult, as may be evidenced by an open or half-open mouth.

Lips. During examination of the lips, a herpetic rash (herpeslabialis) can be detected; This rash and its diagnostic significance were mentioned above. In patients with heart and respiratory failure, cyanosis of the lips is noted as a manifestation of hypoxia. Pale lips are often a sign of severe anemia. Cracked dry lips can be found in patients with high body temperature caused by infectious diseases.

The method of examining the oral cavity, pharynx and tonsils is described in the section devoted to methods of examining the digestive system.

Ears. Dense nodules (tophiurici) containing uric acid salts and found in patients with gout are sometimes observed on the auricles. The auricles can be deformed as a result of various pathological processes, in particular, such as tuberculous lupus erythematosus (lupus vulgaris). It is necessary to pay attention to whether there is any discharge from the auditory canals, which may indicate the presence of inflammation of the middle ear.

Neck. During examination of the neck, it is sometimes possible to detect enlarged lymph nodes, scars, goiters (enlarged thyroid gland), venous and arterial pulsation. Dilation and pulsation of the cervical veins is noted in case of tricuspid valve insufficiency. Significant dilation (swelling) of the cervical veins occurs due to impaired blood outflow from the superior vena cava, which is observed in the presence of mediastinal tumors, exudative and adhesive pericarditis. Sometimes neck deformation is noted, for example, in the presence of very enlarged cervical lymph nodes or large goiters. Examination of the chest and abdomen will be described in the sections devoted to methods of examining the respiratory and digestive systems.

Limbs. During the examination of the upper and lower limbs, attention is paid to various changes that are of significant importance for the diagnosis of internal diseases, in particular diseases of the bones and joints. In patients, deformations of bones and joints, swelling, redness of the skin in the affected area, paralysis, trembling of the fingers, varicose veins, usually on the lower legs and thighs, varicose and trophic ulcers, skin lesions, for example, nodular erythema

on the front surface of the lower legs, muscle atrophy, scars that have arisen after injuries, bone tuberculosis and purulent osteomyelitis, etc. During the examination of the hands, it is sometimes possible to detect a bulbous thickening of the terminal phalanges of the fingers in the form of drumsticks. Moreover, the convexity of the nails is noted, their shape resembles the shape of watch glasses. This phenomenon is observed in the presence of chronic abscess, cavernous pulmonary tuberculosis, bronchiectasis, prolonged infectious endocarditis, congenital heart defects, which are accompanied by cyanosis.

In patients with Raynaud's syndrome, which is often the initial manifestation of systemic scleroderma, a symptom of a "dead finger" or "dead fingers" can be observed, when the fingers become pale and cold, like a corpse, their sensitivity is reduced. This phenomenon is associated with vasospasm and can last up to 1-2 hours.

Heberden's nodes, which are dense thickenings on the terminal phalanges of the fingers on the back surface of their base, are found in patients with deforming osteoarthritis. When examining the lower extremities, attention should be paid to the curvature of the lower legs as a result of rickets suffered in childhood, and to saber-shaped lower legs, which are noted in patients with congenital syphilis.

Often on the lower legs and thighs you can notice varicose veins (varices), which look like bluish cords and nodes that shine through the skin. Varicose ulcers can be found on the skin of the lower legs.

Coldness, pallor, numbness, as well as numbness of the toes in the absence of pulsation of the arteries (posterior tibial, dorsal foot) indicates the closure of their lumen, the cause of which is arteriosclerosis, which develops on the background of atherosclerosis, diabetes mellitus, as well as obliterating arteritis and thromboembolism. During the examination of the feet, flat feet can be detected, which sometimes causes pain when walking. Enlargement of the feet is observed in the presence of acromegaly.

Palpation (from the Latin palpatio "feeling") is a method of medical examination. As a method of studying the properties of the pulse, palpation is mentioned in the works of Hippocrates.

Palpation is based on the tactile sensation of the hand, which occurs when the fingers and palm move and press. With the help of palpation, the properties of tissues and organs are determined: their condition, size, shape, consistency, mobility, topographic relationships, as well as the soreness of the organ under study.

There are superficial and deep palpation. Superficial palpation is carried out with one or both palms placed flat on the studied area of the skin, joints, heart, etc. Vessels (their filling, the condition of the wall) are felt with the fingertips at the place of their passage. Deep palpation is carried out using special techniques, which are different when examining the stomach, intestines (sliding palpation, according to Obraztsov), liver, spleen and kidneys, rectum, vagina (during gynecological examination) and other internal organs.

Percussion (Latin percussio - tapping, tapping) is one of the most important methods of examining internal organs. The purpose of percussion is to determine the size and boundaries of internal organs, as well as to detect pathological formations. Percussion retains great practical importance, despite the emergence of new diagnostic techniques.

The principle of direct percussion is to tap the tip of the index or middle finger on the surface of the body. In this form, it is rarely used. Vasily Obraztsov's method is much more common, according to which the index finger of the right hand is placed behind the edge of the middle finger of the same hand. Then the index finger jumps off the edge of the back surface of the middle finger and strikes the surface of the body with a tuft.

During indirect percussion, a finger is tapped on a finger tightly applied to the skin of a certain area of the body. Sometimes a mallet and a plesimeter are used to perform indirect percussion. In this method, a percussion mallet is used to strike a plesimeter lying on the body of the person being examined.

The source of percussion sound is the vibrations caused by the application of a hammer

(finger) to the surface of the body. Thus, the vibrations of the surface are transmitted to the organs located beneath it. For example, the application of a percussion blow to the surface of the chest causes its vibrations, which are transmitted to the organs of the chest cavity and cause their own vibrations of these organs. The vibrations of the internal organs are transmitted to the surface of the body, then to the environment and reach the examiner's ear. The nature of the percussion sound depends on the force of the blow, the surface area, and the properties of the tissues of the percussed organs - their elasticity, tension, airiness.

Direct percussion

The principle of direct percussion is to tap the tip of the index or middle finger on the surface of the body. It is rarely used in this form. Much more common is the Obraztsov method, according to which the index finger of the right hand is placed behind the edge of the middle finger of the same hand. Then the index finger jumps off the edge of the back surface of the middle finger and strikes the surface of the body with a tuft.

Indirect percussion

During indirect percussion, a finger is tapped on a finger tightly applied to the skin of a certain area of the body. Sometimes a mallet and a plesimeter are used to perform indirect percussion. In this method, a percussion mallet is used to strike a plesimeter lying on the body of the person being examined.

During finger-on-finger percussion, percussion blows are applied with the middle finger of the right hand, which should be bent and not touch the other fingers, to the middle phalanx of the middle finger of the left hand, which is tightly pressed to the skin of the examined person. The blows are applied with a bundle of the malleus finger, applying them perpendicularly to the surface of the finger-plessimeter, using movements of the hand in the radiocarpal joint. The blows should be short and elastic, and their force is regulated depending on the purpose of the percussion, but should be the same with each blow. Percussion is performed in an atmosphere of complete silence to enable clear perception and assessment of percussion sounds.

Percussion sounds

Percussion sounds are assessed by four properties - loudness, duration, pitch and timbre

In turn, the denser the tissue, the quieter the percussion sound. Low-density tissues include organs that contain a large amount of air. Such organs (lungs, stomach, intestines) produce a much louder sound than airless organs (heart, liver). The loudness also depends on the space involved in the oscillation. Thus, large lung cavities produce a louder percussion sound than small ones.

Thus, sounds are divided into loud (or clear), quiet (or dull) and shortened (or blunted) by loudness. Dulled sounds have features of both clear and blunt. Physiologically, such sounds are detected over areas of the heart and liver that are covered by the lungs, these are the so-called zones of relative dullness, and over areas of the lungs that contain less air.

By duration, percussion sounds are divided into long and short. Long percussion sounds occur during percussion of air organs (lungs, stomach, intestines). Short sounds, on the other hand, are produced during percussion of airless (heart, liver, spleen) or pathologically compacted organs.

The pitch of the percussion sound depends on the density of the tissue, as well as on the frequency of oscillations. The percussion sound is high in the case of a high frequency of oscillations per unit of time and during percussion of organs of dense consistency (airless). A low percussion sound occurs at a low frequency of oscillations and during percussion of airy organs. A low and loud percussion sound (or box sound) occurs in the case of an increase in the airiness of the lungs and a significant decrease in the elastic tension of the lung tissue, which occurs in the presence of pulmonary emphysema.

By shade (or timbre), percussion sounds are divided into drum and non-drum. Drum sound is loud, long and high in properties and sounds similar to hitting a drum. Drum sound is formed during percussion of closed spaces containing air and surrounded by low-tension walls. Under physiological conditions, such a sound occurs over the larynx, trachea, stomach and

intestines. Under pathological conditions, it can be heard over the lung cavities and during pneumothorax. When the tension of the walls surrounding the air space decreases, the non-drum sound weakens and acquires a drum tone and vice versa. For example, in the case of a decrease in the tension of the lung tissue, a drum sound can be heard. This phenomenon is observed in the presence of two pathological conditions:

• compression atelectasis

• simultaneous filling of the pulmonary alveoli with both air and fluid

In both cases, a dull sound with a tympanic tone is noted during percussion.

Analysis indicators

• Glucose ("blood sugar") - the norm is 3.33-5.55 mmol per liter. An elevated glucose level indicates the threat of diabetes mellitus or impaired glucose tolerance, which requires consultation with an endocrinologist.

• Urea - the permissible value is 2.5-8.3 mmol per liter. A decrease in the level below the norm occurs in severe acute liver failure. Exceeding this indicator indicates insufficient renal excretory capacity and impaired filtration. An increase in the urea content in the blood to 16-20 mmol/l (based on urea nitrogen) is classified as moderate renal dysfunction, up to 35 mmol/l - as severe; over 50 mmol/l - very severe, with an unfavorable prognosis. An increase in the urea level occurs in renal failure, both acute and chronic. In acute renal failure, the level of urea in the blood can reach 50-83 mmol/l.

• Residual blood nitrogen (non-protein blood nitrogen) is the nitrogen of substances that remain after the removal of blood plasma proteins. Residual nitrogen consists of urea nitrogen (50%), amino acid nitrogen (25%), uric acid (4%), creatine (5%), creatinine (2.5%), ergothioneine (8%), ammonia and indican (0.5%); 5% of nitrogen is contained in polypeptides, glutathione, bilirubin and other non-protein compounds. Normally, the content of residual nitrogen in blood serum ranges from 14.3 to 28.6 mmol/l.

• Creatinine is considered in combination with urea. The norm of creatinine is 44-106 micromoles per liter. Like urea, creatinine indicates kidney function.

• Total lipids — blood content of 5-7 g/l.[1]

• Cholesterol or cholesterol — an organic compound, a natural fatty (lipophilic) alcohol, contained in the cell membranes of all animal organisms.

When analyzing blood biochemistry, the cholesterol level is reflected in the following parameters: LDL cholesterol (low-density lipoproteins, LDL), HDL cholesterol (high-density lipoproteins, HDL), triglycerides, total cholesterol.

The norm of total cholesterol is from 3.6 mmol/l to 7.8 mmol/l, the recommended cholesterol level is <5 mmol/l. High cholesterol signals the threat of atherosclerosis.

• LDL cholesterol — low-density lipoproteins, LDL. The norm for men is 2.02-4.79 mmol/l, for women 1.92-4.51 mmol/l.

• Cholesterol-HDL - high-density lipoproteins, HDL. The norm for men is 0.72-1.63 mmol/l, for women 0.86-2.28 mmol/l.

• The normal content of potassium in the blood is 3.4-5.3 mmol/l, sodium - 135-155 mmol/l, chlorine - 95-110 mmol/l, and calcium - 1.05-1.3 mmol/l, which is approximately 50% of the total calcium content in the blood.

Instrumental methods of examining patients: electrophysiological (ECG), X-ray, endoscopic and cytological, ultrasound.

X-ray examination methods include radiography, fluoroscopy, tomography, a screening method for early detection of diseases of the respiratory system - fluorography, as well as a method of examination with the creation of high-resolution images of organs - computed tomography. Close to this method, although using different physical phenomena, are magnetic resonance imaging and positron emission tomography. X-ray examination methods using radiocontrast drugs can also be used in diagnostics.

X-ray methods - radiography, fluoroscopy - allow you to diagnose the presence of pneumonia, tuberculosis, malignant tumors, etc.

instrumental and laboratory studies allow to identify additional objective manifestations of the disease, which allows to confirm (or refute) the diagnosis of the disease.

Laboratory methods of examining patients (general tests, biochemical tests). Their practical significance.

Clinical blood test (general) - quantitative and qualitative study of blood-forming elements (erythrocytes, leukocytes, platelets, reticulocytes, etc.).

A complete blood count includes the following indicators:

• Erythrocyte sedimentation rate (ESR)

• Hemoglobin count

• Red blood cell count

• Calculation of the color index (average hemoglobin content in one erythrocyte)

• Leukocyte formula (granulocyte content - basophils, eosinophils, rod-shaped and segmental neutrophils; agranulocytes - lymphocytes, monocytes)

• Reticulocyte count

• Platelet count

• Description of the morphology of peripheral blood cells

• Presence of plasma cells.

Indications for the analysis:

 Screening and dispensary examinations.

 Monitoring of the therapy being carried out.

 Differential diagnosis of blood diseases.

For clinical blood tests, venous blood is taken from a vein, by venipuncture using a syringe with a needle or a vacutainer with a needle, or capillary blood from the pad of the ring finger (IV). A special disposable needle, a scarifier, is used for this.

Clinical blood test results may vary depending on the time of day the blood was collected, and may also be related to the food consumed and physical activity that preceded the blood sample.

Certain diseases are determined by an absolute increase or decrease in the number of individual types of blood cells.

Changes in the composition of the blood are precursors of many diseases, for example:

• leukocytosis may be a sign of infection.

• thrombocytopenia may be a consequence of drug poisoning.

• pancytopenia, as a rule, is the result of a decrease in the production of blood cells by the bone marrow, and is also a common complication of anticancer chemotherapy, often occurring in AIDS.

Biochemical blood analysis is a laboratory method of research used in medicine, the results of which allow us to judge the functional state of organs and systems of the human body. It allows us to determine the function of the liver, kidneys, the presence of an active inflammatory process, impaired water-salt metabolism and imbalance of trace elements, etc. Biochemical analysis helps to make a diagnosis, prescribe and adjust treatment, and also determine the stage of the disease.

For biochemical blood analysis, venous blood is taken (from a vein), by venipuncture using a syringe with a needle or a vacutainer with a needle. It is necessary to take into account the time of transportation of the taken blood (especially when taken with a syringe or in ordinary test tubes) so that the blood does not clot, which would make it impossible to perform any tests.

