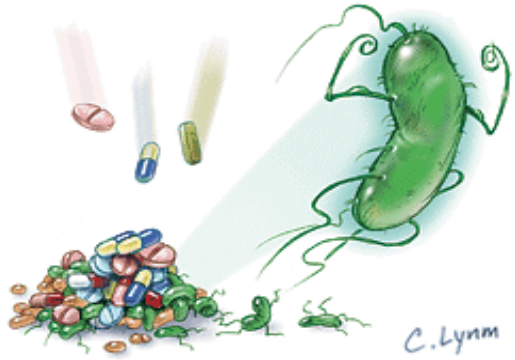
National University of Pharmacy
Pharmacology Department



ANTIFUNGAL, ANTIVIRAL, ANTIHELMINTHIC DRUGS

LECTURER
Shchokina Catherine

Doctor of Pharmacy
Professor of the Pharmacology department

Antifungal drugs

This medicine used to prevent and treat fungal diseases (mycoses)

Mycoses are:

1. Local
2. Systemic

Local mycoses are fungous diseases developing in the site of pathogen invasion, e.g. skin (dermatomycosis), nail (onychomycosis), hairy area of the head (trichomycosis), mucous membranes mycoses.

Systemic mycoses are fungous diseases, in which the pathogen while circulating in blood affects different organs simultaneously (e.g. generalized candidiasis, histoplasmosis, blastomycosis etc.).

Participation in the pathological process of tissues and organs in the localized mycosis

Causes of mycoses

1. The bad social, economic and environmental situation
2. Reduction of the protective function of skin
3. Reduced immunity
4. HIV infection
5. Cancer
6. Using drugs with immunological activity (cytostatics, hormones)
7. Irrational use of antibiotics

Marketing analysis of antifungal drugs

- **Now in medical practice in the world more of 35 antifungal substances are used. On the basis of them are produced more than 130 drugs.**
- **50% of antifungal drugs appeared in the pharmaceutical market over the past 10-15 years.**
- **The part of new drugs including antifungal antibiotics is 14%, among them 70% of the azole group and 50% - other chemical groups**

- **Fungicidal effect** is the ability of the medicine to cause death of a fungous cell.

- **Fungistatic effect** is the ability of the medicine to inhibit growth and reproduction of a fungous cell.

