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Germanyuk T.A., Bobruk V.P., Lysogora V.V.

GENERAL PHARMACOLOGY and PHARMACOLOGY of the drugs affecting mediatory processes, vegetative and central nervous systems

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Reviewers:
Voloshchuk N.I. – doctor of medical sciences, Professor of pharmacology department of National Pirogov Memorial Medical University, Vinnytsya
Shtrugol S.Y. – doctor of medical sciences, Professor of pharmacology and toxicology department of National University of Pharmacy
Piniazhko O.R. – doctor of medical sciences, Professor of pharmacology department of Lviv National Medical University
Kryvoviaz O.V. – PhD, associate Professor, head of Pharmacy department of National Pirogov Memorial Medical University, Vinnytsya
Dudikova L.V. – PhD, associate Professor, head of department of Foreign languages of National Pirogov Memorial Medical University, Vinnytsya

G 39 **General Pharmacology and Pharmacology of the drugs affecting mediatory processes, vegetative and central nervous systems tutorial /** Germanyuk T.A., Bobruk V.P., Lysogora V.V. – Vinnytsya: Nilan-LTD, 2016 – 334P.

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The tutorial contains data concerning general conception of pharmacokinetics, pharmacodynamics, data about drugs affecting mediatory processes, vegetative nervous system, central nervous system, their classifications, lists of the drugs (International Nonproprietary Name, Proprietary commercial / brand / trade / generic names), medicinal forms, routs of administration and dose of the drugs, mechanisms of their action, pharmacological effects, including adverse effects and the ways to reduce them, indications, contraindications, the principles of rational combined use of the drugs, pharmacological drug safety and custody.

The tutorial is designed for students in higher pharmaceutical education institutions of III-IV level of accreditation of the specialty “Pharmacy” and “Clinical pharmacy”.

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Contents

Foreword

The tutorial "Pharmacology of the drugs affecting vegetative and central nervous system" includes the foundations of modern knowledge of the pharmacology of drugs that act on the peripheral and central nervous system (CNS) and is intended for students of a pharmacy department in specialty "Pharmacy" and "Clinical pharmacy".

Necessity to write a tutorial is caused by the need to provide the main aspects of current knowledge in pharmacology of drugs acting on the autonomic and central nervous system in accordance with the requirements of the credit-module system. According to the authors, the tutorial will be useful, given the fact of the necessity to intensify the efforts towards the students' independent work for the obtaining of knowledge in pharmacology.

The tutorial presents the key components of the pharmacokinetics and pharmacodynamics of the drugs with examples for better learning. In accordance with the tasks of pharmacology in this tutorial there are classifications of the drugs that affect the autonomic and central nervous system, according to the chemical structure, mechanisms of action, pharmacological effects; list of drugs (their INN and trade names, medicinal forms and routes of administration); mechanisms of action, pharmacological effects, including adverse effects, ways of reducing of the possible negative impact of a drug on the organism, indications and contraindications for use of the drugs, application features, pharmacological safety and pharmacological custody of the drugs, use of antidotes and symptomatic drugs in case of both, an overdose of drugs and the emergence of dangerous toxic effects.

The presented chapters of a tutorial show a close relationship of pharmacology with biology, normal and abnormal physiology, physics, normal and abnormal anatomy, biological chemistry, physical chemistry, pharmaceutical chemistry, etc. That is what allows correlating pharmacology with related medical sciences, to rethink the actions and uses of the drugs, to emphasize the applications of pharmacokinetics and pharmacodynamics to therapeutics to create the book that will be useful for the students of pharmacology, for the teachers of pharmacology and for the physicians.

The tutorial has a list of references, which were used by the authors and may be used by the students, teachers and physicians for improving personal knowledge in pharmacology.

The tutorial is written in accordance with the Program of pharmacology for the students of pharmaceutical faculty of higher educational institutions of III-IV accreditation levels for specialties 7.12020101 – "Pharmacy" and 7.12020102 – "Clinical Pharmacy" according to the educational qualification characteristics and educational and professional training program approved by the order of the Ministry of Healthcare of Ukraine dated 07.12.09 № 931 (period of study in this field – 5 years).

