Ministry of health of the Republic of Belarus
Educational institution
«Gomel State Medical University»

Department of general and clinical pharmacology

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METHODOLOGICAL RECOMMENDATIONS

for a practical lesson on the discipline "Clinical pharmacology"
with six-year students of the Faculty of Foreign Students,
studying at the specialty 1-79 01 01 "General medicine"

TOPIC 2: «DRUGS AND RECEPTORS. CLINICAL PHARMACOLOGY OF ANTIALLERGIC DRUGS. ANAPHYLAXIS. EMERGENCY MEDICAL CARE. CLINICAL PHARMACOLOGY OF NON-STEROIDAL AND STEROIDAL ANTI-INFLAMMATORY AND NARCOTIC ANALGESICS».

Time: 6 hours

Approved at the meeting of the department of general and clinical pharmacology

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LEARNING AND EDUCATIONAL GOALS, OBJECTIVES, MOTIVATION FOR LEARNING THE TOPIC

Allergic diseases are among the most pressing problems of modern medicine. According to the World Health Organisation, they are on a scale comparable to the pandemic in the developed world. However, despite recent developments, pharmacological guidelines and international guidelines for anti-allergy therapy, the problem is far from being solved, and often patients are not adequately treated. For this reason, the knowledge and skillful use of drugs with antiallergic effects is one of the most important tasks of modern pharmacology.

Pain and inflammatory syndromes are among the most pressing problems of modern practical medicine. According to the World Health Organization, they are comparable to a pandemic in the developed world. However, despite the relevance, pharmacological developments, international guidelines and recommendations for anti-inflammatory and antipain therapy, the problem is far from being solved and patients are often not adequately treated. For this reason, knowledge and skillful use of drugs with anti-inflammatory and analgesic effects is one of the most important tasks of modern pharmacology.

Learning objective:

– To develop scientific knowledge of the pharmacokinetics and pharmacodynamics of medicines and the ability to justify and provide rational differentiated pharmacotherapy for acute and chronic allergic reactions, angioneurotic edema, primary and secondary immunodeficiencies. Formation of scientific knowledge about analgesic and anti-inflammatory drugs and mastering the features of pharmacotherapy of pain and inflammatory syndromes, taking into account the features of pharmacokinetics and pharmacodynamics of drugs on the topic of the lesson

Educational purpose:

– – to develop their value-personal, spiritual potential, to form the qualities of a patriot and citizen, ready for active participation in the economic, industrial, socio-cultural and public life of the country; to realize the social significance of their future professional activities, to learn to follow academic and work discipline, standards of medical ethics and deontology.

Tasks:

As a result of the study lesson, the student should

know:

– clinical and pharmacological classification of medicines used in the treatment of diseases on the topic of the lesson, their pharmacokinetic and pharmacodynamic features;

– indications and contraindications to prescribing medicines according to the occupation, features of their use in various age groups and with various concomitant diseases; dosage regimen of drugs and their interaction with other pharmacological groups;

– principles of monitoring the effectiveness and safety of relevant medicines, possible side effects, methods of their prevention and correction;

be able to:

– collect pharmacological and allergological anamnesis and make an adequate choice of medicines, taking into account the peculiarities of their pharmacokinetics and

pharmacodynamics for the treatment of a particular patient;

– inform patients about the nature of the action of the medicines prescribed to them, the rules of admission and possible manifestations of side effects;

– to correct the dosage regimen in case of pathological changes in the functions of organs and systems responsible for biotransformation and elimination of medicinal products, as well as in the combined use of medicines;

– evaluate scientific information on the effectiveness of medicines and other means, work with reference and other literature on medicines;

possess:

– the ability and willingness to analyze the features of absorption, distribution, biotransformation and excretion of drugs;

– the ability and willingness to rationally dose the drug, including the choice of dosage form, routes of administration and dosage regimen;

– skills in the use of medicines in the treatment, rehabilitation and prevention of various diseases and pathological conditions, taking into account the basic pharmacodynamic parameters;

– skills of searching, analyzing and summarizing information about the use and effect of various medicines.

Motivation for mastering the topic:

The specifics of the training of doctors in this specialty determines the need for students to purposefully study knowledge about the pharmacokinetics and pharmacodynamics of medicines on the topic of the lesson and the ability to justify and conduct rational differentiated pharmacotherapy of acute and chronic allergic reactions, angioedema, primary and secondary immunodeficiency, pain and inflammatory syndromes.

MATERIAL EQUIPMENT

Reference and informational literature, charts, tables, presentations, drug collections.

CONTROL QUESTIONS FROM RELATED DISCIPLINES

– **from biochemistry and physiology:** physical properties and structure of cell membranes, transport of substances through biological membranes in norm and pathology;

– **from general and bioorganic chemistry:** fundamentals of chemical kinetics and catalysis, buffer solutions and systems, pH calculation;

– **from biochemistry:** kinetics of enzymatic reactions, the Michaelis-Menten kinetics equation, the concept of enzyme inhibitors, types of enzyme inhibitors;

– **from the Latin language:** the basic rules for the coordination of parts of speech and registration of prescription prescriptions when prescribing medicines;

– **from pharmacology:** general issues of pharmacology, pharmacokinetics and pharmacodynamics of drugs, general formulation and rules for prescribing drugs;

– **from immunology:** organs, cells, molecules of the immune system, allergy, hypersensitivity, features of the immune system in patients of different age categories;

– **from pediatrics**: physiological features of childhood, especially pathological conditions and diseases in children;

– **from obstetrics and gynecology:** physiology and pathology of pregnancy and lactation period;

– **from allergology:** features of the collection of an allergological history and the time of referral of patients to an allergist, clinical manifestations, specific diagnostic methods and differentiated diagnosis of allergic diseases, anaphylactic shock, variants of its course and treatment, medical tactics and medical and social expertise in allergic diseases;

– **from internal diseases:** features of clinical and anamnestic data in patients with pain and inflammatory syndromes, etiopathogenesis and modern approaches to the diagnosis of major diseases accompanied by pain and inflammatory syndromes.