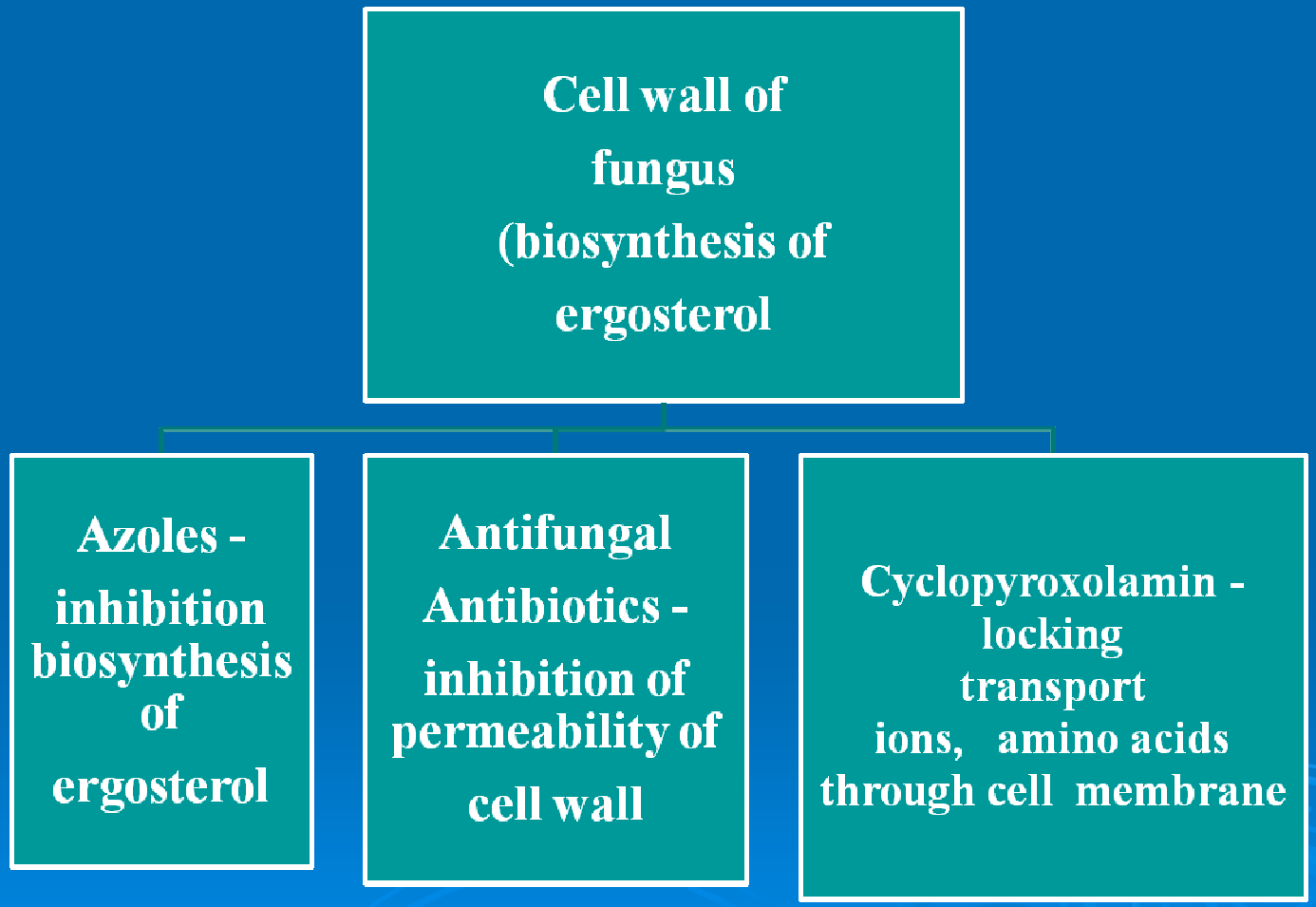
Classification of antifungal drugs

1.Antifungal antibiotics

2. Antifungal drugs synthetic origin:

- **Azoles**
- **Allilamins**
- **Pyrimidines**
- **Nitrophenols**
- **Undecylenic acid derivatives**
- **Derivatives of other chemical groups**

Mechanism of action of antifungal drugs



Antifungal antibiotics

1.Polyene antibiotics:

- **Amphotericin B, Nystatin, Levorin, Natamicyn.**
- **<u>Mechanism of action</u> - bind to ergosterol of the cell wall of fungus, which leads to increase the permeability of plasma cell membranes of fungus and loss of potassium and sodium ions, amino acids and other components of the cytoplasm.**

Type of action - fungicidal

Spectrum of action:

- *Candida - all medicines*
- *Agents of systemic mycoses: cryptococci, blastomicets, histoplazma – amphotericin B, amphoglucamin, micogeptyn, ambizom*
- *Tryhomonads – Levorin*
- *Amoeba, leishmanii – Nistatin*
- *Dermatophytes – Natamycin*

Indications of polyene antifungal antibiotics

- Local mycosis - skin, mucous membranes, nails, hair body parts (All)
- Dermatomycosis (Natamycine)
- Systemic candidosis (Amphotericin B, Nistatin)
- Trichomoniasis (Levorin)
- Prevention of candidosis during the chemotherapy (Nistatin, Levorin)
- Tropyc mycosis (Amphotericin B)

Side effects of polyene antifungal antibiotics

1. **All medicines in local application:**
   - **Redness, burning skin**
2. **All medicines in resorbtive use:**
   - **Nausea, vomiting, diarrhea**