In today's pharmaceutical market there are so many drugs, which require a high level of knowledge of pharmacists and clinical pharmacists. The volume of

information about the mechanisms of drug action, their pharmacological effects, and the possibility of clinical use is growing rapidly. The position mentioned above leads to the necessity of teaching pharmacology to a much greater extent than it is provided in curriculum. Thence, the tutorial has been prepared based on the State Formulary of Ukraine, and the the British National Formulary of drugs, the Russian Register of medicines, Compendium and the current literature on pharmacology and pharmacotherapy.

The authors of the tutorial are the teachers of the pharmacy department of Vinnitsa National Pirogov Memorial Medical University, Faculty of Pharmacy, with experience of teaching of pharmacology both in terms of previous training programs, and in terms of credit-modular system.

The authors are grateful to the reviewers who have put great efforts to improve the tutorial and gratefully accept all comments and suggestions from readers for further improvement of the tutorial.

List of abbreviations

AA - arachidonic acid
AANAT - arylalkylamine N-acetyltransferase
ACE - angiotensin-converted-enzyme
ACEI - angiotensin-converted-enzyme
inhibitor Ach - acetylcholine
AchE - acetylcholine esterase
ACTH - adreno-cortico-tropic hormone
ADME - absorption, distribution, metabolism, excretion of the
drugs ARs - adrenergic receptors
API - active pharmaceutical ingredient
ADP - adenosine diphosphate
ALX receptor(s) - lipoxin eceptor(s)
AT receptor - angiotensin receptor
ATP - adenosine triphosphate
AV - block - atrio-ventricular blockage
AV- node - atrio-ventricular node
AVP - additional vasodilating propertie(s)
AUC - area under curve
Axe - acethylcholinesterase
BAS - biologically active substance(s)
BBB - blood brain barrier
BCSFB - blood-cerebrospinal fluid barrier
Ca^{+2} - calcium ion(s)
$C_{el.}$ - constant of elimination
cAMP - cyclic adenosine monophosphate
cGMP - cyclic guanosinemonophosphate
Cl - total clearance
CNS - central nervous system
CO - carbon monoxide
COMT - catecol-orto-methyl-transferase
COX - cyclooxygenase
CysLT receptor(s) - cysteinyl leukotriene receptor(s)
D - dopamine
DAG - diacylglycerol
DNA - deoxyribonucleic acid
DDC - decarboxylase
DGLA - dihomo-γ-linolenic acid
EET - Epoxy-eicosa-trienoic acid
e.g. - for example
Ep - epinephrine
EPA - icosapentaenoic acid
E2 (PGE_2) - prostaglandin E2

F2α ($PGF_{2\alpha}$) - prostaglandin F2α
FDA - Food and Drug
Administration FFA - free fatty acid
fMLP - Formyl-Methionyl-Leucyl-Phenylalanine
GIT - gastrointestinal tract
GPCR - G-protein-coupled receptor(s)
H_2S - hydrogen sulphide
h/chl. - hydrochloride
h/tr. - hydrotartrat
I2 (PGI_2) - prostacyclin
i.e. - that is
IHD - ischemic heart disease
i/m - intramuscularly
INN - international nonproprietary name
IP_3 - inositol 1,4,5-trisphosphate
ISA - intrinsic sympathomimetic
activity i/v - intravenous
$K_{el.}$ - constant of elimination
LTs - leucotriens
LXA4- lipoxin A4
MAO - monoaminoxydase
MAOI - MAO inhibitor
MIC - minimum inhibitory concentration
MF - medicinal form
MP - medicinal preparation
NE - norepinephrine
NO - nitric oxide
OTC - over-the-counter
P receptor(s) - purine receptor(s)
PAE - “postantibiotic” effect
PAF - platelet-activating factor
PB - placental barrier
PGs - prostaglandins
PI - phosphatidylinositol
PLA2 - phospholipase A2
PLC - phospholipase C
RNA - ribonucleic acid
s/c - subcutaneously
Se - serotonine
SNRI(s) - serotonine-norepinephrine reuptake inhibitor(s)
SSRI(s) - selective serotonine reuptake inhibitor(s)
SVT - supraventricular tachycardia
TCA(s) - tricyclic antidepressant(s)
TG - triglyceride(s)