CONTROL QUESTIONS ON THE TOPIC OF THE CLASS

1. The concept of receptors. Types of receptors.
2. Types of interaction of drugs with receptors.
3. The mechanism of development of immediate hypersensitivity reactions (urticaria, Quincke's edema, anaphylaxis, etc.).
4. Clinical and pharmacological characteristics of the main groups of antiallergic drugs.
5. Anaphylaxis, drug anaphylactic shock. Clinical manifestation, diagnosis and prevention of drug anaphylactic shock.
6. Prehospital and hospital stages of emergency medical care for anaphylactic shock.
7. Types of drug interactions with receptors.
8. Affinity and selectivity of action. Quantitative variations of the reaction to the drug.
9. Mechanisms of development of pollinosis, anaphylaxis.
10. Clinical pharmacology of antiallergic drugs;
11. Drug anaphylactic shock. Clinic, diagnosis, treatment, prevention.
12. Immunotropic drugs.
13. Clinical pharmacology of steroid anti-inflammatory drugs. Classification. Mechanisms of influence of drugs on various phases of inflammatory reactions. Comparative characteristics of systemic and local drugs. Indications for use. Principles of steroid therapy. Undesirable side effects. Complications of glucocorticosteroid therapy: prevention and possible methods of correction. The main contraindications. Drug interactions.
14. Clinical pharmacology of nonsteroidal anti-inflammatory drugs (NSAIDs). Classification (by chemical structure and selectivity of action on various types of COX). Pharmacological effects, mechanisms of anti-inflammatory action. Tactics of the use of NSAIDs, as well as combined medications for hyperthermic and pain syndrome.
15. Comparative characteristics of NSAIDs. Advantages and disadvantages of non-selective COX-1 and COX-2 inhibitors, as well as agents selectively blocking COX-2. Application, possible complications, main contraindications. Mechanism of development and prevention of "nonsteroidal gastroduodenopathy". Drug interactions.
16. Clinical pharmacology of opioid and non-opioid analgesics: mechanism of action, pharmacokinetics and pharmacodynamics, features of individual drugs. Principles of

choosing an analgesic agent. Comparative characteristics of opioid agonists in terms of efficacy, duration of action, and toxicity. Areas of medical use of narcotic analgesics. Side and toxic effects.

17. Analgesics of a mixed type of action (tramadol). The concept of neuroleptanalgesia. Auxiliaries for the elimination of acute and chronic pain syndromes: clonidine, amitriptyline, ketamine, carbamazepine, benzofurocaine, baclofen, diphenhydramine. Mechanisms of analgesic action, application.

PROCESS OF THE STUDY

Theoretical part

Theoretical questions are described in the appendix to the methodological recommendations.

The practical part

1) Take notes of the theoretical material demonstrated by the teacher;

2) Master the methodology of solving problems and prescribing prescriptions on the topic of the lesson.

Monitoring the assimilation of the topic

It is carried out in the form of independent written work (solving practical problems and prescribing prescriptions for an individual task).

METHODOLOGICAL RECOMMENDATIONS FOR ORGANIZATION AND EXECUTION OF STUDENTS' INDEPENDENT WORK (SIW)

The time given for independent work can be used by students for:

– preparing for the practical classes;
– completing the tasks on the topic of the class in the workbook;
– preparing thematic reports, essays and presentations;
– taking notes from academic literature.

The main methods of organizing independent work:

– completing tests and practical tasks of the electronic educational-methodical complex (EEMC) for self-monitoring and self-assessment.

The list of tasks of the SIW:

– solving practical problems in the EEMC;
– completing the test tasks of the EEMC;
– writing an educational medical history.

Control of the SIW is carried out in the form of:

– assessment of an oral answer to a question, report, report, or solution of a task in a practical class;
– individual conversation;
– checking the educational history of the disease.

METHODOLOGICAL RECOMMENDATIONS FOR ORGANIZATION AND EXECUTION OF CONTROLLED INDEPENDENT WORK OF STUDENTS (CIWS)

Recommended forms of CIWS organization:

- doing exercises on the topic of the class in the workbook;
- writing an essay on a given topic;
- preparing a report and a multimedia presentation on a given topic.

The list of tasks of the CIWS:

Topics of essays / multimedia presentations:

1. Mechanisms of development of pollinosis and anaphylaxis.
2. Acute toxic-allergic reactions (Stephen–Johnson syndrome). Classification. Diagnostics. Treatment.
3. Lyell's syndrome. Treatment tactics.
4. Hereditary angioedema. Pathogenesis. Treatment.
5. Preferential and selective COX-2 inhibitors in the treatment of inflammatory diseases of the musculoskeletal system.
6. Modern medicinal forms of SPVS of combined action.
7. NSAIDs – problems of self-treatment.
8. Medical and social aspects of the fight against drug addiction.

Forms of control of CIWS realization:

– checking the educational history of the disease;
– review and evaluation of the abstract on a given topic;
– checking and evaluating a multimedia presentation on a given topic.

LIST OF REFERENCES

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Antihistamines - drugs that block H1-histamine receptors.