The most toxic drug Amphotericin B has: nephrotoxicity, hematotoxicity, hepatotoxicity, fever, muscle pain, headache, hypotension, heart failure, phlebitis

Griseofulvin ***- binds with microglobular proteins that leads to decrease of the reproduction of fungal cells***

- Type of action - fungistatic
- The spectrum of action: dermatophytes
- Indications – dermatophytomycoses
  Side effects - rash, pain in epigastrium, headache, dizziness, weakness, disorientation, photosensibilisation,leukopenia, changes in renal function and liver

Antifungal drugs – azoles

Imidazole derivatives:

Clotrimazole (Kanesten) Miconazole (Daktarine), Ketoconazole (Nizoral), Bifonazole (Mycospor), Econazole (Pevaril)

Triazole derivatives:

Fluconazole (Diflyucan), Itraconazole (Orungal)

Antifungal drugs – azoles

Type of action – fungistatic

Spectrum of action - broad:

- **Fungi of the Candida**
- **Dermatophytes**
- **Agents of deep mycoses: cryptococci histoplazma, blastomicets**
- **G+ - bacterias (stafilococci, streptococci**
- **Trichomonas – (Clotrimazolum)**

Indications of azoles:

- **Mycosis of the skin and mucous membranes including secondary complication infections**
- **Onychomycosis – (Itraconazole)**
- **Systemic mycosis – (Ketoconazole, Fluconazole, Itraconazole, Myconazole)**

Side effects of azoles:

- **Hepatotoxicity (All)**
- **Pain in epigastrium**
- **Reduced level of testosterone and ACTH – (Ketoconazole)**
- **Psychosis, heart arrhythmias – (Myconazole)**
- **Redness and feeling of skin burning - all medicines**

Characteristic of antifungal drugs from different chemical groups

- **Allilamins - Terbinafine (Lamizil), Naftifine (Exoderil)**

Mechanism of action - inhibit fungi enzyme and ergosterol synthesis

Type of action – fungistatic

Spectrum - broad (dermatophytes, candida)

- **Have skin and nail expression of action**

Indications - Treatment of mycoses of skin, nails, hair

Side effects - Rash

Pyrimidines - *Flucytosine (Ancotyl)*

Type of action – fungistatic

Spectrum - broad (Candida, cryptococci, fialofora)

- **Penetrates well into the tissues and fluids, through the BBB**

Indications - systemic candidosis, cryptococcosis,

Side effects - dyspepsia, hepatotoxicity

Undecylenic acid derivatives

Zincundan, Undecin, Mycoseptin

Mechanism of action – bind to sterols of cell membranes, that leads to destruction of fungal cells

Type of action – fungicidal and fungistatic

Spectrum - broad (Candida, dermatophytes)

- **Have skin and nail expression of action**

Indications - systemic candidosis, dermatomycosis

Side effects - erythema, rash

Combined medicines of antifungal drugs

Clion D, Pimafucort, Mycozolone, Ganderm-BG

Type of action - fungicidal and fungistatic

Spectrum - Candida, dermatophytes (are used only localy)

Indications – local mycoses: candidosis, trichophytosis, microsporosis, epidermophytosis

Side effects – burning, rush

Antifungal drugs with the action against Candida

INN	Mono-medicines	Combined medicines
Decamine	Dequalinyl	
Levorin	Levorin sodium	
Micoheptin		
Myconazole	Hino-dactarine Dactarine Mycatine Monostat-derma	Acnydazile Dactocine Clion-D Mycozolone
Nystatin	Anticandine Mycostatine Fungistatine	Nystaform Polyginax Fasigine
Fluconazole	Diflucane	
Flucytosin	Ancotyl	

Antihelminthic drugs

Antihelminthic drugs are used for treatment and prevention of Helminthiases

More than 250 species of helminthoses are known, which parasitize in humans, of them approximately 40 species are found in Ukraine

Causes of helminthoses:

- **Increasing the number of animals without veterinary control**
- **Low level of purification of canalization system**
- **Migration of people from countries with hot climate**
- **It is not always possible to control the movement of foodstuffs in the market**

- The majority of helminthiasis pathogens belong to **nemathelminths** (round worms, nematodes), **flatworms** (cestodes), **flukes** (trematodes). Helminthiases are respectively divided into **nematodoses**, **cestodoses** and **trematodoses**. Helminths parasitize in GIT (**intestinal helminths**), other organs: liver, gall bladder, blood and lymphatic vessels, subcutaneous fat (**extraintestinal parasites**).
- Ascarids, seatworms, hookworms, whipworms are nematodes that most frequently parasitize human intestines and cause ascariasis, enterobiasis, ancylostomiasis and trichocephaliasis respectively.

Classification of human Helminthiases

Helminthosis	**Worms**
Nematodoses	**Round helminths**
Ascariasis	**Ascaris**
Trichocephaliasis	**Vlasohlav**
Enterobiasis	**Ostrycya**
Ancilostomosis	**Ancilostoma**
Cestodoses	**Flatworms**
Trichinosis	**Tryhinela**

Classification of human Helminthiases (continuation)

Cestodoses :	***Band helminths:***
Difilobotriosis	***Great band***
Taeniarhynchosis	***Bovines***
Taeniosis	***Swines***
Himenolepidosis	***Dwarf***

Classification of human Helminthiases (continuation)

Trematodoses:	***Extraintestinal helminthes***
Opisthorchiasis	***Opistorhis***
Clonorchiasis	***Klonorhys***
Fascylosis	***Fascyola***

Classification of medicines

- **Medicines used in intestinal nematodoses (*-broad spectrum ones)**

Mebendazole*
Albendazole*
Pyrantel
Levamisole
Prasiquantel*
Tansy flowers

- **Medicines used in intestinal cestodoses and trematodoses***

Aminoacrichine
Prasiquantel
Mebendazole
Ethylene tetrachloride*

Classification of medicines

- **Medicines used in extraintestinal helminthiases**

Prasiquantel

Mebendazole

Albendazole

Mechanism of action

- **Pyrantel, levamisole, aminoacrichine** disturb the neuromuscular system functions in helminths. **Albendazole** and **mebendazole** disturb metabolic processes in helminths.
- **Prasiquantel** increases calcium ion permeability of cell membranes of helminths promoting the increase of their muscular tone turning into spastic paralysis. **Ethylene tetrachloride** has paralizing effect on helminths.
- Antihelminthic effect of **Tansy flowers** is caused by volatile oils present there.

Pharmacological effects

- **All drugs - antihelminthic**
- **Immunomodulatory - Levamizole**
- **Laxative - Piperazine, Bipynite**
- **Cholagogic - Tansy flowers**
- **Antiprotozoal - Aminoacrychine**

Indications of antihelminthic medicines

Ascariasis

(Albendazole, Levamisole, Pyrantel, Mebendazole)

Enterobiasis (Albendazole, Pyrantel, Mebendazole)

Cestodoses

(Albendazole, Aminoacrichine, Prasiquantel, Mebendazole)

Ancylostomiasis (Albendazole, Mebendazole, Pyrantel)

Side effects of antigelminthic drugs

Medicines	Nausea	Vomiting	Pain in epigastria	Diarrhea	Headache	Allergy
Piperazine	+		+		+	
Bephynite	+	+		+		
Mebenda-zole			+	+		+
Levamizole	+	+	+	+		

Side effects of antigelminthic drugs (continuation)