Computed tomography makes it possible to obtain three-dimensional images: CT allows us to obtain three-dimensional images of internal organs and structures. This can be especially useful when planning surgical interventions or when assessing complex anatomical relationships. At the same time, it has a high sensitivity to tumors: CT is a very sensitive method for detecting

tumors and other abnormalities. It can help doctors determine the size, location and nature of the tumor, which is important for planning treatment.

Endoscopic examination methods, the principle of which is to observe changes in the internal organs and cavities of the human body using a special device - an endoscope, are used mainly for the diagnosis of diseases of hollow and cavity organs.

These include fibrogastroduodenoscopy, colonoscopy, sigmoidoscopy, rhinoscopy, laryngoscopy, bronchoscopy, cystoscopy, colposcopy, laparoscopy, arthroscopy and a number of other examinations. Endoscopic methods can combine both a diagnostic goal, including taking a biopsy of the affected organ, and therapeutic manipulations can also be performed during these examination methods. In addition, video capsule endoscopy is most often used to study the condition of the digestive system organs, during which a video capsule is inserted into the patient's digestive tract, which independently moves through the digestive tract and takes pictures of the walls of the digestive system organs, which helps the doctor better assess the condition of the affected organ.

Ultrasound examination methods are used to examine dense organs. Ultrasound can detect not only organic pathology, but also functional disorders. During the examination of the abdominal organs, the specialist examines the liver, spleen, as well as the pancreas, gallbladder and ducts. Ultrasound examination is used to diagnose diseases of the liver, pancreas, gallbladder, spleen, kidneys, urinary bladder, prostate, female genital organs, mammary glands, heart and blood vessels, joints, and is also used to diagnose pathological conditions in the fetus. Ultrasound allows you to detect stomach ulcers, the presence of cysts in the kidneys, liver, etc.

To diagnose disorders of some systems and organs, methods of recording the electrical activity of organs are used, which include, in particular, ECG and EEG.

Electrocardiography (abbreviated ECG) is a method of graphically recording electrical phenomena that occur in the heart muscle during its activity, from the surface of the body. Electrocardiography is one of the main methods of studying the heart and diagnosing diseases of the cardiovascular system. ECG is indispensable in the diagnosis of rhythm and conduction disorders, hypertrophy, ischemic heart disease.

Electroencephalography (EEG) is a method of graphically recording brain biopotentials, which allows analyzing its physiological maturity and condition, the presence of focal lesions, general brain disorders and their nature. It consists in recording and analyzing the total bioelectrical activity of the brain - electroencephalogram (EEG). EEG can be recorded from the scalp, from the surface of the brain, as well as from deep brain structures. Typically, an electroencephalogram is understood as a surface recording, that is, made from the skin. EEG is most often used to diagnose epilepsy, which causes EEG abnormalities. It is also used to diagnose sleep disorders, depth of anesthesia, coma, encephalopathy and brain death. EEG was used as the primary method of diagnosing tumors, stroke, and other focal brain disorders.

Cytological examination is a diagnostic method that consists of studying cells under a microscope. It allows you to assess the structure, size, shape, and other characteristics of cells, which helps to detect pathological changes, such as inflammation, infections, or cancer cells.

Other examination methods can also be used in the diagnosis of various diseases, including the introduction of radioactive isotopes into the body and obtaining an image by determining the radiation they emit (scintigraphy); registration of heat released from the human body (thermography); puncture biopsy, and a number of other methods of diagnosing diseases that are specific to different branches of medicine.

Diagnosis methodology - preliminary, differential, and final diagnosis.

Diagnosis is a concise written conclusion about the existing disease, expressed using medical terms that denote the name of the disease. When diagnosing, it is necessary to trace the development of the disease from the identification of the etiological moment and assessment of the body's condition in the initial period through the entire course of the pathological process to

the clinical picture at the time of examination. Since there are no diseases that would have the same course in all people, it is necessary to identify the individual features of the development of the pathological process in a particular patient - the diagnosis of the disease (individual diagnosis). When making a diagnosis, the doctor is guided by the patient's subjective complaints, anamnesis, examination of the patient (condition of the skin, mucous membrane of the nasopharynx, measurement of temperature, pulse and pressure, auscultation, etc.), the results of medical diagnostic studies and monitoring of the further course of the disease. In this case, age, gender, work, social status, locality and other non-medical factors are also taken into account.

The diagnosis of the disease can be:

 preliminary (made on the basis of complaints, anamnesis of the disease, anamnesis of life and anamnesis of allergy, as well as data of examination of the patient);

 this is when the clinical picture of this differential is compared with the symptoms of other probable diseases;

 final (made on the basis of the preliminary diagnosis, as well as data of instrumental and laboratory studies).

Based on the diagnosis, it is possible to proceed to the determination of those drugs that can be used to treat the disease detected in this patient, that is, to pharmacotherapy.

The main types of pharmacotherapy: etiotropic, pathogenetic, symptomatic, replacement.

Etiotropic therapy is an ideal type of pharmacotherapy. This type of FT is aimed at eliminating the cause of the disease. Examples of etiotropic FT can be the treatment of infectious patients with antimicrobial agents (benzylpenicillin for streptococcal pneumonia), the use of antidotes in the treatment of patients with poisoning with toxic substances.

Pathogenetic therapy - aimed at eliminating or suppressing the mechanisms of disease development. Most of the currently used drugs belong to the group of drugs for pathogenetic FT. Antihypertensive drugs, cardiac glycosides, antiarrhythmic, anti-inflammatory, psychotropic and many other drugs have a therapeutic effect by suppressing the corresponding mechanisms of disease development.

Symptomatic therapy - aimed at eliminating or limiting individual manifestations of the disease. Symptomatic drugs include painkillers that do not affect the cause or mechanism of disease development. Antitussives are also a good example of symptomatic drugs. Sometimes these drugs (elimination of pain syndrome in myocardial infarction) can have a significant impact on the course of the underlying pathological process and at the same time play the role of pathogenetic therapy.

Replacement therapy - used in cases of deficiency of natural biogenic substances. Substitution therapy includes enzyme preparations (pancreatin, panzinorm, etc.), hormonal drugs (insulin for diabetes, thyroidin for myxedema), vitamin preparations (vitamin D, for example, for rickets). Substitution therapy preparations, without eliminating the causes of the disease, can ensure the normal existence of the body for many years.

A drug (substance) or medication (drug) is a pharmacological agent (substance) that has undergone clinical trials and is approved for use for the treatment, prevention and diagnosis of diseases by the authorized body of the country.

Drugs are distinguished that are intended for:

 treatment of diseases (pharmacotherapeutic and chemotherapeutic drugs);

 prevention of diseases; diagnosis of diseases.

Pharmacotherapeutic drugs are used to correct the function (s) of organs and systems

impaired as a result of the disease;

Chemotherapeutic drugs - are used to act on atypical (tumor) cells, pathogenic microorganisms and helminths in order to suppress their vital activity.

Medical documentation: a) outpatient patient's medical record; b) inpatient medical history; c) prescription list.

In accordance with the order of the Ministry of Health of Ukraine, in each outpatient health care institution, a medical card of an outpatient patient is opened for a patient in the form No. 025/o. It is the main primary medical document of a patient who is treated outpatiently or at home, and is filled out in all polyclinics that conduct outpatient reception. One card is kept for each patient in the polyclinic, regardless of whether he is treated by one or several doctors. The title page of the medical card of an outpatient patient provides a place for recording the diseases for which the patient was taken under dispensary supervision, indicating the date when the patient was taken or removed from the dispensary registration, and the reason for the removal.

A patient may be under dispensary supervision for the same disease by several specialists (for example, for gastric ulcer, chronic cholecystitis by a therapist and a surgeon), it is recorded on the title page once by the specialist who first took the patient under dispensary supervision.

If a patient is observed for several etiologically unrelated diseases by one or more specialists, then each of them is recorded on the title page. If the nature of the patient's disease changes (for example, ischemic heart disease joins hypertension), then a new diagnosis is recorded on the title page of the form without a date of registration, and the old record is crossed out. The results of tests and examinations, final epikrisis of inpatient treatment, advisory opinions of specialists of all levels are glued to the medical record. In the case of hospitalization of a patient in a hospital, the registry office transfers the medical record to the department where the patient is sent. After the patient is discharged from the hospital, the medical record is returned to the registry office, where it is stored. In the event of the patient's death, simultaneously with the issuance of a medical certificate of death, a record is made in the card about the time and cause of death of the deceased and transferred to the archive of the medical institution.

Currently, the outpatient card is kept in electronic form. Prescriptions are also written out electronically.

The inpatient medical record (also known as the "medical record") is a medical document that is filled out for each patient admitted for inpatient medical treatment, maintained in all healthcare institutions that provide inpatient medical care and in sanatoriums. The document contains all data on the patient's condition during the period of stay in the hospital, the organization and conduct of treatment, as well as data from objective, functional, radiological, laboratory and other examination methods.[2] The inpatient medical record is used to monitor the proper organization of the medical and diagnostic process and to provide materials upon request (by law enforcement agencies, courts, etc.). In Ukraine, form No. 003/o "Medical record of a hospital patient No. ____" is approved by the relevant order of the Ministry of Health of Ukraine[3] and is a form of primary accounting documentation[

"Medical prescription sheet" (form No. 003-4/o is an operational document intended for registering the patient's stay in the hospital, the diet prescribed for him, examination methods, drug treatment, physiotherapeutic and psychotherapeutic procedures.

It is filled in by the attending physician on the day of the patient's hospitalization in the hospital with the necessary adjustments made during the patient's treatment.

Records (names of drugs, procedures, local treatment, etc.) are kept in Ukrainian, legibly.

A special folder is kept in each department to store medical prescription sheets for the period of treatment of patients in the hospital.

Daily, mid-level medical workers make notes on the fulfillment of prescriptions.

After the patient is discharged from the hospital, the medical prescription sheet is glued to "Medical record of a hospital patient" (form N 003/o) and is stored together with it.

Questions for self-control on the topic:

1. Definition of the subject - clinical pharmacology, history of development in the world in Ukraine.
2. The fundamental difference between clinical pharmacology and pharmacotherapy.
3. The main goals of clinical pharmacology.
4. The main tasks of clinical pharmacology:
 clinical testing of new pharmacological agents;
 clinical research and reassessment of old drugs;
 development of methods for the effective and safe use of drugs;
 organization of information services and advisory assistance of various specialists;
 training of students and doctors.
5. Basic concepts of clinical pharmacology:
 medicinal substance.
 drug - brand names, generic names - advantages and disadvantages, the concept of bioequivalence;
 the concepts of "chemical name", "international non-proprietary name", "trade name", "brand name" of drugs.
 OTC drug;
6. Medical monitoring: concepts, conditions that determine the need for medical monitoring.
7. Clinical pharmacodynamics: definition, basic concepts.
8. Clinical pharmacokinetics: definition, basic concepts.
9. Pharmacotoxicodynamics: definition, basic concepts.

List of sources on the topic:

1. Clinical pharmacology: textbook. M.V. Khaitovich, G.V. Zaichenko, I.O. Afanasyeva et al. Medicine. 2024. 335 p.
2. Clinical pharmacology: textbook / E. I. Shorikov, G. I. Shumko, O. S. Khukhlina et al. Vinnytsia: Nova Kniga, 2019. 512 p.
3. Pharmacology: textbook for students of medical and dental faculties of the Higher Medical University. / I. S. Chekman, V. M. Bobyrev, V. Y. Kresyun [and others]. Vinnytsia: Nova kn., 2020. 471 p.
4. Pharmacotherapy: in 2 books. — Book 1: textbook (VNI 4th year of study) / B.A. Samura, A.S. Svintsitsky, Yu.M. Kolesnyk and others. — 3rd ed., revised and supplemented. All-Ukrainian Specialized Publishing House "Medicine". 2012. 952 p.
5. Pharmacotherapy with pharmacokinetics: a teaching aid for students of higher education. / I.V. Kireyev, O.O. Ryabova, N.V. Zhabotynska and others. ; edited by I.V. Kireyev. Kharkiv: National University of Physics and Technology: Golden Pages, 2019. 384 p.
6. Pharmacology in drawings and diagrams: a textbook / V. V. Godovan; [ed. by V. Y. Kresiun]; Odessa National Medical University - Vinnytsia: Nova Knyga, 2019. - 462 p.
7. Pharmacology according to Rank and Dale: 9th edition: in 2 volumes. Volume 1 / James M. Ritter, Rod Flower, Graham Henderson, Yun Kong Louk, David McEwen, Humphrey P. Rank-Kyiv: Medicine, 2021. - 364 p.
8. Pharmacology: a textbook / I.V. Nekoval, T.V. Kazanyuk and others. . Kyiv: All-Ukrainian Specialized Publishing House "Medicine", 2022. - 552 p.

LECTURE 2. TOPIC

"Pharmacotoxicodynamics of drugs, side effects of drugs (types, examples). System of pharmacological supervision of the safety of drug use in Ukraine and the world"

Relevance of the topic: Pharmacotoxicodynamics studies the classification of adverse drug reactions and etiopathogenetic mechanisms of their occurrence, as well as factors affecting the safety of drug use. It is necessary to master the basic provisions of the organization of the state system of pharmacological supervision of adverse drug reactions in Ukraine.

Purpose: training specialists who have knowledge about the main undesirable effects of drugs, mechanisms of their development, measures to prevent their development and prevent the occurrence of toxic effects.

Basic concepts (list of questions):

1. Basic concepts of pharmacotoxicodynamics, terminology.
2. Causes of side effects of drugs and consequences.
3. Classification of adverse drug reactions (ADRs):

• type A: frequent, predictable reactions associated with the pharmacological activity of drugs (pharmacodynamic, toxic, secondary);

• type B: infrequent, unpredictable reactions (drug intolerance, idiosyncrasy, allergic reactions);

• type C: reactions associated with long-term therapy (drug dependence);

• type D: carcinogenic, mutagenic and teratogenic effects of drugs.

4. Other types of adverse drug reactions (withdrawal syndrome, withdrawal syndrome, para-drug, drug resistance).
5. Clinical manifestations of the negative impact of drugs.
6. Prediction of adverse drug reactions and prevention.
7. Pharmacovigilance system in the world and in Ukraine. The role of a doctor and pharmacist.
8. Prevention of the occurrence and ways to correct the negative effects of drugs
9. Principles of combination therapy.

Lecture material content (lecture text)

Basic concepts of pharmacotoxicodynamics, terminology.

The main requirements for modern drugs, along with effectiveness, are the quality and safety of their use. The problem of drug safety (drugs) in recent years has become one of the most urgent health problems in the world. This is due to the emergence of many drugs with high biological activity, which has increased people's sensitization, the interaction of drugs with each other (often doctors, prescribing certain drugs, do not think about, and sometimes do not know about their incompatibility). Lethality from side effects of drugs took 4th place in the world (after cardiovascular diseases, lung diseases, oncological diseases).