Classification	**I generation**	**II generation**	**III generation**
Drugs	1. Diphenhydramine 2. Clemastin (Tavegil) 3. Chloropyramine (Suprastin) 4. Mebrogroline (Diazolin) 5. Quifenadine (Fenkarol) 6. Prometazine (diprasine, Pipolphen)	7. Loratadin (Claritin) 8. Dimethindene (Fenistil) 9. Ebastin (Kestin) 10. Azelastine (Allergodyl) 11. Astemizole (Gismanal) 12. Terfenadine (Bronal, Histadine)	13. Cetirizine (Zirtek) 14. Fexofenadine (Telfast) 15. Desloratadine (Erius)
Mechanism of action	Block H1-histamine receptors, as well as cholinergic and serotonin receptors	H1-histamine receptors are blocked	
Pharmacological effects	1. Antihistamine 2. Sedative, hypnotic (1-3, 6) 3. Antiholinergic (1-4, 6) 4. Hypotensive (1,6) 5. Resistance 6. Antiemetic (1,6)	***Unlike the Ist generation:*** 1. Do not have a sedative and hypnotic effect (poorly penetrate through the blood-brain barrier) 2. Do not have anticholinergic and α-adrenergic blocking properties 3. Do not cause resistance 4. Are long-acting (about 24 hours)	***Unlike the II generation:*** 1. Are active metabolites of anti-histamine drugs of the previous generation. 2. DO NOT affect the QT interval
Indications	1. Urticaria, eczema, itchy skin, dermatitis 2. Allergic rhinitis and conjunctivitis 3. Quincke's edema 4. Anaphylactic reactions with cutaneous manifestations 5. Marine and air sickness (1,6)		
Side effects	1. Drowsiness 2. Dry mouth 3. Hypotension (1.6) 4. Dyspeptic phenomena	1. Dyspeptic phenomena 2. Dry mouth 3. Cardiotoxicity: prolongation of QT, rhythm disturbance (11, 12)	1. Dyspeptic phenomena 2. Dizziness, headache
Contraindications	1. Closed-angle glaucoma (1-4, 6) 2. Hypertrophy of the prostate (1-4, 6) 3. Severe liver diseases, erosive-ulcerative lesions of the gastroduodenal zone 4. Pregnancy, breast-feeding	1. Pregnancy, breast-feeding	
NB!	1. Drugs with sedative and hypnotic effects can’t be prescribed to drivers and other persons whose job requires a rapid mental and motor reaction. 2. Groups of drugs with antihistamine action: glucocorticosteroids, mast cell stabilizers, leukotriene receptor inhibitors, "universal" adrenomimetic (epinephrine).		

Drug interactions	1. 1 generation drugs potentiate the effects of opioid analgesics, ethanol, hypnotics, tranquilizers, can increase the effects of CNS stimulants on children. 2. With prolonged use, they can reduce the effectiveness of drugs metabolized in the liver, e.g. glucocorticoids, anticoagulants, fenilbutazone. 3. When combined with anticholinergics can dramatically increase their effects. 4. MAO inhibitors can enhance the effects of antihistamine drugs. 5. Some 1st generation drugs potentiate epinephrine and norepinephrine effect the CVS.	1. Fenistil: enhances the action of anxiolytics, hypnotics. With simultaneous use of ethanol, psychomotor retardation happens. Tricyclic antidepressants and muscarinic antagonists increase the risk of IOP increase. MAO inhibitors enhance antiholinergic and depressing effect on the CNS. 2. Ebastine should not be used with erythromycin and ketokonazole (QT elongation). 3. Increased risk of ventricular arrhythmias in simultaneous use of astemizole and itraconazole, ketoconazole and other antifungals - imidazole and triazole derivatives, macrolides clarithromycin, eritromycin, terfenadine, serotonin reuptake inhibitors, HIV protease inhibitors (ritonavir, indinavir).	Клинически значимых нежелательных взаимодействий не выявлено

Acute management of anaphylaxis

I line management	1. Assess respiratory tract patency, the presence and adequacy of breathing, the level of consciousness, the state of skin.
	2. Adrenaline (epinephrine) 0,1% 0,3-0,5 ml i/m into the middle of the anterolateral lateral surface of the thigh or IV
II line management	3. Cardiopulmonary resuscitation in cardiac or respiratory arrest. Ratio of breaths to compression – 2:30
	4. When hypotension: lay the patient with raised lower limbs, ensure the supply of moistened oxygen (if available), the introduction of sodium chloride solution 0,9% IV (to 20 ml/kg)
	5. When bronchospasm: sitting position of the patient, ensure the supply of moistened oxygen (if available), inhalation of β2-agonists – salbutamol 100 mkg via a metered aerosol inhaler (1-2 doses) or a nebulizer 2,5 mg/3 ml
	6. If there is no response within 5-10 minutes, reapply adrenaline 0,1% 0,3-0,5 ml
III line management	7**.** Corticosteroids (prednisolone 90-120 mg)
	8. Introduction of antihistamines for the treatment of skin symptoms: IM clemastine 2 mg or chloropyramamine 20 mg or definehydramine 25-50 mg IM, IV or orally

NB!	*If only an angioedema or urticaria it's not anaphylaxis*. *In this case management includes:* 1. Antihistamines IM, IV, clemastine 2 mg orally, chloropyramamine 20 mg, definehydramine 25-50 mg 2. corticosteroids (prednisolone 25-30 mg)

Immunomodulators are medicines correcting immunity disorders.

Classification	Interferons	Interferon inductors	Interleukins	Colony-stimulating factors
Drugs	*Natural:* 1. Human leukocyte interferon (α-feron) 2. Velferon (α-feron) 3. Toraferon (β-feron) *Recombinant:* 4. Reaferon, Viferon (α2A-interferon) 5. Intron-A, Laferon (α2B-interferon) 6. Betaferon, Fron (β-feron) 7. Gammaferon, Immukin (γ-feron)	8. Amiksin 9. Poludan 10. Arbidol 11. Ingavirin	12. Interleukin-2 (Roncoleukin) 13. Interleukin 1ß (Betaleikin)	14. Filgrastim (Myelastra) 15. Molragostim (Leicomax) 16. Lenograstim (Granocyte)
Mechanism of action	1. ↑ expression of Antigens of histocompatibility classes I и II; activate cytotoxic effector cells 2. ↓ the effect of tumor growth factors, ↓ The formation of new vessels in the tumor, inhibit metastasis 3. Activate latent endoribonuclease which destroys viral RNA; ↓ Synthesis of viral matrix RNA, ↓ synthesis of viral envelope proteins 4. Disrupt the metabolism of the bacterial cell and cause its death	1. Stimulate the synthesis of endogenous interferon in the body	1. ↑ The amount of lymphocytes and their cytotoxicity, the activity of cell-killer killers, and the activity of tumor necrosis factor	1. ↑ expression of class II histocompatibility antigens on human monocytes and ↑ production of antibodies; ↑ phagocytosis of bacteria, activate cytotoxic effector cells 2. Activates the maturation of myeloid and lymphoid cells
Pharmacological effects	1. Immunomodulating 2. Antineoplastic 3. Antiviral 4. Antibacterial	1. Immunomodulating 2. Antiviral	1. Immunomodulating	
Indications	1. Influenza, ARVI (1) 2. Hepatitis B and C (1-7) 3. Severe bacterial infections (7) 4. AIDS-associated Kaposi's sarcoma (1, 4, 5) 5. Hairy cell leukemia (1, 2, 4) 6. Chronic myelogenous leukemia (1, 2, 5) 7. Kidney cancer (1, 2, 4, 5) 8. Multiple sclerosis (1, 6, 4) 9. Larynx papillomatosis (2, 4)	1. Influenza, ARVI 2. Hepatitis A, B and C (8) 3. Keratitis, uveitis (9)	1. Septic conditions accompanied by immunosuppression 2. Renal cell carcinoma (12) 3. Pulmonary tuberculosis (12, 13) 4. Toxic leukopenia of 2-4 grade complicating chemo- and radiotherapy of malignant tumors (13)	1. Antitumor agents-induced neutropenia; HIV infection 2. Neutropenia in patients with myelodysplastic syndrome (15) 3. Bone marrow transplantation
Side effects	1. Asthenovegetative syndrome 2. Flu-like syndrome 3. Nausea, diarrhea, anorexia 4. Thrombocyto-, leukopenia (2-7) 5. Hepatotoxicity 6. Nephrotoxicity (2-7) 7. Convulsive syndrome (2-6) 8. Depression (1-6) 9. Cardiotoxicity (2-7)	1. Dyspeptic phenomena 2. Short-term chills (8)	1. Flu-like syndrome 2. Dyspeptic phenomena 3. Hematotoxicity (anemia, thrombocytopenia, leukopenia), cardio-toxicity (myocardial ischemia, atrial arrhythmias), arterial hypertension (12) 4. Neurotoxicity (drowsiness, delirium)	1. Anorexia, nausea, vomiting, diarrhea, abdominal pain 2. Headache, dizziness 3. Hypotension, arrhythmia, heart failure 4. Bronchospasm