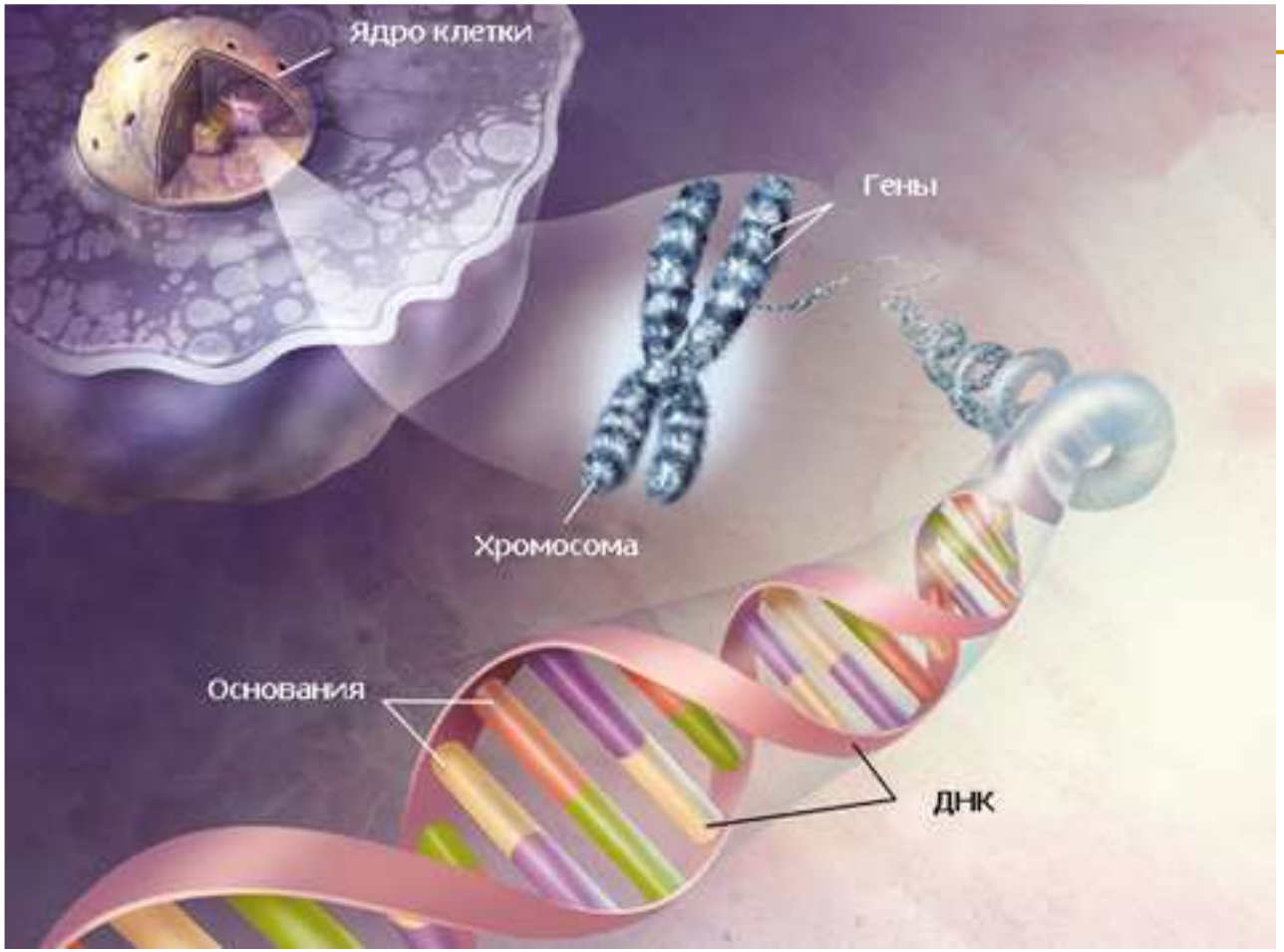
Medicines	Nausea	Vomiting	Pain in epigastria	Diarrhea	Headache	Allergy
Pyrantel	+	+		+	+	+
Pyrvinium pamoate	+	+		+		+
Niclosa-mide	+	+	+			+
Prazyquan-tel	+		+			+
Thiabenda-zole	+	+		+		