"…There is no medicinal product (MED) that is not associated with risk…" — WHO (Information Bulletin No. 293, March 2014)

Side effects of drugs are becoming an increasingly urgent medical and social problem. According to various authors, adverse drug reactions are observed in 10-30% of the population, in 3% of cases they are the reason for seeking medical attention, in 5% they are the reason for hospitalization, in 3% they are the reason for intensive care, in 12% they lead to a significant increase in the length of stay of patients in the hospital, and in 1% of patients they can even be the cause of death.[

Currently, Ukraine has developed a legal and administrative framework for monitoring the safety of drugs – a pharmacological surveillance system. Pharmacological surveillance - a state system for collecting, scientific evaluation and control of information on adverse reactions/side effects of drugs in order to make appropriate decisions at the stage of clinical trials and its medical use in accordance with current legislation.

Side effect of drug - any undesirable reaction caused by the pharmacological properties of drugs and observed in therapeutic doses (atropine - dryness of the mucous membranes).

Adverse reaction of PR - an undesirable reaction dangerous to health, when the connection between the reaction and the use of drugs cannot be excluded (dyspeptic phenomena).

Types of PR - possible, reliable, unforeseen, predicted, etc.

Side effects - any adverse medical manifestation that is not necessarily associated with the use of drugs (change in lab data, symptom, disease that coincided with the use of drugs).

Predicted adverse events – have a certain clinical picture (parkinsonism when taking aminazine, arterial hypertension when using glucocorticoids).

Unpredicted adverse events – develop rarely, are not always associated with the pharmacological action of the drug, are not described in the literature (celecoxib cardiotoxicity).

By the nature of the occurrence of adverse events – direct and indirect

direct toxic effects – overdose, idiosyncrasy, pharmacological action of drugs used in therapeutic doses.

indirect or indirect side effects – Jarish-Herxheimer reaction; changes in the course of the disease associated with the uneven distribution of drugs in the body, with the suppression of immunobiological reactions; dysbacteriosis and superinfection (drug resistance of the pathogen and its “addiction”).

By localization - local and systemic

Local - changes at the injection site (infiltrates, irritation of the skin and mucous membranes, dysphonia, candidiasis of the mucous membranes when using inhaled GCs).

Systemic - during GC therapy (growth disorders, osteoporosis, hyperglycemia, increased blood pressure, hypokalemia), during therapy with antitumor agents (regeneration disorders, growth, hair loss, carcinogenic effect).

By the severity of the clinical course of PB -

 mild - there is no need to cancel the drug or special treatment, side effects disappear when the dose of the drug is reduced

 moderate - drug withdrawal and special treatment are necessary

 severe - [syndromes that pose a threat to the patient's life, for example, complete atrioventricular (AV) conduction block], fatal.

Causes of side effects of drugs.

The frequency of RP depends on:

 individual characteristics (allergy)

 gender, age of the patient (children, elderly, women, men)

 severity of the main and concomitant disease (liver, kidneys, heart)

 pharmacodynamics (heart rate atropine) and pharmacokinetics (gastrointestinal tract, liver diseases)

 Dose (weight) duration of use (cumulation)

 routes of drug administration (phlebitis, infiltrates)

 drug interaction (potentiation)

Most often, RP is caused by cardiac glycosides, acetylsalicylic acid, glucocorticoids, diuretics, hypotensive agents and indirect anticoagulants, antibiotics, diuretics, potassium preparations, analgesics, tranquilizers, antidiabetic agents.

1. Factors not related to the action of drugs:

• characteristics of the patient's body (age, gender, genetic characteristics, susceptibility to allergic reactions, specific course of the disease, bad habits);

• external factors related to the patient (the doctor who conducts pharmacotherapy, environmental environment, working conditions, etc.).

2. Factors related to the action of drugs:

• features of the clinical and pharmacological characteristics of drugs;

• adequacy of the choice of drug;

• method of drug administration;

• drug interaction in polypharmacy.

Among the additional factors that influence the increase in the frequency of PD cases, the following are indicated:

• constant increase in the number of generic drugs;

• violation of storage conditions and use of drugs after the expiration date;

• fetishism and myth-making in pharmacotherapy;

• self-medication and poor-quality advertising of drugs;

• prevalence of dietary supplements and their uncontrolled prescription.

The analysis of errors showed that:

 error in the choice of drug and dose – 56%

 polypharmacy – 53.2%

 underestimation of the anamnesis – 47.7%

 incorrect duration and change of dose – 34%

 Iatrogenic reactions (due to the fault of paramedical staff and pharmacists) 10%

 inadequate dissemination of information by manufacturing companies – 28% of medical errors

 non-compliance with the standards of instructions (PR, PP) 42% of drugs

 falsified - 30% of drugs in the world

 According to WHO, 50% of drugs for sale on the Internet are counterfeit.

The analysis of possible falsification of drugs showed that there are:

 substandard drugs (Substandardmedicalproducts; also called “those that do not meet the specifications”) — registered drugs that do not meet quality standards and/or specifications;

 unregistered/unlicensed medical products — medicinal products that have not been evaluated and/or are not authorized by the NRA for the markets in which they are sold/distributed or used, in accordance with the regulatory requirements of national or regional legislation;

 falsified medical products — medicinal products in which their name, composition or manufacturer is intentionally/fraudulently incorrectly indicated.

It has been established that the frequency of adverse reactions in outpatient treatment reaches about 10-20%; and in about 5% of such cases, patients require hospitalization for the treatment of this complication.

The analysis of the pharmaceutical showed that the following groups of drugs most often show side effects of drugs:

 ANTIBIOTICS - 42%

 NSAIDs

 Drugs for the treatment of cardiovascular diseases

 Hormones - 20%

Classification of side effects (SED) of drugs (drugs):

1. Classification of side effects (SED) of drugs (drugs):

• type A: frequent, predictable reactions associated with the pharmacological activity

of drugs (pharmacodynamic, toxic, secondary);

• type B: infrequent, unpredictable reactions (drug intolerance, idiosyncrasy, allergic reactions);

• type C: reactions associated with long-term therapy (drug dependence);

• type D: carcinogenic, mutagenic and teratogenic effects of drugs.

TYPE A: frequent, predictable reactions associated with the pharmacological activity of the drug (pharmacodynamic, toxic, secondary);

Often, side effects of drugs are associated with pharmacological activity, due to:

 pharmacological properties of the drug (atropine - dryness of the mucous membranes, increased intraocular pressure, constipation, etc.; neuroleptics - depression, decreased blood pressure, atropine-like effect, hypodynamia);

 pharmaceutical (pyrogenicity - when using blood substitutes, change in ingredients);

 pharmacokinetic:

 change in absorption (noshpa + adsorbent);

 change in biotransformation:

 potentiation of microsomal enzymes (hypnotics - barbiturates, NSAIDs - phenylbutazone, anticonvulsants - carbamazepine, rifampicin, griseofulvin, cordiamine, antihistamines; - diphenhydramine, chloropyramine, oral hypoglycemic drugs - glutethimide);

 inhibition of microsomal enzymes - antiulcer drugs (cimetidine), antibiotics - chloramphenicol, tetracyclines, macrolides, antifungals - ketoconazole, antidepressants - imipramine, narcotics - morphine, codeine, metronidazole, allopurinol;

 pharmacodynamic (liver disease, change in water-salt metabolism - hypokalemia when using diuretics);

 pharmacogenetic abnormalities (isoniazid slow and fast "acetylators")

 use of large doses or overdose of drugs (barbiturates, anesthetic effect), drug interaction;

 drugs with a narrow therapeutic range: heparin, SG, lidocaine, gentamicin.

Often, side effects of drugs are due to relative or absolute overdose of drugs

• absolute - too large a dose is taken (vasodilators cause collapse, stimulants - convulsions, hypnotics - anesthesia);

• relative - the dose is therapeutic, but the concentration in the blood and cells is too high due to the peculiarities of the pharmacokinetics of the drug in this patient (liver, kidney disease, genetic characteristics);

For example, digitoxin, in the presence of hypoproteinemia, does not bind to blood protein, enters cardiomyocytes, its effect increases, which leads to toxic effects.

TYPE B: infrequent, unpredictable reactions (drug intolerance, idiosyncrasy, allergic reactions);

 Violation of immunobiological properties (when using antibiotics - dysbacteriosis, the appointment of glucocorticoids leads to a decrease in immunity)

 immunological (allergy - rashes often occur when using antibiotics, photosensitization occurs when prescribing tetracyclines, novocainamide causes the appearance of systemic lupus erythematosus);

 pseudoallergic (aspirin asthma and rash occur due to impaired metabolism of arachidonic acid under the influence of NSAIDs, an increase in leukotrienes that irritate bronchial receptors, bronchospasm occurs; ampicillin causes the appearance of

erythema);

 Pharmacogenetically determined changes (idiosyncrasy) associated with defects in enzyme systems (the use of sulfonamides in individuals with G6PDH deficiency causes hemolytic anemia, drugs - malignant hyperthermia).

TYPE C: reactions associated with long-term therapy (drug dependence);

 Adaptive changes (long-term use of β-adrenomimetics in bronchial asthma leads to a decrease in receptor sensitivity, long-term use of psychotropic drugs - addiction and dependence - narcotics, tranquilizers, hypnotics);

 The phenomenon of "rebound", when with a sharp withdrawal of the drug after long-term use, the symptoms that were before the start of treatment return (hypnotics) and "withdrawal", when the function of the organs affected by the drug changes (with long-term use of GCs, their own GCs are not synthesized, they are not administered externally, acute adrenal insufficiency occurs);

 organo- and systemic toxic effects (chloroquine causes keratopathy, amiodarone – pulmonary fibrosis).

TYPE D: carcinogenic, mutagenic and teratogenic effects of drugs.

 carcinogenicity (oral contraceptives can cause liver tumors);

 mutagenicity is caused by dioxidine, antitumor agents;

mutagenic effect, i.e. the ability to cause changes in hereditary information — mutations — in germ and somatic cells.

 decreased fertility - potency, infertility are caused by antidepressants - MAO inhibitors, antitumors - chlorbutin, cyclophosphamide, immunosuppressants - sulfosalazine;

 teratogenic effect (manifested in the occurrence of developmental defects and deformities) - tetracycline leads to hypoplasia of tooth enamel, phenytoin - anomalies of the limbs and craniofacial region, bleeding, sodium valproate - spinal cleft.

Teratogenic effect is the occurrence of developmental defects of internal organs, the central nervous system, limbs in the embryo, i.e. deformities. The danger of teratogenic effects of drugs became obvious in the late 1950s. after about 7 thousand children were born in Western Europe to women who used the sedative and hypnotic drug thalidomide with malformations of the limbs (due to impaired collagen synthesis in bone tissue), gastrointestinal tract, hemangiomas on the face, etc. Teratogenic effects most often develop in the first trimester, especially from the beginning of the 4th to the end of the 8th week of pregnancy, that is, during the period of organ formation. The specific type of defect depends on the duration of pregnancy - on which organs are formed and intensively formed during the use of the drug. The likelihood of its development is determined not only by the drug used, but also by the age of the pregnant woman (the risk increases at the age of ≤17 or ≥ 35 years, when prenatal damage to the eggs is more common), the woman's health status (especially diseases of the organs that eliminate drugs and their metabolites - the liver, kidneys, as well as the cardiovascular and endocrine systems), the genetic characteristics of the parents and the fetus, the dose of the drug, the duration of its use. Among the causes of congenital malformations, up to 25% are genetic disorders, about 10% - infections (cow rubella, influenza, etc.), radiation, injuries. In approximately 65% of cases, the causes remain unclear, and a significant part of them is explained by the action of drugs or xenobiotics. It is important that teratogenic effects can occur not only as a result of transplacental entry of drugs (xenobiotics) into the fetus, but also as a result of their action on the father's body on the eve of conception, which can cause genetic abnormalities of spermatozoa, impaired viability, and motility. Getting into the female genital tract with seminal fluid, the drug can act locally, disrupting the early stages of pregnancy.

 Embryotoxic effects are damage to the zygote or embryo located in the lumen of the fallopian tube or uterine cavity, i.e. before implantation - in the first 3 weeks after fertilization.

Damage and even death of the embryo can be caused, in particular, by estrogenic, progestational hormonal drugs, deoxycorticosterone acetate, somatotropic hormone, salicylates, barbiturates, sulfonamides, cytostatics and a number of other xenobiotics, e.g. nicotine.

 fetotoxic effect (from Latin foetus - fetus) is an adverse effect of drugs on the condition of the fetus in the womb (more often - in the last weeks of pregnancy) and the newborn (β2-adrenomimetics (partusisten), used to reduce the contractile activity of the uterus, provoke fetal hyperglycemia and, as a result, stimulation of insulin secretion, which is slowly excreted from the body of the fetus and newborn child, contributing to hypoglycemia in the neonatal period). These drugs can also cause metabolic acidosis, hyperbilirubinemia, hypocalcemia, intestinal obstruction.

Magnesium sulfate, which is also used for tocolytic purposes, due to suppression of the fetal CNS can cause muscle weakness, respiratory and sucking disorders in the newborn). Aminoglycoside antibiotics (streptomycin, gentamicin, etc.) - hearing impairment, deafness, indomethacin and other NSAIDs - premature closure of the ductus arteriosus; this disrupts blood circulation and causes heart failure and even fetal death, and after birth provokes pulmonary hypertension in the child

Other types of side effects of drugs (withdrawal syndrome, "stealing" syndrome, para-drug, drug resistance, drug dependence, idiosyncrasy).

Withdrawal syndrome is a pathological condition, a clinical syndrome that develops when drugs are suddenly discontinued, which, as a rule, have been used for a long time and/or in large doses (for example, psychotropic or narcotic substances).

Most often, it develops after the sudden cessation of taking:

- hormonal drugs (glucocorticoids, thyroidin, etc.),
- antihypertensive drugs (clophenin),
- antianginal drugs (beta-blockers),
- barbiturates (phenobarbital, barbamil, etc.),
- H2-histamine blockers (cimetidine, etc.).

Gradual reduction of drug doses before stopping its use minimizes the risk of withdrawal syndrome

After sudden withdrawal of clonidine (0.2 mg or more per day), blood pressure (BP) may increase sharply. Patients complain of headache, insomnia, irritability, tremor, nausea, severe vomiting, palpitations. The concentration of catecholamines increases in the blood and urine, signs of hypertensive crisis are noted 1-2 days after withdrawal. To stop the crisis, alpha-adrenergic blockers (phentolamine) are used in combination with propranolol or clonidine is resumed.