Contraindications	1. Hypersensitivity 2. Expressed violations of the liver, kidney, heart functions, hematopoiesis system 3. Epilepsy, mental illness	1. Hypersensitivity 2. Childhood	1. Hypersensitivity 2. Autoimmune diseases 3. Severe cardiovascular diseases	1. Hypersensitivity 2. Myeloid leukemia

Drug interactions	1. Vellferon, interferon alfa-2b ↓ the activity of cytochrome P450 metabolism and slow methabolizm of cimetidine, phenytoin, pentoxiphylline, theophylline, diazepam, propranol, some cytostatics. 2. Velferon may violate mental status when combined with drugs affecting the CNS. 3. Intron-A to be carefully administered in combination with narcotic analgesics, sedatives and hypnotics as well as with drugs with potentially myelosuppressive effects (e.g., zidovudine). 4. Intron-A can potentiate the toxic effects of chemotherapeutic drugs (including doxorubicin, cytarabine, cyclophosphamide, teniposide). 5. When reaferon is applied simultaneously with theophylline, control of serum theophylline concentration is needed.	1. Combination of poludan with preparations of enzymes its clinical effectiveness ↓ because enzymes destroy interferon.	1. Activity of ronleukin can be ↓ after long-time GCs use.	1. Filgristime use: 24 h interval with mielosupressants to be observed due to sensitivity of actively proliferating myeloid cells к миелосупрессивной chemotherapy. 2.Molgramostime-induced albumin plazma level decrease can be stimulated by use of drugs highly binding to proteins. 4.Lenograstim can ↑ myelotoxicity of other drugs.

Immunomodulators (continued)

Classification	Thymus preparations	Synthetic drugs	Substances of bacterial origin	Vegetable drugs
Drugs	1. Timalin (Timosin) 2. Tactivin 3. Timopentin	4. Levamisol (Decaris) 5. Leakadine 6. Berlopentin	7. Prodigiosan 8. Ribomunil 9. Broncho Munal 10. Imudon	11. Echinacea purpurea
Mechanism of action	1. Regulates the number of T- and B-lymphocytes, enhances the response of cellular immunity and phagocytosis, as well as the regeneration and hemopoiesis processes in case of their inhibition (1) 2. ↑ α- and γ-interferons, restores the activity of T-killers, normalizes immunity indices (2) 3. ↑ number of T-lymphocytes (3)	1. Stimulates the function of T-lymphocytes, macrophages, strengthens cellular immunity mainly, and also disrupts the bioenergetic processes of helminthes (4) 2. ↓ level of T-suppressors, normalizes the ratio of T-helpers and T-suppressors, ↑ cytotoxicity of natural killers and monocytes, inhibits tumor growth (5) 3. ↑ the proliferation and differentiation of bone marrow stem cells without increase in pathological immune responses (6)	1. Activates T-lymphocytes and adrenal cortex function, ↑ formation of endogenous interferon (7) 2. Stimulates the formation of specific antibodies to the antigens of klebsiella and streptococci, activates T and B lymphocytes, the formation of interleukin-1 and interferon-α (8.9) 3. Stimulate local humoral immunity, ↑ the production of lgA in the mucus-stern of the upper respiratory tract and ↑ the content of lysozyme (10)	1. Activates leukopoiesis and ↑ phagocytic activity of macrophages → ↓ bacterial growth and helps to kill pathogenic bacteria.
Pharmacological effects	1. Immunomodulating	1. Immunomodulating 2. Antiparasitic (4) 3. Antineoplastic (5)	1. Immunomodulating	1. Immunomodulating 2. Antiviral 3. Antibacterial
Indications	1. Acute and chronic bacterial and viral infections 2. Malignancies (2,3) 3. Chronic viral hepatitis (2,3)	1. Auxiliary postoperative cancer treatment (4) 2. Nematodeases (4) 3. Kaposi's sarcoma, skin lymphoma (5) 4. Psoriasis (5) 5. Immunodeficiency in HIV / AIDS (6)	1. Decreased immunity due to chronic inflammatory diseases, after operations (7) 2. Chronic bronchitis, tracheitis, rhinitis (8, 9, 11) 3. Gingivitis, periodontitis, stomatitis (10)	1. Uncomplicated viral and bacterial diseases of the respiratory tract.
Side effects	1. Allergy	1. Nausea, vomiting, diarrhea 2. Risk of agranulocytosis (4) 3. Thrombocytopenia (5) 4. ↑ blood pressure (5) 5. Burning pain at the injection site (6)	1. Headache (7) 2. ↑ body temperature (7) 3. Allergic reactions 4. Nausea, vomiting	1. Allergy
Contraindications	1. Hypersensitivity 2. Atopic asthma (2)	1. Hypersensitivity 2. Agranulocytosis (4) 3. Thrombocytopenia (5) 4. The gastroduodenal ulcer (5)	1. Central nervous system lesions (7) 2. Myocardial infarction (7) 3. Autoimmune diseases (8)	1. Hypersensitivity 2. Autoimmune diseases