Terms of rational use of antihelminthic drugs

- ***dosing regimen***
- ***special diet***
- ***simultaneous administration of laxatives, proper treatment scheme.***
- ***Mebendazole, Pyrantel, Prasiquantel do not require any preparation and special diet, administration of laxatives is also unnecessary.***
- ***Use of Ethylene tetrachloride and Tansy flowers requires special diet and administration of laxatives.***
- ***To use medicines on empty stomach to ensure maximal contact of the medicine with the parasite.***

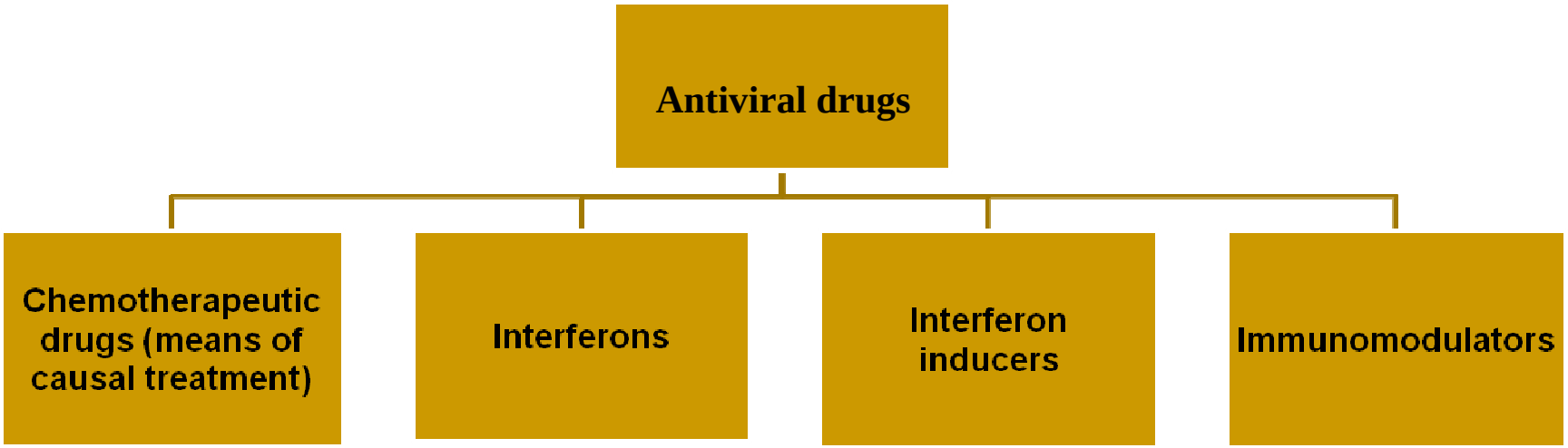
Contraindications to the use of antigelminthic drugs

- **Pregnancy**
- **Liver disease**
- **Organic diseases of central nervous system**
- **Heart disease**
- **Kidney disease**
- **Diseases of the GIT**



ANTIVIRAL DRUGS

Antiviral agents - drugs for the treatment and prevention of viral infections



Classification of ANTIVIRAL MEDICINES

Anomalous nucleosides	**Adamantane and other groups* derivatives**	**Pyrophosphate analogues**
Acyclovir Ribavirine Gancyclovir Famcyclovir	Remantadine Amantadine Oxolin*	Sodium foscarnet
Interferons and immunoglobulins*	**Interferon synthesis inducers (interferonogens)**	**HIV- proteinase and reverse transcriptase inhibitors***
Interferon-(α-1, α-2B, β-1B) Normal human immunoglobulin*	Cycloferon Amixin Inosine pranobex	Saquinavir Nelfinavir Didanosine* Zidovudine*

The mechanism of action of Antiviral drugs

Inhibit an early stage of specific viral replication after their penetration into a human cell.

- **Adamantane derivatives** inhibit viral RNA release from protein, altering RNA penetration into cell nucleus.
- **Anomalous nucleosides** inhibit viral RNA and DNA synthesis.
- **Pyrophosphate analogues** inhibit viral DNA-polymerase.
- **Interferons** block viral-specific protein synthesis.