One of the manifestations of the withdrawal syndrome is the development of dependence on drugs and other substances (addiction). According to the conclusions of the WHO expert committee, drug dependence is a mental state, sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioral and other reactions that always include a desire to take the drug. Constantly or periodically, in order to prevent discomfort that occurs without taking the drug. A person may be addicted to more than one drug.

Drug dependence occurs with addiction. Addiction is a strong, sometimes irresistible desire to systematically use certain drugs and other substances that cause euphoria, to improve mood, improve well-being, as well as eliminate unpleasant experiences and sensations that arise when these drugs are discontinued.

"Stealing" syndrome. Its essence lies in the fact that drugs, improving (or enhancing) the function of a separate organ or its parts, thereby worsen the activity of adjacent systems and individual links. Thus, the use of strong vasodilators leads to increased volumetric blood flow in areas where the vascular system copes well. This leads to the outflow of blood from regions where the vessels are sclerosed and do not respond to vasodilation. For example, the use of

dihydropyridamole in severe coronary atherosclerosis is characterized by the development of ischemia (angina pain), myotropic agents (dipyridamole), vasotropic calcium channel blockers (nifedipine).

Drug resistance is often encountered in medical practice, although sometimes it is difficult to draw a line between it and low sensitivity to the drug. It should be considered PD in the case when the lack of effect from the drug is not overcome by increasing the dose, or it manifests itself at a dose that always causes unwanted PD. In most cases, we are not talking about resistance, but about a decrease in individual sensitivity.

Para-drug side effects. They are not associated with the action of the active substance itself. They may be due to the properties of the filler, psychogenic effects (after familiarization with the annotation, replacement of the drug of well-known companies, the price of the drug, etc.).

Idiosyncrasy, i.e. congenital hypersensitivity to drugs, is an infrequent manifestation of side effects of a non-allergic nature. For example, in individuals with a genetic defect (low activity) of the cholinesterase enzyme in the blood, the depolarizing muscle relaxant dithylin can cause very prolonged — up to several hours — skeletal muscle relaxation with respiratory impairment. The causes and mechanisms of idiosyncrasy are studied by pharmacogenetics.

Clinical manifestations of the negative effects of drugs.

Clinical and pharmacological signs of the development of complications of drug therapy are due to both the state of the body and the pharmacological properties of drugs. In a pathological state of the body, the biotransformation of medicinal substances changes significantly, which causes the occurrence of various complications in a number of cases. In various pathological processes, metabolism is sharply disrupted, including the intensity of biological oxidation, as a result of which the function of the nervous system decreases, adaptive and compensatory mechanisms, excretory properties of the kidneys, antitoxic function of the liver, motor and secretory activity of the intestines are disrupted. The listed factors can be the cause of increased drug action, up to the occurrence of toxic effects, or a distortion of the pharmacodynamics of drugs.

Important is the violation of the function of the kidneys, liver, cardiovascular system, digestive system, immunobiological properties of the body. The occurrence of complications of drug therapy is played by the diet, working conditions, meteorological factors. The dosage form, dose and concentration of the drug, and the route of administration into the body play a certain role in the development of PR / PD. A wide variety of clinical manifestations of side effects of medicinal substances are possible. The most common are skin rashes, itching, fever, nausea, vomiting, dizziness, headache, neuropsychiatric disorders, including hallucinations, drowsiness, depression, etc.

The dependence of pathological changes on taking the drug may be suspected if the drug was prescribed shortly before their appearance. The connection becomes obvious if the drug is discontinued and the side effects disappear, and its repeated administration leads to their recurrence. In some cases, it is not easy to establish the drug etiology of the pathological process, for example, in drug-induced hepatitis and nephritis. After the drug is discontinued, the symptoms of these diseases persist for a long time.

According to the systemic principle, the side effects of drugs are classified as follows:

1. Multi-organ disorders.
2. Endocrine disorders.
3. Metabolic disorders.
4. Skin lesions.
5. Hematological disorders.
6. Cardiovascular disorders.
7. Respiratory disorders.

8. Digestive disorders.
9. Kidney and urinary system disorders.
10. Nervous system disorders.
11. Visual disorders.
12. Musculoskeletal disorders.
13. Mental disorders.

By frequency, side effects are divided into (according to WHO):

• Very common, ≥ 1⁄10 (occurring in more than 10% of patients using the drug)
• Common (frequent), from 1⁄10 to 1⁄100 (from 1 to 10% of cases)
• Uncommon (uncommon), from 1⁄100 to 1⁄1000 (0.1-1% of cases)
• Rare, from 1⁄1000 to 1⁄10000 (0.01-0.1% of cases)
• Extremely rare, < 1⁄10000 (less than 0.01% of cases)

Side effects of drugs can even cause fatal consequences. For example, the most common are:

1) gastrointestinal bleeding and peptic ulcers (GCs, NSAIDs, anticoagulants);
2) other types of bleeding (anticoagulants, cytostatics) aplastic anemia (chloramphenicol, phenylbutazone, gold preparations, cytostatics);
3) liver damage (chlorpromazine, isoniazid, tetracycline);
4) kidney damage (NSAIDs, aminoglycosides);
5) decreased resistance to infections (cytostatics, glucocorticoids);
6) allergic reactions (penicillin preparations, novocaine).

Prediction of adverse drug effects and prevention.

The basic principles of pharmacotherapy and prediction of adverse drug effects include safety, rationality, controllability, and individualization. Justification of the safety of any drug is determined by minimizing pharmacotherapy. The principle of rationality assumes such an optimal ratio of efficacy and safety of pharmacotherapy, which ensures the maximum possible therapeutic effect of drugs with the lowest risk of their undesirable effects.

Rational pharmacotherapy in a specific clinical situation allows you to justify the choice of the most adequate drug in a specific dose, dosage form, and route of administration. Pharmacotherapy must be controlled. This principle involves the analysis and assessment of both expected and unexpected results of drug use, which allows you to timely adjust the selected treatment tactics by changing the dose and method of administration, replacing an ineffective drug, etc.

The choice of pharmacotherapy is made in accordance with the established diagnosis, possible complications, and prognosis. At the same time, the goals are specified, the achievement of which is ensured by the use of the drug, based on knowledge of its pharmacodynamics and pharmacokinetics. Possible contraindications to pharmacotherapy and incompatibility of drugs and treatment methods are also assessed. In the process of determining the volume, indications for complex pharmacotherapy are established, that is, the use of drugs for different purposes and their combination to achieve one of the treatment goals.

The purpose of the combination of drugs can be to enhance the therapeutic effect, reduce the dose of the active substance, and also reduce their undesirable effects. Strengthening the therapeutic effect, as well as reducing the dose, is achieved by a combination of synergists or drugs of additive action, which mutually complement the spectrum of pharmacological action, as well as by combining the main drug with another that enhances or complements its pharmacological effect.

The choice of drugs or their combination is one of the most important elements of pharmacotherapy. It contains a comparison of the features of action, pharmacokinetics, toxicity and other properties of drugs of the same type in purpose with the features of the pathogenesis of the disease and its course in a particular patient (taking into account his general condition, the presence of concomitant diseases), as well as the possible interaction of drugs if necessary, their combination, and other data on both the drug and the patient. In an urgent situation, one of the important criteria for choosing a particular drug is the speed of onset of effect. The determination of the dose of the drug is carried out taking into account the route of its administration into the body. In this case, the differences in dosage can be very significant. The selection of criteria and means of controlling the action of drugs is necessary both for assessing the therapeutic effect and for identifying their undesirable effects. In the process of complex pharmacotherapy, the need to cancel a certain drug or their combinations is established to achieve the goal, which is usually associated either with the completion of the pathological process, or with the restoration or compensation of a certain function, the violation of which served as an indication for prescribing the drug. In addition, the justification for the withdrawal of a drug during therapy may be a decrease or disappearance of the therapeutic effect due to the peculiarities of its pharmacological action, the formation of irreversible changes in target organs during the course of the disease, the prevalence at a certain stage of pharmacotherapy of contraindications to the use of the drug based on the dynamics of the pathological process due to the increased risk of dangerous consequences; the detection of toxic or side effects of drugs, which excludes the possibility of replacing the drug (e.g. digitalis intoxication is an absolute contraindication to the use of all cardiac glycosides). In some diseases, as well as congenital and acquired pathological conditions, there is a need for so-called maintenance pharmacotherapy for a long time, sometimes lifelong. To comply with one of the basic principles of treatment - "Do no harm", it is necessary to take into account not only the positive therapeutic properties of drugs, but also their ability in some cases to cause complications.

To prevent drug interactions, the following rules must be followed.

1. Drugs should be recommended only according to indications, in optimal doses, preferably orally.

2. It is imperative to find out the medical history of each patient, and if necessary, conduct special studies to determine possible hypersensitivity to the prescribed drug or its intolerance.

3. You should not use several drugs with the same mechanism of action at the same time, because polypharmacy increases the risk of side effects of combined drug therapy.

4. Make a treatment plan for each patient.

5. Take into account the state of tissue "targets" with which the drug will interact, as well as changes in the function of vital organs and systems (liver, kidneys, digestive system, blood system, muscles), which play a major role in the biotransformation of pharmacological drugs. Take into account the peculiarities of the action of drugs in childhood and old age.

6. If the patient has an inadequate reaction to the drug, it should be replaced with another drug.

7. Antibiotics and sulfonamides, which are widely used in clinical practice and often cause side effects, should be prescribed taking into account the etiology of the disease, the type and properties of microorganisms, as well as their sensitivity to antibacterial drugs.

8. Widely apply the method of "covering" the PD of the drug with other drugs. For example, use levorin and nystatin to prevent candidiasis, unitiol - to reduce the toxic effect of cardiac glycosides.

9. Conduct extensive explanatory work aimed at combating uncontrolled use of medications, self-medication, and explain the need for strict adherence to drug shelf life.

Pharmacovigilance system in the world and in Ukraine. The role of the doctor and pharmacist.

The pharmacovigilance system is a state system for collecting and scientifically evaluating information on adverse reactions to medicinal products during their medical use in order to make appropriate regulatory decisions.

Approaches to pharmacovigilance, defined by the World Health Organization (WHO), are the same in all countries of the world.

The implementation of pharmacovigilance in Ukraine is regulated by the Order of the Ministry of Health of Ukraine dated 26.12.2006 No. 898 “On Approval of the Procedure for Monitoring Adverse Reactions of Medicinal Products Allowed for Medical Use” (registered with the Ministry of Justice of Ukraine on 29.01.2007 No. 73/13340) (hereinafter referred to as the Procedure). According to the Procedure, in the event of an adverse reaction, every doctor of any healthcare institution must report it. Information on adverse reactions is also provided by drug manufacturers, it can be obtained from literary sources, from WHO and other world organizations dealing with the safety of drug use, etc.

In connection with significant changes in EU legislation on pharmacovigilance, the need to regulate relations between structures involved in the drug circulation process, in order to adequately use the human and technical potential of each of them, avoid duplication of functions, and include all participants in the drug use process in the reporting process on adverse drug reactions, amendments and supplements were made to the current legislation of Ukraine on pharmacovigilance by the Order of the Ministry of Health of Ukraine dated 29.12.2011 No. 1005 “On Amendments to the Order of the Ministry of Health of Ukraine dated 27.12.2006 No. 898”.

From 02.04.2012, after the entry into force of the Order of the Ministry of Health of Ukraine No. 1005, not only doctors, but also nurses, paramedics, obstetricians, pharmacists and pharmacists must submit information on cases of adverse reactions and/or lack of effectiveness of medicines. Patients, their representatives and organizations protecting patients' rights will also be involved in this process.

Methods for receiving reports on adverse drug reactions/adverse drug reactions are classified as follows:

1. Spontaneous reporting — allows for population involvement, monitoring of adverse drug reactions of all drugs approved for medical use in the country; the time frame for studying adverse drug reactions is not limited; there is a possibility of dividing patients into appropriate groups; does not significantly disrupt the course of events; low research costs;

2. Active monitoring of inpatients — is based on the fact that monitors collect demographic, social and medical data on all patients admitted to the hospital;

3. Prescription monitoring — is based on the systematic collection and analysis of prescriptions written out for a new drug; during this, contact is established with the doctor, who personally reports on the effect of the drugs;

4. Study in groups — in principle involves determining a group of patients who use the corresponding drug; determining (allocating) a control group of patients (for comparison); comparing the effectiveness and safety of pharmacotherapy between the specified groups of patients;

5. Comparative study - based on the selection of patients who are characterized by a specific negative reaction when prescribing a relevant drug; selection of patients who do not have a specific negative reaction when using a relevant drug.

The Ministry of Health of Ukraine has entrusted the supervision of adverse reactions to medicinal products approved for medical use to the State Enterprise "State Pharmacological Center" of the Ministry of Health of Ukraine (hereinafter referred to as the Center), namely to its subdivision - the Department of Post-Registration Supervision (hereinafter referred to as the Department). It is here that information about adverse reactions that have arisen during the

medical use of medicinal products is received, processed and analyzed.

The Department of the Center includes 27 regional departments, whose employees work with heads of medical institutions and doctors on pharmacovigilance issues in all regions of Ukraine.

According to the WHO definition, an adverse reaction (AR) is an unintended and harmful reaction to the human body that occurs when a drug is used in normal doses for the purpose of prevention, treatment and/or diagnosis.

Sometimes the medical use of medicinal products (MEDs) may be accompanied by a lack of efficacy (VE) of the drug. The latter may be associated not only with inadequate quality of the drug, because the effectiveness of the drug depends on many factors. The genetic characteristics of both each organism separately and the nation as a whole play an extremely important role. Therefore, instructions for the medical use of the same drug may differ in different countries of the world, and sometimes on different continents. After all, in some nations a certain drug is safe and can be used to treat certain diseases, while in others it is not (or with some reservations).

Modern approaches to drug safety supervision in Ukraine involve collecting information about all drugs, including medical immunobiological drugs. In this regard, the form of the report card has changed. The updated card includes columns that allow for the full collection of information with its subsequent analysis on adverse reactions to vaccines, toxoids and tuberculosis allergen.

1) Adverse reaction report card (AR), Patients or their representatives and the requirement to fill it out, in accordance with Appendix 2 to the Pharmacovigilance Procedure.

2) Adverse reaction report card (AR), Medical and pharmaceutical workers in accordance with Appendix 6 to the Pharmacovigilance Procedure.

What to report:

Any adverse reactions or adverse events of drugs registered in Ukraine, including radiographic contrast agents and herbal preparations, should be reported; adverse effects on the fetus and newborns during pregnancy and lactation, as well as complications resulting from drug abuse and dependence. This should be done both in the case of self-medication and prescription of drugs.