NB!	Bacillus Calmette–Guérin (BCG) vaccine is also an bacterial immunomodulator (vaccine against tuberculosis)			
Drug interactions	1.Timalin shouldn't be combined with drugs with similar mechanism of action.	1.Levamisole is not compatible with lipophilic co-unity, e.g., carbon tetrachloride, tetrachlorethylene, chloroform, ethers (↑ possible toxicity), alcohol and Surgery-drugs. 2. Levamisole ↑ effects of phenytoin and indirect anticoagulants 3. In combination with myelotoxic drugs haemato-toxicity of levamizole ↑.	1.No interactions	1.Immunal contains alcohol and increase effect of CNS supressors

Immunosuppressive drugs are drugs inhibiting or preventing activity of the immune system.

Monoclonal antibodies are antibodies that are made by identical immune cells that are all clones of a unique parent cell.

Classification	For cancer	For organ transplantation	For autoimmune diseases	For infectious, allergic diseases and other diseases
Drugs	1. Avastin (Bevacizumab) 2. Herceptin (Trastuzumab) 3. MabThera (Rituximab) 4. Erbitux (Cetuximab)	5. Simulekt (Baziliximab)	6. Actemra (Tocilizumab) 7. Humirah (Adalumumab) 8. Remicade (Infliximab)	9. Xolar (Omalizumab) 10. Lucentis (Ranibizumab)
Mechanism of action	1. Selectively binds to the growth factor of the endothelial vessels and neutralizes it → violation of angiogenesis, ↓ vascularization and depression of growth of the tumor (1) 2. Blocks human epidermal growth factor receptor type 2 (HER-2) on tumor cells → ↓ division of malignant cells (2) 3. ↓ level of circulating CD20 + B-lymphocytes (3) 4. Blocks epidermal growth factor receptor (EGFR) →	1. Blocks the α-chain of the interleukin-2 receptor (CD25) → ↓ T cell proliferation (5)	1. Suppresses receptors of interleukin-6 (6) 2. Inhibit tumor necrosis factor-α (TNF-α) (7,8)	1. It binds to Ig E and prevents its interaction with Fc-R1 → ↓ Ig E (9) 2. Prevents the interaction of endothelial growth factor of the vessels (VEGF-A) with receptors on the surface of endothelial cells → ↓ neovascularization and vascular proliferation (10)
Pharmacological effects	1. Antitumor effect	1. Immunodepressive effect	1. Immunodepressive effect 2. Anti-inflammatory effect	1. Antiallergic effect (9) 2. Antiproliferative effect (10)
Indications	1. Metastatic colorectal cancer (1.4) 2. Breast and pulmonary cancer (1,2) 3. Renal cell carcinoma (1) 4. Stomach cancer (2) 5. Squamous cell carcinoma of the head and neck (4) 6. B-cell CD20-positive non-Hodgkin's lymphomas, chronic lymphocytic leukemia (3)	1. Prevention of kidney transplant rejection	1. Rheumatoid arthritis 2. Ulcerative colitis and Crohn's disease (7,8) 3. Plaque psoriasis in children (7)	1. Atopic bronchial asthma (9) 2. Chronic idiopathic urticaria (9) 3. Neovascular (wet) form of age-related macular degeneration (10)
Side effects	1. Perforation of gastrointestinal tract (1) 2. Bleeding, thromboembolism (1) 3. Neutropenia, leukopenia, thrombocytopenia (1-3) 4. Hypertension 5. Diarrhea, nausea, vomiting, abdominal pain 6. Heart failure, tachyarrhythmia (1-3) 7. Upper respiratory and urinary infections 8. Allergic reactions	1. Diarrhea, nausea, vomiting, abdominal pain 2. Hypertension, headache 3. Hyperkalemia, hypercholesterolemia, hypophosphaemia4. Upper respiratory and urinary infections 5. Allergy	1. Upper respiratory infections 2. Hypertension, headache 3. Leukopenia, neutropenia 4. ↑ hepatic enzyme activity 5. Benign tumors (7) 6. Allergic reactions	1. Upper respiratory and urinary infections (10) 2. Anemia (10) 3. Intraocular inflammation, visual disturbances (10) 4. Headache 5. Allergic reactions
Contraindications	1. Hypersensitivity 2. Patients with dyspnea at rest (2)	1. Hypersensitivity	1. Hypersensitivity 2. Sepsis, active tuberculosis	1. Hypersensitivity 2. Eye infections (10)

NB!	Other drugs with immunosuppressive action: cytostatics, glucocorticoids, immunoglobulins (antitimocyte immunoglobulin)

Drug interactions	1.Combined use of erbitux and fluorouracil: ↑ frequency of hand-foot syndrome, coronary ischemia and thrombosis (while there is a high risk of myocardial infarction). Combined use with platinum drugs: ↑ the frequency of severe leukopenia or severe neutropenia. In combination with capecitabine: ↑ frequency of severe diarrhea .	1.No interactions	1. Combined use of adalimumab with other biological antirheumatic agents: increased risk of infections and other complications. 2.Methotrexate use ↓ formation of antibodies to infliximab and ↑ plasma concentration. 4. Not recommended to combine the use of remicade with abatacept.	1.No data

NSAIDs are drugs with anti-inflammatory, antipyretic and analgesic effects.