The mechanism of action of Antiviral drugs

- **Interferon synthesis** inducers stimulate synthesis of endogenous interferon in human body. Interferon synthesis in human cells is human organism's natural mechanism of protection against viruses.
- **HIV-proteinase inhibitors** inhibit viral proteinase through binding to specific receptors.
- **Reverse transcriptase inhibitors** disturb the process of replication and viral DNA formation through reverse transcriptase inhibition

- **Herpes** is a viral disease caused by herpes viruses and characterized by vesicular rash appearing on skin and/or mucous membranes (herpes simplex) and along the nerve (herpes zoster).
- **Influenza** is a severe viral respiratory disease. **Interferons** are endogenous species-specific low-molecular proteins produced in cells as a response to viral, antigenic affection on the organism and protecting organism from being contaminated.

Pharmacodynamics (effects) of *antiinfluenza medicines*

- **All drugs have antiviral activity.**
- ***Adamantane derivatives - antiparkinsonic action*.**
- ***Arbidol - immunomodulating and antioxidant activity.***

Indications of antiinfluenza medicines

- **Treatment and prevention of influenza A – (Amantadine, Rimantadine, Oxolin)**
- **Treatment and prevention of influenza A and B – (Ribavirine, Gancyclovir, Interferon, Cycloferon, Amixin)**

Antiherpesetic medicines

- ***Herpes (from the Greek. Herpes - Creepy) - one of the most prevalent and poorly controlled human infections.***
- ***Opened more than 80 representatives of the family of herpes viruses, 8 of which are pathogenic for humans.***
- ***All herpes viruses are DNA-containing viruses. Getting into the human body, herpes viruses persists their, sometime cause various severity relapses depending on the immune system.***

Pharmacodynamics of antiherpetic drugs

- **Antiherpetic - all drugs.**

<u>Herpes simplex and zoster</u> – (Acyclovir, Foscarnet, Ribavirine, Famcyclovir, Oxolin, Immunoglobulin, Cycloferon, Amixin, Inosine)

<u>Cytomegalovirus</u> - (Acyclovir, Foscarnet, Gancyclovir, Cycloferon, Amixin, Inosine)

Side effects and contraindications of antiherpetic drugs

Side effect	Contraindications
Gematotoxicity, mutagenic action (Ganciclovir)	**Neutropenia, pregnancy, lactation, children under the age of 12 years**
Nephrotoxicity, hepatotoxicity (Foscarnet)	**Acute liver and kidney diseases**

Antiretroviral medicines

- **HIV infection - a disease that develops as a result of infection with human immunodeficiency virus (HIV), accompanied by impairment of the immune system and leads to a condition called acquired immunodeficiency syndrome (AIDS).**
- **HIV - the RNA virus belonging to the family of retroviruses.**
- **There are two types of the virus - HIV-1 and HIV-2, which differ in the structure of the genome**

Antiretrovirals.

1. Inhibitors of reverse transcriptase

1. Nucleoside

Didanosine

Zidovudine

2. Combination Therapies

Combivir

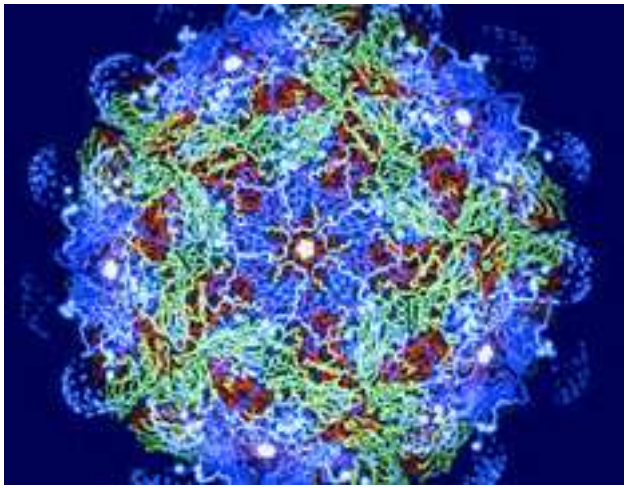
Trizivir

3. Nonnucleoside

Efavirenz

Nevirapine

Delaverdin



Antiretrovirals

- **HIV- proteinase and reverse transcriptase inhibitors***

Saquinavir

Nelfinavir

Didanosine*

Zidovudine*

Indications, side effects and contraindications of antiretroviral drugs.