Therefore, the following should be reported:

• expected and unexpected adverse reactions of drugs;

• serious and non-serious adverse reactions of drugs;

• adverse events (lack of efficacy)

It is also necessary to monitor for the possible occurrence of delayed adverse reactions. For example, oncological diseases, chloroquine retinopathy, retroperitoneal fibrosis may occur months or years after drug use, as well as congenital malformations that may occur after a certain period of time after drug use by a pregnant woman.

Special attention is required when prescribing drugs to patients at risk of developing adverse reactions – patients with kidney and liver diseases, the elderly and senile, children, pregnant women and breastfeeding women.

Any manifestations of adverse reactions should be reported – whether it is dry mouth when using tricyclic antidepressants, constipation when using narcotic analgesics (opioids), cough when using ACE inhibitors, blood disorders when using metamizole sodium, renal failure when using acetaminophen, jaundice when using nimesulide, visual disorders when using ethambutol, etc.

In addition to informing about the clinical manifestations of adverse reactions, it is also necessary to report whether there have been changes in laboratory test results or complications of the course of the disease, which may be associated with taking the drug.

Who should report

ADRs or VEs of medicinal products should be reported by doctors of all specialties, in accordance with the order of the Ministry of Health of Ukraine dated 27.12.2006 No. 898 “On approval of the Procedure for monitoring adverse reactions of medicinal products permitted for

medical use”.

If an VER or VE occurs in a patient who is being treated at home, he must inform his doctor about it, and he must act in accordance with the current legislation of Ukraine.

How to report

To provide information, a special form of a report card is used, which contains information about the patient, a description of the VER or VE (time of occurrence, course of treatment, examination results, consequence), data about the suspected medicinal product, all other prescribed medicinal products (as well as preparations for self-medication), risk factors and other data, as well as the name and address of the person who can be contacted in case of need to clarify the data of the report.

Confidentiality of the information provided is guaranteed!!!

It should be emphasized that reporting an adverse drug reaction or adverse drug reaction not only does not result in any administrative negative measures, but on the contrary, it indicates the doctor's high professionalism.

What to do if any questions arise when detecting an adverse drug reaction or adverse drug reaction or when filling out a notification card

If any questions arise when detecting an adverse drug reaction or adverse drug reaction or when filling out a notification card, the doctor can contact the employees of the regional departments of the Department or the Department's pharmacovigilance department (contact phone number (044) 498-43-58 or by e-mail: vigilance@pharma-center.kiev.ua).

It should be noted that employees of the regional departments constantly conduct educational work among doctors on pharmacovigilance, in particular on the question "what to do in the event of an adverse drug reaction?" However, sometimes doctors speak out in newspapers or other media about the lack of effectiveness or danger of using a particular drug. The latter only upsets the population, forms a negative attitude towards certain drugs, reduces the effectiveness of treatment, but does not contribute to the safety of drug use. A doctor should not act in a way other than that specified in the order of the Ministry of Health of Ukraine No. 898. Only the notification cards sent by doctors are official confirmation of the occurrence of an adverse event or adverse reaction. It is these documents that are the basis for making appropriate decisions on making changes and additions to the instructions for medical use, restrictions or prohibitions on the use of drugs.

Where to find a report card for providing information on adverse drug reactions or adverse drug reactions

A sample report card for adverse drug reactions or adverse drug reactions in medical use can be obtained at the address indicated on the official website of the Center: www.pharma-center.kiev.ua. A sample report card is also available in the Order of the Ministry of Health of Ukraine dated 27.12.2006 No. 898 and in the State Formulary of Medicines (tear-off sheets are placed on the inside of the back cover).

Deadlines for submitting report cards for adverse drug reactions or adverse drug reactions

Information on all non-serious adverse drug reactions or adverse drug reactions must be submitted to the Department of Pharmacovigilance within 15 days, and on all serious adverse drug reactions or adverse drug reactions – within 48 hours.

Where should information about adverse drug reactions or adverse drug reactions be sent?

All information should be sent to the Pharmacovigilance Department of the Department in any of the following ways:

• by letter or telegram to the address: Pharmacovigilance Department of the Department of Post-Registration Monitoring of the Safety and Efficacy of Medicinal Products of the State Enterprise "State Pharmacological Center" of the Ministry of Health of Ukraine, 40 Ushynskogo St., Kyiv, 03151;

• by telephone or fax: (044) 498-43-58;

• by e-mail: vigilance@pharma-center.kiev.ua

What to do if an adverse drug reaction or adverse drug reaction may be associated with inadequate quality of the medicinal product

During the medical use of medicinal products, there is a possibility of adverse drug reactions or adverse drug reactions that may be associated with inadequate quality of the medicinal product. Such adverse drug reactions should not be confused with adverse drug reactions that occur with adequate quality of the medicinal product. The State Inspectorate for Quality Control of Medicines in Ukraine deals with the problems of inadequate quality of medicines. If a patient has an adverse reaction or adverse event during the medical use of a medicine, and the doctor suspects that the medicine is of inadequate quality (for example, the color of the medicine has changed, turbidity has appeared, an unpleasant odor, taste, physical impurities have been detected, the medicine does not dissolve well, etc.), he must also report this to the State Pharmaceutical Center of the Ministry of Health of Ukraine, which will inform the State Inspectorate for Quality Control of Medicines about this.

The importance of post-registration surveillance for the safety and efficacy of drugs

The implementation in Ukraine of collecting and analyzing information on PR or VE of drugs has allowed to make important regulatory decisions, in particular, to significantly limit the medical use of such drugs as gentamicin, metamizole sodium (analgin), oseltamivir; detoxification solutions containing low molecular weight polyvinylpyralidone. The use of Hemodez, drugs containing kava-kava, cimetidine, furatsilin tablets for internal use is prohibited.

Only during 2006-2009. the use of drugs was prohibited:

• Euphyllin, where the stabilizer was ethylenediamine - due to the increased risk and frequency of allergic adverse reactions;

• rofecoxib in a daily dose of more than 50 mg, as well as in persons with increased risk from the cardiovascular system (suffered heart attacks, strokes, clinical forms of atherosclerosis that progress) aged 65 years and older - due to the risk of complications from the cardiovascular system;

• nimesulide has an adsorbing effect in children under 12 years of age, in patients with fever, flu-like symptoms, with liver and kidney diseases, with alcoholism and drug addiction, and the indications for their use are also significantly limited (acute pain, symptomatic treatment of painful osteoarthritis, primary dysmenorrhea) due to the hepatotoxicity of nimesulide;

• thioridazine - it is forbidden to use in a daily dose of more than 300 mg, the indications for its use are significantly limited due to the increased risk of adverse reactions;

• oseltamivir – in childhood due to mental disorders in this category of patients;

• efalizumab (Raptiv) – due to the occurrence of a rare progressive and demyelinating disease of the central nervous system – progressive multifocal leukoencephalopathy – against the background of its use;

• rimonabant (Acomplia) – due to the fact that after the beginning of the widespread medical use of this drug, the number of cases of mental disorders, including depression, sleep disorders, suicides increased (compared to placebo – 2 times).

It should be noted that the basis for making the relevant regulatory decisions in all of the above cases were reports of unexpected adverse reactions.

More detailed information about the activities of the Department can be obtained on the official website of the Center www.pharma-center.kiev.ua

Prevention of the occurrence and ways to correct the negative effects of drugs

How to prevent the occurrence of drug adverse reactions:

• do not use any drugs if the appropriate indication for their use is not in the information about the drug (instructions for medical use);

• if the patient is pregnant or breastfeeding - do not use the drug without urgent need;

• do not use any drugs if the patient is hypersensitive to them. Ask the patient if he has previously had manifestations of hypersensitivity, allergy or idiosyncrasy;

• avoid polypharmacy as a possible factor of adverse drug interactions. Before prescribing a drug, ask whether the patient is taking other drugs, including self-medication drugs, food supplements, herbal remedies;

• consider that the patient's age, the presence of liver and kidney diseases may alter the metabolism or excretion of the drug, requiring adjustment of its dose. Genetic factors may also be the cause of variations in metabolism;

• clearly and concisely inform the patient about the method, doses and consequences of taking the drug, especially for the elderly and other patients who may misunderstand the doctor's recommendations.

Every doctor, when conducting drug therapy, must:

– form ways of positive compliance with the patient;

– not to oversaturate the pharmacotherapy regimen with a large number of drugs at one time;

– give preference to drugs in one pharmaceutical form, the frequency of administration should not be more than four times a day;

– prevent a template approach when choosing drugs;

– be sure to take into account the criterion of “effectiveness/safety”;

– select drugs taking into account the criterion of “effectiveness/price”.

– timely report on drug adverse reactions.

In order to prevent drug adverse reactions during pharmacotherapy, we consider it necessary to adhere to the following:

1. Drugs should be prescribed only according to indications, in optimal doses, and by the appropriate route of administration.

2. It is imperative to find out the drug history of each patient, and if necessary, conduct special studies to determine possible hypersensitivity to the prescribed drug or its intolerance.

3. Do not use several drugs with the same mechanism of action at the same time, since polypharmacy increases the risk of side effects of combined drug therapy.

4. Take into account the state of tissue “targets” with which the drugs will interact, as well as changes in the function of vital organs and systems (liver, kidneys, digestive system, blood system, muscles), which play a major role in the biotransformation of pharmacological drugs. Take into account the peculiarities of the action of drugs in different age categories.

5. If a patient develops a drug intolerance, it should be replaced with another drug. 6. Conduct educational work aimed at combating uncontrolled use of medications, self-medication, and explain to each patient the need to strictly adhere to the drug regimen, as well as the conditions and terms of storage of drugs.

There were no absolutely safe drugs and there are none. The effectiveness and relative safety of drugs are determined by studying pharmacokinetics and pharmacodynamics during clinical trials. And the proper quality of the drug is not a guarantee that treatment will not cause adverse effects, because compliance with the requirements of good manufacturing practice (GoodManufacturingPractice — GMP) is only part of the quality assurance system that guarantees that the product is manufactured and controlled according to quality standards in accordance with the trade license and corresponds to its intended purpose.

However, a drug is a compound that interacts with the body. On the one hand, this causes a therapeutic effect, which is what is expected from the drug, and on the other hand, the occurrence of side effects (the body's reaction), which in no way depend on compliance with GMP standards. Therefore, all medicines, regardless of their origin (synthetic or natural), can be more or less dangerous and have both a therapeutic effect and side reactions. It is more appropriate to talk about the "acceptable danger" of a medicine when the risks and the corresponding indications for its use are comparable.

Reasons that cause adverse reactions after using medicines

• Pharmacological properties of medicines;

• features of the body's response to the administration of the drug;

• medical errors when concomitant factors and prescriptions are not taken into account;
• use of medicines not according to indications;
• without taking into account contraindications;
• inadequate quality of the medicine;
• polypharmacy — when several drugs are taken at the same time, and their simultaneous effect on the body may be unexpected (it is recommended to take no more than 5 drugs at the same time);
• self-medication (not taking into account all possible risks from drugs).

Typical self-medication errors:

• use of several drugs under different trade names that contain the same active ingredient;
• simultaneous use of incompatible drugs;
• failure to comply with the rules of drug dosage (especially geriatric patients) and duration of treatment;
• leveling the presence of concomitant diseases (usually elderly people — polymorbid — have several diseases).

At the end of the last century, the World Health Organization (WHO) formulated requirements for medicines: effectiveness, safety, accessibility and acceptability for the patient, which were concentrated around the main criterion - benefit/risk, which should, from the standpoint of evidence-based medicine, ensure rational pharmacotherapy, that is, the patient's quality of life.

Over the past 40 years, the interest of international organizations, national health services and the public in the issues of safe medical use of medicines has significantly increased and has become increasingly subject to various regulatory influences. A pharmacovigilance system has been organized - an international and national regulatory mechanism for supervising the safety of medicines - a scientific field and practical activity related to the detection, assessment, understanding and prevention of adverse negative effects or any other problem related to medicines.

According to the WHO definition, adverse drug reactions/side effects include any reaction to a medicinal product that is harmful and undesirable for the body and occurs when a normal dose of a medicinal product is administered for the treatment, diagnosis, prevention of diseases or modification of body functions.

In Ukraine, pharmacovigilance is regulated at the state level in accordance with the European Economic Community directives on pharmacovigilance by the following laws and orders of the Ministry of Health (MOH):

• Law of Ukraine “On Medicinal Products”;
• Order of the MOH of Ukraine No. 426 “On Approval of the Procedure for Conducting Expertise of Registration Materials for Medicinal Products Submitted for State Registration (Re-Registration), as well as Expertise of Materials on Making Changes to Registration Materials During the Validity of the Registration Certificate”;
• Order of the MOH of Ukraine No. 690 “On Approval of the Procedure for Conducting Clinical Trials of Medicinal Products and Expertise of Clinical Trial Materials and the Model Regulation on Ethics Committees”;
• Order of the Ministry of Health of Ukraine No. 898 “On Approval of the Procedure for Pharmacovigilance”;
• Order of the Ministry of Health of Ukraine No. 857 “On Timely Provision of Information on Cases of Adverse Reactions and/or Lack of Effectiveness of Medicinal Products by Healthcare Institution Employees”.

Principles of Combination Therapy.

Patients (especially the elderly or those with serious chronic diseases) are rarely prescribed a single drug. The issue of the danger of polypharmacy (the simultaneous prescription

of many medicines or medical procedures) is very acute for doctors and patients.

Drug interactions can be desirable or undesirable, that is, beneficial or harmful to the body. Desirable interactions are used to increase the effectiveness of drug therapy, for example, in tuberculosis or hypertension (HT). By introducing two drugs that act by different mechanisms, for example, in GC, a hypotensive effect is achieved without causing adverse reactions. Treatment of morphine overdose with naloxone also serves as an example of a rational combination of 7 drugs. However, each time a new drug is added, the risk of undesirable effects cannot be excluded.

Combination therapy is based on knowledge of all aspects of therapy and properties of drugs (pharmacokinetics, pharmacodynamics, pharmacotoxicodynamics).

Questions for self-control on the topic:

1. Classification of side effects of drugs.
2. Toxic side effects.
3. Allergic reactions, classification, prevention, treatment.
4. Groups of drugs with antiallergic activity.
5. Dysbacteriosis, candidiasis: definition, mechanisms of development, prevention, treatment.
6. Withdrawal syndrome: mechanism of development, prevention.
7. Embryotoxicity, teratogenicity, fetotoxicity of drugs: examples, methods of prevention.
8. Carcinogenicity, mutagenicity of drugs: examples, prevention.
9. Clinical signs of acute and chronic drug intoxication.
10. Principles of treatment of drug poisoning.
11. The concept of antidote therapy, classification, mechanisms of action.
12. Examples of the most commonly used antidotes.