Classification	Non-selective COX inhibitors	Preferential COX-2 inhibitors	Selective COX-2 inhibitors	Antipyretic analgesics
Drugs	1. Acetylsalicylic acid (Aspyrin) 2. Diclofenac sodium (Voltaren, Ortho-fen) 3. Ibuprofen (Ibufen, Nurofen) 4. Ketoprofen (Ketonal, Ultrafastteen, Fastum gel) 5. Indomethacin (Metindol) 6. Phenylbutazone (Butadione)	7. Meloksikam (Movalis) 8. Nimesulid (Sulide, Coxtal, Sintal-gin, Octaprin, Nimesil) 9. Eudolacus (Elderin)	10. Celecoxib (Celebrex) 11. Rofecoxib (Rofika, Denebol)	12. Mephenamic acid (Pomstal) 13. Paracetamol 14. Ketorolac 15. Metamizole (Analgin)

Mechanism of action	1. Inhibition of COX-1 and COX-2 (1-6) or COX 2 (7-10) → suppression of prostaglandin synthesis (PG) from arachidonic acid; inhibition of thromboxane A2 synthesis 2. Affect the synthesis of PG associated with the mobilization of Ca in smooth muscle (anti-Ca mechanism of anti-inflammatory effect) 3. Block the interaction of bradykinin with tissue receptors → Restoration of impaired microcirculation, ↓ extradilatation of capillaries, ↓ exudation of plasma, its proteins, proinflammatory factors and blood cells (bradykinin mechanism of anti-inflammatory effect) (1-3, 5) 4. Inhibit the release of histamine, serotonin and biogenic amines (antihistamine and antiserotonin component of anti-inflammatory effect) 5. Bind to with G-protein in the cell membrane → affect the transmission of membrane signals, ↓ transport of anions, affect biological processes (membrane stabilizing component of anti-inflammatory effect) 6. Inhibition of inflammation → ↓ pain, because inflammation in the peripheral tissues stimulates pain receptors 7. ↓ synthesis of prostaglandins (PG E1) stimulating thermoregulation center in the hypothalamus, peripheral vasodilatation → ↓ body temperature 8. ↓ capillary permeability → impair immunocompetent cells contact with antigen and antibodies contact with a substrate; macrophages lysosomal membranes stabilization 9. ↓ chemotaxis of monocytes, eosinophils, lymphocytes, leukocytes 10. Inhibition of subcortical pain centers (central action) and pain impulses transmission to the CNS (12-15)
Pharmacological effects	1. Anti-inflammatory effect (1-11) 2. Analgesic effect 3. Antipyretic effect 4. Antiplatelet effect (1) 5. Immunosuppressive effect (3, 5, 6) 6. Desensitizing effect
Indications	1. Rheumatic diseases (rheumatoid arthritis, gouty and psoriatic arthritis, ankylosing spondylitis, etc.) (1-11); 2. Non-rheumatic diseases of the musculoskeletal system (osteoarthritis, myositis, tendovaginitis, trauma, etc.); 3. Moderate pain syndrome of various etiologies (headache and toothache, postoperative pain, algodismenorea) (12-14); 4. Neurological diseases (neuralgia, radiculitis, etc.) (12-14); 5. ↑ body temperature >38,5°C (1,3,13,15); 6. Prevention of "white" (arterial) thrombi formation (1).

Side effects	1. *NSAID-induced gastropathy* (inhibition of the synthesis of PG and prostocycline → ↓ pH; ↓ mucosa reparation- 1-6) 2. *Nephrotoxicity* (vasoconstriction and deterioration of renal blood flow due to PG-E2 and prostacyclin synthesis inhibition in the kidneys → ischemic changes in the kidneys, ↓ glomerular filtration and volume of diuresis → water retention, edema, hypernatremia, hyperkalemia, ↑ serum creatinine level, ↑ blood pressure - most expressed in 1,5,6; direct influence on the renal parenchyma → interstitial nephritis - most expressed in 1,5,6,15) 3. *Coagulopathy* (antiplatelet and moderate anticoagulant effect due to inhibition of prothrombin formation in the liver → bleeding - 1) 4. *Hematotoxicity* (hypochromic microcytic anemia, hemolytic anemia, thrombocytopenia - 1, 5; leukopenia, agranulocytosis and thrombocytopenia due to hematopoiesis suppression in the bone marrow - 15) 5. *Hepatotoxicity* (immunoallergic hepatitis at the beginning of the drug taking – more often 6; in long intake and high doses - toxic hepatitis more often at 2, 6) 6. *Allergic reactions* *7. Reye syndrome* (rapidly progressive, vitally threatening acute encephalopathy combined with liver damage and caused by the intake of NSAIDs against the background of a viral infectious disease - more often 1) 8. Dizziness, headache 9. Retinopathy, keratopathy (5); optic neuritis (3) 10. Bronchospasm (more often in people with bronchial asthma - most pronounced in 1)
Contraindications	1. Erosive-ulcerative lesions of the digestive tract 2. Severe dysfunction of the liver and kidneys 3. Cytopenia 4. Individual intolerance 5. Pregnancy
NB!	• NSAIDs should be taken after meals and washed down with milk or alkaline water. • NSAIDs should be administered with caution to patients with bronchial asthma, as well as individuals who previously identified unwanted reactions when taking any other NSAIDs. • Patients with hypertension or heart failure should choose those NSAIDs, Which have the least effect on the renal blood flow. • Older people should take minimum effective doses and undergo short courses of NSAIDs.
Drugs interactions	1. Can enhance the effect of anticoagulants and antiplatelet agents with increased bleeding risk 2. In combination with other NSAIDs and systemic corticosteroids increase the risk of gastrointestinal ulcers and bleeding 3. ↑ effect of antidiabetic drugs, thereby ↓ blood sugar (1) 4. When combined with methotrexate, lithium, digoxin their blood serum concentration and toxicity ↑ 5. It should, if possible, avoid concomitant administration of NSAIDs and diuretics, since, on the one hand, ↓ diuretic effect and, on the other hand, the risk of renal failure. The most dangerous is the combination of indomethacin with triamterene. 6. NSAIDs ↓ effect of antihypertensive agents. 7. When combined with the NSAID selective serotonin reuptake inhibitor may ↑ risk of GIT

Opioid (narcotic) analgesics are drugs that block or impair transmission of pain impulses at different levels of the CNS, including the cerebral cortex, and change emotional perception of pain and reaction to it.