- **Treatment of infections caused by HIV-1 and HIV-2**
- **Prevention of prenatal HIV infection and HIV infection in infants**
- **<u>Side effects</u> - hepatotoxicity, hematotoxicity, neurotoxicity,**
- **<u>Contraindications</u> - diseases of the liver, heart failure**

Interferons and their inducers

Interferons (IFN) are specific low molecular weight proteins (glycopeptides), which are produced by cells in response to viral, antigens or mitogenic effect on the organism, have a protective effect

The classification of interferon drugs

Nature	Recombinant
Alpha interferon	Alpha interferon
Human leukocyte IFN leykinferon, vellferon	A-2a - reaferon, realdiron, Roferon A, Pegasys
Beta interferon	A-2b - Intron A, viferon, PegIntron
Human fibroblast IFN, Feron	A-2c - berofor

Pharmacodynamics of interferon drugs

Type of pathology	Interferon preparations
Hepatitis B	Roferon, Intron, vellferon, berofor, realdiron, y-interferon
Hepatitis C	Roferon, Intron, vellferon, viferon, realdiron, Pegasys
Hepatitis A	Roferon, Intron, viferon
Genital herpes	Roferon, Intron, Fearon

Pharmacodynamics (continuation)

Herpetic keratitis and adenovirus	**Alpha and beta - interferon**
Zoster	**Roferon, berofor**
Laryngeal papillomatosis	**Intron, berofor**

Pharmacodynamics (continuation) - antitumor effect

AIDS	**Roferon, Intron, vellferon, Fearon, realderon**
Multiply sclerosis	**Betaferon, Fearon, avoneks, realderon**
Encephalitis	**Realderon**
Kidney cancer	**Reaferon, berofor**
Ovarian cancer	**Intron A, y-Fearon**

Pharmacodynamics (continuation)

Bladder Cancer	**Intron A, berofor**
Skin cancer, acute lymphoblastic leukemia	**Reaferon**
Melanoma	**Roferon A, Intron A, realdiron, berofor**
Leukemia	**Roferon A, realferon, realdiron**
Chronic myelogenous leukemia	**Roferon A, reaferon, realdiron, berofor**

Interferon inducers

The classification of drugs

Chemical structure	*Preparation*
Natural polymers	**Larifan, ridostin**
Polyphenols (gossypol)	**Megasin, Kagocel, savrats, rogasin, gozalidon**
Synthetic low-molecular compounds	**Amiksin, tsikloferon, Neovir**
Synthetic polymers	**Poludan, poliguatsil, amp-ligen**

Pharmacological effects

Medicines	Synthesis of IFN	Effects
Amiksin, cycloferon	Alpha, beta and gamma	Antiviral, antibacterial, immunocorrective
Neovir, larifan, ridostin	Alpha < beta and gamma	Same
Poludan, poliguatsil	Alfa	Antiviral
Rogasin, savrats, megasin	Alpha and beta	Antiviral, antibacterial, radioprotector

Indications

Indications	Medicines
Influenza, hepatitis, RA, neuroinfections, multiple sclerosis, chlamydia, CMV	Amixin, tsicloferon, Neovir
Herpes simplex, HIV, rabies	Poludan, poliguatsil
Chlamydial infections, enterovirus infection, hepatitis	Rogasin, savrats, megasin, larifan
Influenza, neuroinfections, HIV	Ridostin


Thank you