List of sources on the topic:

1. Clinical pharmacology: a textbook. M.V. Khaitovich, G.V. Zaichenko, I.O. Afanasyeva and others. Medicine. 2024. 335 p.
2. Clinical pharmacology: a textbook / E. I. Shorikov, G. I. Shumko, O. S. Khukhlina and others. Vinnytsia: Nova Knyga, 2019. 512 p.
3. Pharmacology: a textbook for students of medical and dental faculties of the Higher Medical University / I. S. Chekman, V. M. Bobyrev, V. Y. Kresyun [and others]. Vinnytsia: Nova Knyga, 2020. 471 p.
4. Kraydashenko, O. V. Side effects of drugs. Pharmacological surveillance system in Ukraine [Text] / O. V. Kraydashenko, M. P. Krasko, O. M. Glavatskyi - Z.: FPO, 2015. - 49p.
5. Side effects of drugs: textbook / Belenichev I.F. and others - Vinnytsia. : Nova kniga, 2021. - 360 p.
6. Side effects of cardiovascular pharmacotherapy: textbook / V.I. Palamarchuk. - Khmelnytskyi, 2023. - 160 p.
7. Pharmacovigilance in Ukraine: adverse reactions of drugs // Pharmacist. - 2015. - N 5. - P. 4-6.0
8. Kashuba, O. V. Adverse reactions caused by drugs: terminology and classification, mechanisms of development and clinical manifestations / O. V. Kashuba // Pharmacology and medical toxicology. - 2013. - N 3. - P. 80-92.

LECTURE 3. TOPIC

"Drug interactions, types of interactions, examples. Polypharmacy: definition, the doctor's place in preventing undesirable effects of drug interactions"

Topic relevance: Adverse drug reactions can occur as a result of drug interactions between themselves and with food consumed. There are many reasons for drug interactions. For example, one drug can change the pharmacokinetics of another, there may be competition for one receptor, signaling pathway, prescribed drugs can have the same undesirable effects, which will lead to poisoning.

Purpose: training specialists who have knowledge about drug interactions when used in combination, mechanisms of their development, measures to prevent their development and prevent the occurrence of toxic effects.

Basic concepts (list of questions):

1. Drug interactions. Definition of the term, classification of types of interactions, causes.
2. Pharmaceutical drug interactions. Mechanisms and causes of development. Examples.
3. Pharmacokinetic interaction of drugs, its features and types. Examples.
4. Pharmacodynamic interaction of drugs. Types. Examples.
5. Polypharmacy and polypharmacy, definition of the term. Consequences of polypharmacy, examples.
6. The doctor's place in preventing undesirable effects of interaction.

Lecture content (lecture text)

Drug interaction. Definition of the term, classification of types of interaction, causes

Drug interaction is a change in the activity or appearance of side effects of a drug that occurs when taken simultaneously with food, drink, supplement or other drug.

In the modern world, it is not uncommon for patients with chronic diseases to take half a dozen or even more drugs. Drug interactions are becoming more common as we have more medications and combinations of medications available to us than ever before. This can make one or more medications less effective, and can also cause other side effects.

There are many reasons why drugs interact. For example, one drug can alter the pharmacokinetics of another. In other cases, there may be competition for a single receptor or signaling pathway.

The risk of drug-drug interactions increases with the number of medications taken. More than one-third (36%) of older adults in the United States regularly take five or more medications or preparations, and 15% have a significant risk of experiencing a drug interaction.

One possible consequence of a drug interaction is an overreaction of the body to one of the components of the drug, which can lead to serious complications or a noticeable change (increase, decrease, or complete loss) in its effectiveness. This concept can also include the unpredictability of the specific action of the drug, when the pharmacokinetic or pharmacodynamic properties of the active substance are not sufficiently studied.

In medical practice, it is customary to distinguish four drug interactions:

 Class A - when the drug interaction is not clinically significant, for example, ranitidine with phenobarbital;

 Class B - when the drug interaction is not described;

 Class C - when the therapeutic effect changes as a result of the drug interaction and adjustment of the drug dosage regimens is necessary, for example, cimetidine with theophylline;

 Class D - when simultaneous administration of drugs is impossible due to the

development of dangerous reactions or therapeutic ineffectiveness, for example, indomethacin with triamterene.

The unpredictability of drug interactions causes the problem of the need for careful monitoring and supervision of combined pharmacotherapy in order to prevent dangerous cases of drug interactions, which are increasingly being detected in medical practice. Despite the complexity of the problem of drug interactions in general, combination pharmacotherapy is generally recognized, when another drug is prescribed together with the main drug in order to modify the effects of the previous one (enhance the effectiveness or reduce the side effects). There are numerous cases when drug interactions are used in clinical practice for a specific purpose, for example, in antidote therapy.

Factors that cause drug interactions include:

 the ability of medicinal substances to affect several physiological systems simultaneously (when pharmacotherapy takes into account the primary effect and ignores the weaker secondary effect, which may be significantly manifested when taking two or more drugs simultaneously);

 prescribing drugs with different trade names or simultaneous use of prescription and non-prescription drugs that have the same drug substances;

 simultaneous use of drugs and dietary supplements and other cases;

 incompetence of patients;

 violation of the recommendations of specialists (doctor, pharmacist) by patients;

 inattention to the recommendation (instructions) on the method of using drugs, especially several at the same time.

Pharmaceutical drug interaction. Mechanisms and causes of development. Examples.

 Pharmaceutical interaction is associated with the physical, chemical, physicochemical properties of substances and what happens in the process of manufacturing, storing, mixing drugs (insufficient solubility, melting, stratification, absorption).

Pharmaceutical interaction of medicinal substances is possible even before their introduction into the body or directly at the site of their introduction. Usually occurs outside the body during the production of drugs, in clinical practice when mixing drugs in one syringe or infusion system.

Usually pharmaceutical interaction is the result of physicochemical reactions of medicinal substances (for example, acids and alkalis). In this case, insoluble compounds may be formed, the color, smell, pharmaceutical properties of medicinal substances may change. As a rule, this type of interaction occurs when drawing up irrational prescriptions of medicinal substances. For example, cardiac glycosides partially disintegrate in an alkaline environment, which leads to the loss of their activity.

Types of pharmaceutical interaction:

 Physical interaction;

 Chemical interaction.

An example of physical interaction is the formation of so-called eutectic mixtures of medicinal substances. They are formed when mixing medicinal substances with high cryoscopic constants with medicinal substances with a low melting point. As a result of their interaction, a wet mass unsuitable for use is formed. This property must be taken into account when prescribing powders of ascorbic acid, menthol, camphor bromide, phenazone. The combination of caffeine with sodium benzoate is considered eutectic.

The result of physical interaction is not always negative. Thus, this type of interaction is used when adsorption is necessary (binding of medicinal molecules, toxic substances or salts of heavy metals, etc.). Enterosorbents act in the gastrointestinal tract, preventing the absorption of these compounds.

Chemical interaction of medicinal substances is a type of pharmaceutical interaction and

can be observed when forming insoluble complexes of tetracyclines with a number of ions of Ca++, Al+++, Fe++, Mg++, etc. Acidic solutions cannot be used as bases for drugs that are weak acids, since precipitation of drugs is possible; heparins, aminophylline, etc. are unstable in such solutions. Barbiturates, phenytoin, phenothiazines, furosemide and B vitamins are not recommended to be mixed with solutions of other drugs.

Chemical interaction is also used for therapeutic purposes, for example, acid neutralization reactions. However, such interaction can lead to the development of adverse reactions.

Pharmaceutical interaction is also possible at the level of absorption of drugs in the gastrointestinal tract. For example, sorbents taken simultaneously with other drugs reduce their absorption and bioavailability. Calcium ions, binding to tetracyclines, prevent the absorption of the latter. Ion exchange resins (for example, cholestyramine) interact with a number of drugs (digoxin, indirect anticoagulants, etc.), which become insoluble and are excreted through the intestines. Thus, inhibition of the absorption of thyroid hormone drugs under the influence of cholestyramine can lead to the development of hypothyroidism in patients receiving hormone replacement therapy.

Pharmaceutical interactions are also associated with the stability and photosensitivity of drugs.

According to the definition of the United States Pharmacopeia (USP), the stability of a drug is the preservation of its therapeutic properties and characteristics, which it acquires immediately after manufacture, throughout the entire period of its storage and use. The stability of the drug is associated with its resistance to various chemical, physical and microbiological agents that can change its initial properties during transportation, storage, use.

- Unstable drugs for 2-4 hours (ampicillin);
- Stable drugs for 6-8 hours (diazepam, furosemide, benzylpenicillin);
- Stable drugs for 12 hours.

Photosensitive drugs that should be administered 6 hours after preparation (amphotericin, cephaloridine).

Necessary rules: do not mix drugs and do not add to infusion solutions (except glucose and sodium chloride), when changing solutions (precipitation, turbidity) - do not use, prepare solutions if necessary, all bottles with infusion solutions must have labels.

Pharmacokinetic interaction of drugs, its features and types. Examples.

Pharmacological interaction is divided into:

- Pharmacokinetic;
- Pharmacodynamic;
- Biopharmaceutical (chemical and physicochemical interaction of drugs in the body's environments).

Pharmacokinetic interaction occurs at all stages of pharmacokinetic processes in the body.

- At the absorption stage:

The features of the interaction at this stage of the pharmacokinetics of drugs depend on the speed and completeness of absorption. Changing the absorption rate is important in cases where it is important to quickly achieve the maximum effect of the drug. It also plays a role in choosing the time of administration of the drug in a maintenance dose during long-term therapy in order to prevent a decrease in the concentration of the drug below the minimum therapeutic. A change in the rate of absorption can affect the effectiveness of medicinal substances, the therapeutic effects of which depend not on the concentration of the drug in the blood, but on the rate of change in this concentration. When the rate of absorption slows down, the systemic bioavailability of poorly soluble drugs may decrease.

For example:
 Decreased peristalsis (M-cholinolytics, morphine-like, tricyclic antidepressants)
 Absorption (carbogen, enterosgel)
A change in the completeness of absorption affects the bioavailability of the drug, and therefore, its systemic effects. In some cases, a change in the completeness of absorption can affect the nature of the distribution of the drug in the body.
A change in absorption is noted if the medicinal substances:
• chemically interact with each other (tetracycline - metal salts);
• change the acidity of the stomach (proton pump inhibitors - weak acids);
• affect the speed of chyme passage through the gastrointestinal tract (laxatives, cholinomimetics, cholinolytics);
• compete through the transport systems of the small intestine (β-lactam antibiotics - furosemide);
• affect the intestinal microflora (antimicrobials).
Thus, when used together, some drugs can affect the speed and completeness of absorption of other drugs, causing a change in their systemic bioavailability. The main mechanisms of drug interaction at the absorption stage include:
• change in the acidity of gastric contents;
• influence on the speed of chyme passage through the gastrointestinal tract;
• competition through the transport systems of the small intestine;
• suppression of the intestinal microflora.
• Interactions due to competition through tubular transport (lithium salts and thiazide diuretics - lithium intoxication).
Interaction at the stage of drug distribution.
Drug substances of systemic action enter the blood from the site of administration. In the blood, they interact with blood plasma proteins and formed elements. As a result, free and bound fractions of the drug substance are formed, which leads to a change in the rate of its metabolism and elimination, and in some cases, to a change in the nature of distribution in organs and tissues. First of all, such interactions are noted with drugs with a high degree of binding to blood proteins.
Usually, drug substances, getting into the blood, bind to plasma proteins to one degree or another. A dynamic equilibrium is established between the free and bound fractions, which can be shifted in either direction. Such a displacement can be carried out by other drugs that have an affinity for the same proteins. It should be taken into account that the pharmacological effect is exerted by the free fraction of the drug substance. A decrease in protein binding from 98 to 96% leads to a twofold increase in the free fraction in the blood. Thus, drugs that have a higher affinity for a certain protein, displacing the drug from its binding, can significantly enhance the therapeutic and toxic effect of the latter, sharply increasing its content in the blood. This is of significant importance for drugs that bind to proteins by 85%.
 Displacement from protein binding (salicylates, sodium valproate, sulfonamides), caffeine increases the permeability of the BBB for penicillin.

Cardiovascular drugs that are ≥85% protein bound: propranolol, warfarin, verapamil, digitoxin, phenytoin, nifedipine, prazosin, furosemide, quinidine, chlorpropamide, clofibrate, dicumarol.

The most well-known therapeutically significant is the displacement of drugs from their binding to blood proteins when administered simultaneously with:

• anticoagulants;
• penicillins;

• oral antidiabetic drugs;
• digitoxin;
• methotrexate.

 At the distribution stage (tricyclic antidepressants inhibit the entry of methyldopa into nerve endings).

Examples of drug interactions associated with competition for binding sites with blood transport systems are observed with the simultaneous use of bilirubin with sulfonamides or vitamin K (jaundice), tolbutamide with salicylates or phenylbutazone (hypoglycemia), methotrexate with salicylates or sulfonamides (agranulocytosis) and in other cases.

 At the stage of metabolism, induction (epileptic seizures on the background of phenytoin, contraceptives - pregnancy) and inhibition (warfarin - chloramphenicol, metronidazole)

Drugs can act as inducers and inhibitors of metabolic enzymes, reducing or increasing their half-life:

• if the half-life decreases (enzyme induction), then to maintain the concentration in the blood plasma within the therapeutic range, it is necessary to increase the dose of the drug or reduce the interval between its doses;

• if the half-life increases (enzyme inhibition), then the dose of the drug should be adjusted to decrease it or increase the intervals between its administrations.

In potentiating the action of one drug by another, it is likely that not only the above-mentioned effects play a role, but also a decrease in the metabolism of substances in liver microsomes.

Strong inducers of hepatic metabolism are barbiturates, carbamazepine, phenytoin, rifampicin, chloral hydrate, chlordiazepoxide, chlorpromazine, meprobamate, diphenhydramine, trifluoperazine, codeine, etc.; active inducers are menthol, coffee, alcohol, as well as some food additives. A number of toxicants - acetone, benzene, DDT (4,4-dichlorodiphenyltrichloroethane) and others increase the activity of hepatic metabolism. At the same time, other toxic substances (lead, mercury, nickel, arsenic, phenols, carbon tetrachloride, aniline, etc.) reduce it.

It should be noted that the induction of liver microsome activity usually develops slowly. Approximately only after 7–10 combined doses of drugs, one of which affects hepatic metabolism, a clinically significant change in the concentration of another drug is detected. At the same time, the concentration of the inducer drug in the blood usually does not significantly affect the degree of enzyme induction. If induction of liver enzymes is determined, the dose of the drug whose metabolism is stimulated should be increased to achieve the desired therapeutic effect.