Classification	Opioid receptor agonists		Agonists-antagonists of opioid receptors and partial agonists *	With mixedmechanist of action	Pure antagonists of opioid receptors
	Strong agonists	**Weak agonists**			
Drugs	1. Morphine 2. Trimeperidine (promedol) 3. Methadone 4. Fentanyl 5. Sufentanil	6. Codeine 7. Oxycodone 8. Hydrocodone	9. Pentazocine 10. Butorphanol 11. Buprenorphine * 12. Loperamide (imodium) *	13. Tramadol	14. Naloxone 15. Nalmefene 16. Naltrexone
Mechanism of action	Bind to opioid receptors of the central nervous system (μ, δ, κ), it leads to inhibition of algogen release (pain mediators) along the entire pain pathway. Inhibit interneurons of the spinal cord, reticular formation, thalamic pain centers, limbic system, summation of CNS.		1. Excit κ-receptors, block μ-receptors (9,10). 2. Has a great affinity for μ-receptors, but excites them poorly (11). 3. Excites peripheral μ-receptors (12).	1. Excites opioid receptors (mostly μ-receptors). 2. Inhibits the reuptake of serotonin.	Opioid receptors are blocked
Pharmacological effects	**Central Effects:** 1. Effects of CNS depression (analgesia, dysphoria, euphoria, oppression of respiratory and cough centers, sleep) (1-11,13); 2. Effects of CNS excitation (vomiting, miosis, convulsions, rigidity of the muscles of the trunk) (1-11,13).		**Peripheral effects:** 1. Constipation, spasm of musculature of biliary tract and ureters, histamine release from mast cells, decreased excretory function of the kidneys, decreased uterine tone (1, 3-11, 13); 2. Antidiarrheal (slows the intestinal motility) (12).		Prevent, weaken or eliminate the effects of opioid agonists
Indications for use	1. Anesthesia: a) severe acute pain (myocardial infarction, pulmonary edema, trauma, burns); b) severe non-inflammatory chronic pain (cancer); c) pain during surgical operations (premedication and immediately during surgery) 2. Hepatic, intestinal, renal colic (2), in the latter case – in combination with antispasmodics) 3. Pain during childbirth (2) 4. Dry cough (1, 6) 5. Non-infectious diarrhea (12)				1. Opioid poisoning 2. Discintinuation of opioids in the postoperative period 3. Alcoholic coma
Side effects	1. Drug dependence (1-11, 13-16) 2. Tolerance 3. Inhibition of respiration (1-11, 13-16) 4. Convulsions (1,2,13) 5. Nausea, vomiting, constipation 6. Psychotomimetic reactions (hallucinations, nightmares and anxiety) (9-10)				1. Nausea, vomiting 2. AH, tachycardia, cardiac arrest
Contraindications	1. Hypersensitivity 2. Inhibition of the respiratory center, severe depression of the central nervous system 3. High ICP, brain trauma 4. Abdominal pain of unclear etiology				1. Hypersensitivity

NB!	1.Neuroleptanalgesia – A combination of a narcotic analgesic (eg, fentanyl) and a neuroleptic (eg, droperidol). Ataralgesia – Combination of narcotic analgesics and tranquilizers. 2.Fentanyl is stronger than morphine, but acts for a short time (up to 30 minutes). 3.Trimiperidine (promedol) is weaker than morphine and less depresses the respiratory center (of choice in obstetrics, pediatrics and geriatrics), and also has a moderate spasmolytic effect on smooth muscles (can be used to treat renal, hepatic and intestinal colic). 4.Methadone causes a softer abstinence syndrome due to prolonged action, therefore it is used to treat opioid addiction.

Drug interactions	1. ↑ action of hypnotics, sedatives, tools for anesthesia, anxiolytics 2. NSAIDs: ↑ analgesic effect, but at the same time ↑ risk of side effects. 3. Agonists-antagonists: opioid receptor agonists action ↓. 4. beta-blockers: may ↑ inhibitory action on the CNS 5. ↑ hypotensive effect of drugs that lower blood pressure. 6. drugs with some anticholynestherase activity (some psychotropic, anti-histamine, antidiarrheals, antiemetics and for the treatment of Parkinsonism) ↑ risk of constipation up to ileus. 7. CYP3A4 inhibitors: ↑ concentration in blood (4-5)	1. ↑ action of hypnotics, sedatives, resulting in sedation, respiratory inhibition (9-11) 2. ↑ inhibitory effect on the CNS of antihistamines, antidepressants and others. (9-11) 3. CYP3A4 inhibitors: ↑ concentration in blood 5. The combination with opioids can cause constipation (12) .	1. Can stimulate seizures, ↑ ability of selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics to cause convulsions 2. CYP3A4 inhibitors: ↑ concentration in blood 3. ↑ a depressing effect of other groups on the central nervous system	1. Eliminates the analgesic action of opioids 2. Patients with opioid dependence: withdrawal syndrome 3. ↓ anti-hypertensive effect of clonidine