Inhibition of liver enzymes usually occurs faster than induction. As a rule, for the development of the inhibition phenomenon, it is enough to achieve a certain concentration of the inhibitor drug. This concentration can be achieved even at its first dose. The higher the concentration of the inhibitor drug in the blood (i.e., the higher the dose), the greater the likelihood of drug interactions associated with inhibition of liver enzymes. When inhibiting hepatic metabolism, it is necessary to reduce the dose of the drug whose metabolism is inhibited, or increase the interval between its doses. Otherwise, the likelihood of developing adverse reactions associated with overdose increases sharply.

Since it is impossible to calculate in advance the degree of induction (inhibition) of hepatic metabolism, long-term combined use of drugs with inducers or inhibitors of hepatic metabolism is an indication for therapeutic drug monitoring.

 At the stage of excretion (accumulation of digoxin - inhibition of secretion by quinidine).

Drug interactions at the elimination stage are often detected through changes in urine pH (sodium bicarbonate increases the rate of excretion of barbiturates and salicylates) and competition of drugs for renal tubular transport systems (probenecid reduces the excretion of penicillins, furosemide slows the excretion of β-lactam antibiotics). Drug interactions at the

elimination stage can cause side effects. For example, phenylbutazone, by inhibiting the excretion of oxyacetohexamedine, leads to the development of hypoglycemia; ammonium chloride leads to the formation of a sulfadimezine derivative, which damages the renal epithelium.

In addition, drugs are divided into those that provoke interaction and those that become objects of interaction.

 Drugs that provoke interaction:

 Drugs that actively bind to proteins and displace the target drug (aspirin displaces SG, sulfonamides);

 Change metabolism - stimulating (phenobarbital, carbamazepine, rifampicin) and suppressing - (chloramphenicol, cimetidine, metronidazole, ketonazole, MAO inhibitors, fluoroquinolones);

 Change renal function and renal clearance (diuretics):

 Drugs that may become the target of interaction:

Pharmacodynamic interaction of drugs. Types. Examples.

Pharmacodynamic interaction can occur:
-in the field of bioreceptors;
-at the level of effector systems, cells and organs;
-at the level of physiological systems of the body.
Pharmacodynamic interaction is associated with a change in the effects of drugs and is due to the following main mechanisms:

✓ competition for receptors (both agonists and antagonists can compete);

✓ change in the pharmacokinetics of drugs at the site of action, which may be associated with a change in their absorption, distribution, metabolism and elimination;

✓ effect on synaptic transmission;

✓ interaction of drug effects:

• summation (additive synergism) - with the combined use of drugs, the strength of their action is equal to the sum of the effects of each of the drugs separately, while the effect of one drug does not depend on the changes in the body caused by the action of another drug. More often found in drugs with a similar mechanism and direction of action. Allows you to lower the dose of drugs and reduce side effects;
• potentiation (supraadditive synergism) - when as a result of the interaction of drugs, a significant increase in the effect of one of the drugs is noted and the final effect exceeds the sum of the effects of each drug separately. It should be remembered that not only positive, but also side effects of drugs are potentiated;
• antagonism - a phenomenon when under the action of one of the drugs the effect of the other decreases or completely disappears. Often the final effect of such a combination depends on the dose of each drug. This is used in toxicology (antidotes), as well as to eliminate or prevent side effects. Antagonists also include substances that interfere with the action of BAS in the body: vitamins, hormones, ions.
Pharmacodynamic interaction can be:
 Direct:

 Antagonism at one point of action (opiates-naloxone);
 Synergism at one point of action (muscle relaxants – aminoglycosides, quinine, polymyxin);
 Summarization, i.e. synergism at different points of action (alcohol-benzodiazepines);
 Indirect:
 Reduction of platelet aggregation (salicylates, dipyridamole increase the effect of warfarin;
 The appearance of gastrointestinal ulcers stimulates bleeding when taking anticoagulants;
 Enhancement of the toxic effect of SG in hypokalemia.

With a high dose-dependent effect and cause toxic effects with a slight increase in dose (SG, anticoagulants, aminoglycosides, oral contraceptives, anticonvulsants).

Interaction at the receptor level most often leads to different results. If two agonists (substances that have a pronounced affinity for the receptor and sufficient internal activity) react with the same type of bioreceptors, then their effects are summed. Summation is understood as such a phenomenon in the interaction of drugs when the strength of their action is equal to the sum of the effects caused by each of them separately. For example, the effect of pilocarpine and carbocholine on intraocular pressure can be summed. If two drugs, changing the function of the body in one direction, act on different bioreceptors, potentiation (significant enhancement) of the effect of one of them is possible. Thus, droperidol, interacting with dopamine receptors, enhances the analgesic effect of fentanyl, which activates opiate receptors in the CNS.

If antagonism (reduction or elimination of the effect of one drug under the influence of another) of two lipids is realized at the level of receptors of the same type, then such a phenomenon is called competitive antagonism. For example, the H1-receptor blocker diphenhydramine eliminates the hypotensive effect of histamine. The effect of the antagonist is reversed, and in its presence the agonist (histamine) can cause an effect if its concentration is higher than in the absence of diphenhydramine.

In non-equilibrium antagonism, the blocker reacts with the receptors permanently. For example, armine and other organophosphorus compounds irreversibly block acetylcholinesterase. As new enzyme molecules are synthesized in the body, acetylcholine is hydrolyzed. Non-competitive antagonism occurs when one of the drugs binds not to the active center of the bioreceptor, but near it, as a result of which the interaction of the agonist with the receptor is weakened or becomes impossible (allosteric blockade). For example, serotonin reduces the effect of the local anesthetic cocaine. The interaction of drugs can disrupt the transmission of the primary stimulus, mediated by mediators, hormones, calcium ions, etc. Most often, the kinetics of the binding of the mediator to the receptor changes. In the amplification and conduction through the cells of the primary stimulus caused by many endogenous and exogenous ligands, secondary mediators are of great importance: for example, cyclic adenosine monophosphate (c-AMP) and cyclic guanosine monophosphate (cGMP). If one of the drugs affects the synthesis, transport, biotransformation and binding to indifferent ("silent") receptors of the "secondary" mediator, then the pharmacological effects of the other drug change in quantitative and qualitative terms.

Thus, with the joint use of salbutamol and theophylline in bronchial asthma, the content of c-AMP in smooth muscles increases, which leads to its relaxation; the therapeutic effect of the drugs is enhanced. Salbutamol, activating β-adrenoreceptors, accelerates the synthesis of c-AMP, theophylline, blocking phosphodiesterase, prevents the hydrolysis of c-AMP.

When drugs interact at the level of effector mechanisms, antagonism may be observed. For example, spasm of bronchial smooth muscle caused by histamine can be eliminated by salbutamol, which activates β-adrenoreceptors.

Antibiotics that have a bacteriostatic effect (tetracyclines, rifampicin, chloramphenicol, erythromycin, lincomycin, etc.) can reduce the effectiveness of bactericidal antibiotics that block the synthesis of components of the microbial envelope only in the growth phase (penicillins, cephalosporins). Such an interaction is realized as undesirable synergism.

In medical practice, drugs with different mechanisms of action are widely used to treat the same disease. For example, cardiac glycosides are used in combination with diuretics for the treatment of cardiovascular failure. With increased secretion of gastric juice, antacid drugs are used together with mcholinomimetics or H2-histamine blockers. With such an interaction, the likelihood of the appearance or intensification of undesirable effects increases. For example, diuretics that cause hypokalemia in combination with cardiac glycosides can cause cardiac arrhythmia.

Since when taking drugs, the interaction of components occurs with the participation of not only physicochemical, but also biochemical laws (with the participation of components of the biosystem or directly in the body), biopharmaceutical interactions should be distinguished from the group of pharmaceutical (i.e. physicochemical) interactions. This is convenient for practical reasons, since physicochemical interactions are, as a rule, undesirable, while biopharmaceutical interactions are usually useful and are used in clinical practice, for example, in antidote therapy.

Biopharmaceutical interactions are due to the chemical and physicochemical properties of drugs that react in the body's environments. For example, the use of antidotes in poisoning. Thiol substances (unithiol, EDTA) form soluble compounds (chelates) with metals and accelerate their excretion, deferoxamine forms a complex with iron, promoting excretion.

Polypharmacy, definition of the term. Consequences of polypharmacy, examples

Polypharmacy (Greek poly - many + pragma - subject, thing) - the simultaneous appointment of a large number of drugs or medical procedures to a patient, often unjustified and irrational. Often, the doctor's desire to prescribe several types of drugs to a patient is associated with damage to several organs or their systems.

In 2017, the World Health Organization (WHO) defined polypharmacy as the simultaneous use of 4 or more drugs (does not apply to cases of serious condition of a patient in the intensive care unit).

I would like to draw special attention to the fact that under medical prescription it is necessary to understand not only the use of drugs, but also excessive conduct of other medical interventions - diagnostic studies (thanks to the development of instrumental and laboratory diagnostic methods over the past decade, many doctors have "sinned" with this), physiotherapy procedures and surgical interventions.

The concept of "polypharmacy" includes the term "polypharmacy", or "polypharmacotherapy", - the simultaneous appointment of several drugs. The term "pharmacomania" (pharmakon - medicine, mania - passion) - an unreasonable desire to take drugs - is used in two meanings:

• an inadequate desire of the patient to use different drugs or to take a certain remedy;

• mass use of drugs by the population (mainly tranquilizers and sleeping pills).

Some authors define this term as a tendency to consume drugs without urgent need; licomania".

Thus, today we have a large number of terms, and the problem associated with them is one.

By resorting to polypharmacy, specialists seek not only to reduce the time of recovery,

increase the effectiveness of therapy, but also to prevent all possible complications. When prescribing a combination of several drugs, the doctor does not fully take into account all aspects of their pharmacological (pharmaceutical, pharmacodynamic, pharmacokinetic) interaction. However, it is this factor that plays one of the key roles in the outcome of therapy. It has been established that against the background of the simultaneous use of 2-3 drugs, drug interactions occur in 6% of patients, when using 5 drugs, their frequency increases to 50%, and in lucky patients who receive ≥10 drugs, drug-drug reactions are almost guaranteed to develop. Since thousands of different biochemical processes occur simultaneously in the body, the intensity of which differs in each person depending on the genetic individuality, nutritional characteristics, drug intake, the influence of environmental factors (temperature, ionizing radiation, etc.), it is impossible to predict the nature of drug interactions. Polypharmacy and its consequences are directly related to the problem of drug interaction - a quantitative or qualitative change in the effects caused by drugs with the simultaneous or sequential use of two or more drugs.

Combinations of drugs can be:

- rational;
- irrational;
- potentially dangerous(!).

A rational combination of drugs is considered if there is an increase in the effectiveness and/or improvement in the safety profile of therapy. An irrational combination of drugs is called a combination of drugs, against the background of which the pharmacological effect of one/several drugs decreases.

A potentially dangerous combination of drugs threatens the patient's life, leads to the development of serious side effects, etc.

The prerequisites for polypharmacy are the presence of several diseases (arterial hypertension (AH) and chronic heart failure (CHF), diabetes mellitus and AH, bronchial asthma and pulmonary emphysema, etc.); insufficient safety or ineffectiveness of monotherapy, for example, in severe infectious processes, CHF, hypertension (it has been proven that only in 25-30% of patients with hypertension with low blood pressure, monotherapy is effective, when taking 2 drugs, adequate control is achieved in 70% of cases, 3 drugs - in 90); taking drugs at the discretion of the patient within the framework of self-medication (irresponsible self-medication) on the advice of friends, acquaintances, under the influence of advertising and others.

Many patients are regular consumers of widely advertised drugs and biologically active supplements. In addition, sometimes the patient is able to provoke drug polypharmacy, simply by not informing the doctor about what he supplemented his prescription with. Pharmacy workers (pharmacists) also make their "significant contribution" to the problem of polypharmacy.

All of the above causes a high probability of drug interaction with each other, which leads to a change in the expressiveness and the nature of the main pharmacological effect, its duration, as well as the strengthening or weakening of adverse and toxic reactions.

According to available data, about 50% of adverse reactions to drug therapy are a consequence of drug interactions; approximately 30% of deaths due to adverse reactions are also associated with it.

In the elderly, polypharmacy is associated with the risk of the appearance or exacerbation of symptoms of geriatric syndromes, such as cognitive impairment (dementia and delirium), falls, urinary incontinence, and eating disorders.

Polypharmacy is the simultaneous use of several drugs and the use of additional drugs to correct adverse effects. Most studies use a numerical definition of the concept of "polypharmacy", indicating that this is the simultaneous use of 5 or more drugs. Intensive polypharmacy is considered when 10 or more drugs are used simultaneously. It is proposed to define polypharmacy as appropriate, or justified, when the prescription of a large number of drugs is justified, and as inappropriate, when the number of prescribed drugs is incorrect and unbalanced. Appropriate (justified) polypharmacy is defined as the optimization of the use of

drugs by a patient with complex and/or multiple diseases, while the use of drugs is consistent with the best evidence. The combination of drugs ensures the maintenance of a high quality of life over the long term and minimizes the harm from drug therapy.

In the case of justified polypharmacy, a patient with ischemic heart disease may take an antiplatelet agent, an antianginal agent, a drug from the statin group, and in certain cases an angiotensin-converting enzyme inhibitor. Most elderly patients also take antihypertensive drugs.

The incidence of polypharmacy is increasing worldwide, even in developing countries. This is due, on the one hand, to an increase in life expectancy, and on the other hand, to an increase in the number of people who have access to certain drugs. In industrialized countries, the prevalence of multimedia is from 25 to 80%, depending on the region studied and the healthcare sector. According to a survey in 2008-2011, the level of polypharmacy (prescription of ≥ 5 drugs) in Germany was 13.6% for adult women and 9.9% for men (71.8% of the drugs taken were prescribed by a doctor, 27.7% - through self-medication.

According to the literature, when using 5 drugs or less, the frequency of adverse drug reactions does not exceed 5%, and when using 6 drugs or more, it increases to 25%.

The prescription of two drugs causes interaction in 6% of patients, the use of 5 drugs increases their frequency to 50%, and with 10 drugs - the risk of drug interactions reaches almost 100%.

A side effect when taking one drug in the elderly occurs in 10%, when taking more than 10 drugs - in almost 100% cases, and the mortality rate is approaching 10%.