Morphine and its analogues intoxication

Main reasons	Acute intoxication: 1. Accidental or intentional overdose with addiction. 2. Overdose during premedication or in the postoperative period in patients with chronic respiratory or hepatic insufficiency, as well as with rapid bolus administration of narcotic analgesics for the treatment of pulmonary edema, myocardial infarction, etc. 3. Hypersensitivity to narcotic analgesics. 4. Children are more likely as a result of accidents or overdose of antitussive drugs. The lethal dose of morphine: 0.5-1 g for oral intake, 0.2 g for IV administration. The fatal blood concentration is 0.14 mg l. Chronic intoxication: long-term administration of morphine and its analogues (opioid dependence).
Clinic	1. Acute intoxication: redness of the face, neck, chest, puffiness of the face, skin itch, fainting ("mediator" syndrome). Instead of euphoria, dysphoria begins with the development of hallucinations. Then the depression of consciousness develops up to the coma, the breath is rare (up to 10 per minute), superficial with apnea. There is a "cholinergic" syndrome - bradycardia, urinary retention. The main diagnostic symptoms of opiate poisoning are pinpoint pupils and the loss of their reaction to light (with the exception of trimeperedine). However, with severe hypoxia of the brain, the pupils dilate (!). With prolonged hypoxia, pulmonary and cerebral edema and hyperkinesis or tonic-clonic seizures develop. Death most often occurs as a result of blockade of the respiratory center. 2. In chronic intoxication the drug discontinuation leads to withdrawal syndrome (a sign of physical drug addiction). Initially, there are signs of mental addiction: nervousness, sweating, need for taking a drug. Then there are signs of severe physical addiction, mostly associated with a violation of the autonomic nervous system ("vegetative storm"): mydriasis, tachycardia, goosebump, intestinal colic, muscle pain, vomiting, diarrhea, dyspnea, fever, yawning, tremor, lacrimation, as well as anorexia and depression. The duration of the withdrawal syndrome depends on the specific drug (for example, for morphine – about 5 days, the peak falls on 1-2 days). Death can come from pain shock, myocardial infarction.
Therapy	1.Acute intoxication: Intravenous administration of opioid analgesics antagonists – naloxone, nalmefene. The effect of naloxone is short (1-2 hours), therefore, when long-acting opioids intoxication (methadone, etc.), it is necessary to re-administer naloxone (!) or administer an antagonist with a longer duration of action – nalmefene (8-10 hours). Restoration of airway passages (artificial lung ventilation and other methods), oxygen therapy, pathogenetic, detoxification and symptomatic therapy are also needed. 2.Opioid addiction treatment: methadone is used. It is a long-acting strong opioid agonist opioid with properties close to morphine. Peak of withdrawal syndrome is week 1 (flows more smoothly, unlike morphine), duration is 3 weeks. Instead of methadone, buprenorphine is often used. Both substances are administered orally with a gradual decrease in the daily dose until withdraw. For the treatment of drug addiction, a long-acting (48 hours) opioid antagonist, naltrexone, is also used to eliminate the use of opioid drugs. Clonidine is also used in addiction treatment to eliminate hyperactivity of nervous system during opioid abstinence.

Glucocorticoids

Glucocorticoids are steroid hormones synthesized by the adrenal cortex, and their synthetic analogs.

Classification	Natural	Synthetic
Drugs	1. Cortisone 2. Hydrocortisone	3. Prednisolone 4. Methylprednisolone 5. Triamcinolone 6. Beclomethasone 7. Fluticazone 8. Budesonide
Mechanism of action	They interact with nuclear receptors that regulate the transcription of genes, and change the synthesis of proteins and enzymes.	
Pharmacological effect	**Anti-inflammatory**: inhibition of phospholipase A2, inhibition of the synthesis of prostaglandins and leukotrienes. **Immunosuppressive**: ↓ activity of leukocytes and tissue macrophages, ↓ lymphocytes count. **Antiexudative**, **antiproliferative** effects. **Anti-shock** effect Suppression of fibroblasts and collagen synthesis. Anabolic: stimulation of gluconeogenesis, lipogenesis. Deposition of glycogen. Catabolic: in the connective, bone, lymphoid tissue. ↑ secretion of ACTH, FSH, TTG. ↑ brain excitability. ↑ production of hydrochloric acid and pepsin.	
Indications for use	1. Chronic adrenal insufficiency 2. Acute adrenal insufficiency 3. Rheumatological diseases 4. Emergencies (asthmatic status, collapse, anaphylactic shock, cerebral edema) 5. Autoimmune diseases	6. Allergic diseases 7. Bronchial asthma 8. Severe inflammatory processes 9. Malignant tumors 10. Prevention of tranplant rejection
Side effects	1. Steroid ulcers 2. Type 2 diabetes mellitus 3. Hypertension 4. Immunosuppression and attachment of secondary infection 5. Poor healing of wounds, striae 6. Inhibition of adrenal function	7. Cushing's syndrome 8. Hypercoagulation 9. Growth retardation in children 10. Hypokalemia 11. Arrhythmias, seizures 12. Hallucinations, psychosis
Contraindications	1. Viral, fungal, bacterial diseases 2. Acid-dependent diseases of the digestive tract 3. Diabetes mellitus 4. Thyrotoxicosis, hypothyroidism 5. Myasthenia gravis 6. Glaucoma 7. Immune deficiency 8. Thrombophilic conditions	Absolute: intolerance. Relative: tuberculosis, viral infections, acute myocardial infarction (scar rupture is possible), psychosis, epilepsy, peptic ulcer, diabetes mellitus.
NB!	Equivalent doses of GCs: 5 mg of prednisolone = 25 mg of cortisone = 20 mg of hydrocortisone = 4 mg of methylprednisolone = 4 mg of triamcinolone = 0.75 mg of dexamethasone = 0.75 mg of betamethasone Glucocorticoid treatment regimens to prevent adrenal supression: - *Alternate-day therapy* — treatment once in every 28 hours. Prednisolone or methylprednisolone in the morning; - *Intermittent therapy* — — short-term therapy (3–4 days) with 4-day breaks between courses; - *Pulse therapy* — short-term high-dose (1 g) urgent therapy. The drug of choice is methylprednisolone (better enters inflamed tissues and less often causes side effects).	

Drugs interactions	1. No interactions for topical use. For other routes of drug administration: 2. microsomal liver enzymes inducers (phenobarbital, phenytoin, rifampin, carbamazepine) ↓ GCs effects 3. GCs ↓ efficiency of hypoglycemic agents 4. GCs can both ↑ and ↓ the effectiveness of anticoagulants 5. The combination of NSAIDs and GCs increases the risk of NSAID-gastropathy. 6. Combination with amphotericin B, diuretics, theophylline, digoxin may ↑ the risk of hypokalemia 7. GCs ↓ efficacy of antihypertensive therapy 8. Oral contraceptives can ↑ serum GCs concentration 9. Erythromycin and ketoconazole can inhibit the metabolism of GCs 10. The risk of hypokalemia ↑ also at high doses of GCs with sympathomimetics e.g., fenoterol, salbutamol, formoterol, salmeterol, etc. 11. High doses of glucocorticoids inhibit the immune system, so you should avoid the use of live vaccines