The incidence of polypharmacy is increasing worldwide, which is due, on the one hand, to an increase in life expectancy, and on the other, to an increase in the number of people who have unhindered access to prescription drugs. A special problem group is the elderly, who take a large number of drugs that are not always compatible with each other. And when a frequent additional symptom appears - pain that is not associated with the main diseases, they also start taking painkillers, not taking into account that such an interaction can lead to the development of side effects, that is, polypharmacy. Due to age-related pharmacokinetics, the risk of developing adverse reactions in the elderly is several times higher than in young people. Geriatric patients are often hospitalized because there is a need to reduce doses, as well as completely abandon the drug that was used.

A special problem group of people is the elderly in nursing homes. According to a survey of Australian nursing homes, the average number of medications taken by seniors was 9, with 72.4% taking at least one inappropriate medication. Due to age-related pharmacokinetics, the risk of adverse reactions in the elderly is several times higher than in young people. Elderly people are often hospitalized for reasons that require dose reductions and complete withdrawal of the drug used. In Germany, seniors over 60 years of age are prescribed more than half of all prescription medications, with an average of about three to four medications. Properly selected medications can provide the necessary support, taking into account the individual risks of each patient individually. Geriatric methods, such as the assessment and consistent use of non-pharmacological treatments, are also innovative in general practice.

It should be noted that patients are increasingly using non-prescription drugs, in particular for the treatment of general medical conditions (respiratory infections, pain, diarrhea, constipation, digestive disorders and headaches). Elderly people use a particularly large number of drugs. One of the factors for the development of undesirable effects in polypharmacy is self-medication.

Typical self-medication errors:

• use of several drugs under different trade names that contain the same active ingredient;

• simultaneous use of incompatible drugs;

• failure to comply with the rules of drug dosage (especially in geriatric patients) and duration of treatment;

• ignoring the presence of concomitant diseases (usually elderly people are polymorbid - have several diseases).

Comorbidity is the presence of two or more independent diseases or syndromes in the same patient, which may be associated with a single cause or single mechanisms of pathogenesis of these conditions or coincide in time (parkinsonism and pain syndrome, depression and pain syndrome, epilepsy and pain syndrome, arterial hypertension and diabetes mellitus, etc.). Since polymorbidity increases with age (several diseases in one patient), its prevalence becomes higher than the prevalence of many socially significant diseases, in particular arterial hypertension, type 2 diabetes mellitus, osteoarthritis, etc. It is known that 65% of patients aged ≥ 65 years have 2 or more diseases, 43% - 3 or more, and 24% - 4 or more diseases. Polymorbidity is considered one of the main causes of mortality and the use of a large number of medications. A patient with two diseases, such as heart failure and chronic obstructive pulmonary disease, usually takes more than five medications. It was found that 37.1% of men and 36% of women aged 75 to 85 years take at least five prescription medications. However, 47.3% take at least one over-the-counter drug, and 54.2% take dietary supplements. The number of medications taken by a patient over 65 years is strongly associated with the risk of hospitalization and mortality. Polypharmacy has been found in 4% of elderly people and in more than 96.5% of hospitalized patients.

In addition to polymorbidity, the causes of polypharmacy include self-medication, inappropriate recommendations, some demographic factors (age, gender, level of education), the level of development of the healthcare system, as well as other factors that affect the number of visits to doctors and medical facilities.

Quite often, it can be found that a patient is prescribed 6–7, and sometimes 8–10 or even more drugs at the same time, which creates conditions for the interaction of not only the starting substances, but also their metabolites, in the process of which highly allergenic complexes and conjugates can arise, which often leads to the development of a dependence syndrome (pharmacomania) and uncontrolled drug interactions. This significantly complicates the treatment of elderly patients and increases the risk of side effects. In the USA, more than 65% of hospitalizations for urgent conditions were associated with the use of warfarin, antiplatelet agents, insulin and hypoglycemic agents, in Japan, anticholinergic and antihistamine drugs, benzodiazepines, sulpiride and digoxin most often cause side effects, in the UK, cardiovascular, psychotropic and non-steroidal anti-inflammatory drugs, together with polypharmacy, are identified as the most significant determinants of the development of side effects.

The most rational approach to the treatment of any disease is etiological or pathogenetic therapy - the impact on the very cause of the disease or on the pathophysiological mechanisms underlying the development of the disease. With this approach, the appointment of only one etiologically or pathogenetically justified drug can relieve the patient from many manifestations of the disease and thus eliminates the need to prescribe a large number of drugs.

Despite their widespread use, NSAIDs, when combined with other drugs, cause many side effects: gastrointestinal (dyspepsia, ulcers, bleeding), hepatic (liver cell damage), cardiological (arterial hypertension, progression of chronic heart failure, edema), renal (decreased glomerular filtration, interstitial nephritis), bone and joint (degenerative effect on cartilage, progression of osteoporosis), bronchopulmonary (aspirin asthma), platelet (aggregation disorders, increased risk of bleeding), neurological (impaired central nervous system function, insomnia, paranoia, depression, forgetfulness). Considering that geriatric patients mostly already have a number of diseases and take certain medications, when recommending NSAIDs that cause a large number of "side effects", one should be especially careful and remember the effect of polypharmacy. It is necessary to take measures to improve the effectiveness and safety of treatment of geriatric patients, especially with regard to NSAIDs used in this age group. The increased frequency of drug interactions occurs precisely in cases where the dosage regimen, existing diseases and concomitant use of other drugs are not taken into account.

Example of drug interactions.

20 medical records of inpatients and prescription letters for them in one of the clinics in Kharkiv were analyzed. The analysis was carried out in accordance with the developed criteria:

- presence of polypharmacy;
- rationality of prescriptions (including compliance with indications/contraindications);
- interaction of prescribed drugs (irrational combination/incompatibility);
- assessment of dosage/administration regimen of drugs, including taking into account individual characteristics (age, severity of condition, complications);
- effectiveness of methods for monitoring the safety of therapy, etc.

The results obtained were predictable and at the same time unexpected: polypharmacy was observed in 100% (!) of cases. In 30% of cases, 12-14 drugs were prescribed simultaneously, in 5% - 17 (!) drugs. In 4 cases, outdated drugs were used (raunatin, reserpine/nepresol); in 3 - drugs that duplicate each other (diclofenac and ibuprofen; propranolol and atenolol), in 4 - drugs when the patient had contraindications to them; in 15 cases, 1-4 drugs were prescribed unreasonably (in the absence of indications). In 11 cases, irrational combinations of drugs were used (pharmacodynamic synergism, pharmacokinetic antagonism), which led to an increased risk of adverse reactions (hemorrhagic syndrome, extrapyramidal disorders, central nervous system depression, etc.). Violations of dosage and frequency of drug administration were registered – 2 episodes each.

The doctor's role in preventing undesirable interaction effects.

From the point of view of common sense, polypharmacy is a negative phenomenon, because it leads to the unjustified introduction of foreign (medicinal) substances into the body and contributes to an increase in the cost of treatment. Polypharmacy remains a common practice of our doctors. In this case, a mass of drugs is prescribed, the use of which is based on personal preferences, and not on the basis of evidence of effectiveness in the treatment of a specific pathology. Polypharmacy often causes insufficient attention by doctors to the search for and correction of causal and contributing factors, especially in geriatric practice, where the doctor's psychology is "forced" due to polymorbidity.

Due to age-related characteristics of pharmacokinetics, the risk of developing adverse reactions in elderly patients is 5–7 times higher than in young patients, and when using 3 or more drugs - 10 times. Elderly people are 2–3 times more likely to be hospitalized for this reason, which necessitates not only minimizing doses, but also limiting the drugs used. Minimizing polypharmacy is possible if the doctor uses in his practice a limited range of effective drugs, about which he has in-depth knowledge of all positive and negative properties, features of pharmacokinetics and pharmacodynamics, mechanisms of their interaction, conditions of use, endogenous and exogenous factors that can affect effectiveness.

The economic aspect of the problem is that the spread of polypharmacy exhausts the already small resources of the domestic healthcare sector, increases the burden on the budgets of patients and insurance companies. The issue under study is closely related to the problem of drug interactions, which often cause adverse reactions (however, sometimes it can be clinically beneficial). The appointment of two drugs causes interaction in 6% of patients, the use of 5 drugs increases their frequency to 50%, and 10 drugs - the risk of drug interactions reaches almost 100%.

At the end of the last century, the World Health Organization (WHO) requirements for drugs were formulated: effectiveness, safety, availability and acceptability for the patient, which were concentrated around the main criterion - benefit/risk, which should, from the standpoint of evidence-based medicine, ensure rational pharmacotherapy, i.e. the patient's quality of life.

Several proposals have been proposed to overcome the problem of unjustified polypharmacy:

1) search and synthesis of new molecules with polyfunctional properties or with a basic property common to various diseases;

2) use of already existing drugs, taking into account their nonspecific effects (hypoxants, anti-inflammatory drugs, etc.);

3) creation of new combinations of drugs of different pharmacotherapeutic groups, including in one dosage form. As is known, rational drug combinations are combinations in which a drug from one group enhances the desired effect and does not increase, and perhaps even reduces, the undesirable effect of a drug from another group.

Physicians should also consider stopping certain medications as a therapeutic intervention. In doing so, the physician should consider the patient's perspective on the goals of therapy, including views on medications and chronic diseases, as well as preferences and priorities for prescribing medications to slow disease progression, prevent health disorders, and eliminate symptoms. This will reduce medication burden and the risk of polypharmacy.

According to the researchers, the key to combating the risks associated with polypharmacy is to ensure that patients are fully involved in the doctor's decision to start taking the drug, as well as to monitor the use of medications to monitor compliance with the appropriate regimen.

This set of measures should include, first of all, informing patients about the potential risks of using the drugs, as well as about their benefits, familiarizing healthcare professionals with regular drug reviews, and timely reporting by patients of any adverse events to their doctor.

An example of optimizing the safety profile is the classic tandem of proton pump inhibitors (omeprazole, pantoprazole, etc.) and NSAIDs; such a combination reduces the risk of NSAID gastropathy.

It is also possible to reduce the effectiveness of therapy. For example, the simultaneous use of antihypertensive drugs and non-steroidal anti-inflammatory drugs leads to suppression of the antihypertensive effect (NSAIDs retain sodium and fluid, reduce renal blood flow, etc., which provokes an increase in blood pressure).

It is necessary to pay attention to the fact that the phenomenon of prescribing or recommending the use of medications by healthcare professionals who do not have the right to do so, such as paramedical staff or pharmacists, is quite widespread worldwide, which additionally entails potential adverse consequences.

Healthcare professionals should strive to balance individual risks and benefits for patients, using all currently available tools, and implement appropriate mechanisms for monitoring and analyzing decisions to prescribe medications to patients, especially high-risk groups.

Therefore, the development and implementation of effective mechanisms to ensure the correct prescription of drugs only in the presence of appropriate indications, patient awareness of the benefits of the chosen therapeutic approach and its possible complications that may arise as a result of treatment, as well as regular monitoring of patients' compliance with the established treatment regimen is an extremely important task of medicine both today and in the future.

An example of a deterioration in the safety of treatment is the suppression of the cardiac conduction system with the simultaneous use of calcium antagonists, in particular the phenylalkylamine derivative verapamil, and β-blockers. Such a combination also increases the risk of heart failure, since both drugs have a negative inotropic effect.

How can (and is it possible at all) to prevent polypharmacy?

 remember the problem of polypharmacy and the risk of complications (!);

 improve qualifications, including regarding drug interactions (“Learning not for life, but through life”), carefully study the instructions for medical use of drugs, especially the section “Interaction with drugs of other groups”;

 do not allow the use of drugs in the absence of appropriate indications;

 when prescribing drugs, you should find out what other drugs the patient is taking (on the advice of another doctor);

 when recommending a new drug, review the list of drugs previously recommended;
 pay special attention to children, the elderly, pregnant women, people with liver and kidney pathology.

Questions for self-control on the topic:

1. Content, basic concepts of the topic "Drug Interaction" in modern medical practice and pharmacy. Types of drug interactions, main classes by clinical significance (A, B, C, D), their practical clinical significance for safe use in patients. Antagonism and synergism, as a consequence of drug interactions. Types of synergism. The concept of pharmaceutical, pharmacodynamic, pharmacokinetic drug interactions.

2. Pharmaceutical drug interactions: causes of development, main mechanisms and possible consequences of interaction. Practical clinical significance of the results of drug interactions.

3. Pharmacodynamic drug interaction: causes of development, main mechanisms and possible consequences of interaction. Practical clinical significance of drug interaction results.

4. Pharmacokinetic drug interaction: causes of development, main mechanisms and possible consequences of drug interaction.

5. The role of the doctor and pharmacist in modern medical practice in reducing the risk of side effects of drugs due to irrational drug interactions, their educational work in reducing the number of cases of irrational use of drugs by patients (polypharmacy) in order to optimize pharmacotherapy for each patient.

6. Drug interactions as a risk factor for medication errors and adverse drug reactions. Combined use of drugs: adverse effects and early detection methods to prevent their development in patients.

7. Study of the main mechanisms and features of drug interactions due to polymorbidity of the patient's morbidity. Assessment of risks associated with the potential likelihood of developing adverse drug interactions among drugs of the main groups of drugs.

8. The effect of food on the absorption and pharmacokinetics of drugs, features of the safe use of drugs of different pharmacological groups. The effect of liquids and drinks on the absorption and pharmacokinetics of drugs, features of the safe use of drugs of different pharmacological groups.

9. Features of drug interactions and issues of effectiveness and safety of the use of drugs together with herbal medicines, food additives, features of the safe use of drugs of different pharmacological groups.

List of sources on the topic:

1. Clinical pharmacology: a textbook. M.V. Khaitovich, G.V. Zaichenko, I.O. Afanasyeva and others. Medicine. 2024. 335 p.

2. Clinical pharmacology: a textbook / E. I. Shorikov, G. I. Shumko, O. S. Khukhlina and others. Vinnytsia: Nova Knyga, 2019. 512 p.

3. Pharmacology: a textbook for students of medicine and dentistry of the Higher Medical University / I. S. Chekman, V. M. Bobyrev, V. Y. Kresyun [and others]. Vinnytsia: Nova Knyga, 2020. 471 p.

4. Kraydashenko, O. V. Side effects of drugs. Pharmacological supervision system in Ukraine [Text] / O. V. Kraydashenko, M. P. Krasko, O. M. Glavatsky — Z. : FPO, 2015. — 49p.

5. Khaitovich M.V. Polypharmacy: definition, risks, management. Original Researches. OriginalResearches. Vol. 2. No. 3. 2021.

6. Bezrukov V., Kuprash L. Geriatric aspects of drug therapy. Visn. pharmacology and

pharmacy. 2005 . No. 12. P. 23–27.
7. Bilay I. M. Drug interaction. Textbook for pharmacists-interns with the specialty "General pharmacy" / I. M. Bilay, E. O. Mykhailiuk, A. I. Bilay. ZhMU. 2019. 82 p.