TI - therapeutic index
TPH - tryptophan hydroxylase
Tx - thromboxane
TxA_2 - thromboxane A2
$T_{1/2}$ - half-life
V - volume distribution
USAN - United States Adopted Name(s)
WHO - World Health Organization
WPW syndrome - Wolff-Parkinson-White syndrome
5-HIAA - 5-hydroxyindoleacetic acid
5-HT - 5-hydroxytryptamine
5-LOX - 5-lipoxygenase

Introduction

Pharmacology is the study of the interactions that occur between medical devices, biologically active substances with a living organism. **Pharmacology** is concerned with the study of medical devices, which are used for treatment, prevention and diagnostics of diseases and pathological conditions. From Greek "**pharmacon**" – there is drug and "**logos**" – there is a science. **Pharmacology** is the branch of medicine which is connected with other disciplines such as biology, chemistry, normal and pathological anatomy, normal and pathological physiology, histology and pharmaceutical sciences such as pharmaceutical chemistry and toxic chemistry, pharmacognosy and drug technology.

To the sciences about drugs belongs not only pharmacology but also pharmacy. And if pharmacology is a science that deals with the effect and usage of medicines, so **pharmacy** is a science that deals with the preparation and dispensing of drugs.

An active pharmaceutical ingredient (medical substance (MS) or active substance) (API) – is any substance or mix of substances that is used in manufacture of drugs and during its usage exerts pharmacological activity. Such substances have pharmacological or other direct effect on the human body; in the composition of the prepared forms of drugs which are used for cure, diagnosis and prevention of diseases, for the change of condition, structures or physiological functions of the organism, for care, treatment and facilitation of symptoms. (The order of The Ministry of Health of Ukraine № 723, completed in accordance with The Ministry of Health of Ukraine № 427 (z0923-13) dated 24.05.2013).

Pharmaceutical drug – is any substance or combination of substances (one or more API and excipients) that has properties and is intended for use in the treatment or prevention of diseases or it's any substance or combination of substances (one or more API and excipients) that can be prescribed for the pregnancy prevention, restoration, correction or change of physiological functions in humans by providing pharmacological, immunological or metabolic actions, or for diagnosis.

Medicinal Form (MF) – is a combination of the form in which a drug is submitted by the manufacturer (release form), and also the forms in which a drug is prescribed for usage including physical form (the form of usage).

Medicinal preparation (MP) – is a drug that is made in the appropriate dosage (medicinal) form. Medical preparations can be simple which are made from medical raw material (usually from plants, but also can be of mineral and animal origin) using a simple processing (drying or grinding), complex or galenicals, which are made by using more complex processing of plant raw materials with extraction (by alcohol, ether, water) of biologically active components and their partial exemption from impurities (ballast substances). These are tinctures and extracts. However galenicals contain many impurities (proteins, coloring substances, mucuses, etc.) which reduce the effect of the preparation, may cause a pharmacological effect which differs from that of the purified substance (e.g., there

is no equality between the pharmacological effect of opium galenic preparations and morphine, between the extract of uterine horn and ergometrine, between the ascorbic acid and rosehip extract, etc.) and do not allow its parenteral use. Neogalenicals are made by the pharmaceutical industry. They are more purified of ballast substances, have a longer expiration date, less of side effects and are suitable for parenteral use. (e.g., atropine, platyphylline, morphine, ephedrine, digoxin, strophanthin etc.). Each MP is registered in the state register of the pharmaceutical drugs of the country.

Some drugs are in an inactive form and in order to convert them into an active form, they should be metabolized in the human body and should form metabolites that have pharmacological activity. These drugs are called prodrugs.

Substances with medicinal properties can be synthesized within the human body (e.g., hormones) or may be xenogenic to the human body, the so-called xenobiotics *(Greek xenos – "alien ")*.

Some drugs are administered as racemic mixtures of stereoisomers. The stereoisomers can exhibit different pharmacodynamic as well as pharmacokinetic properties. More than half of the drugs exist as enantiomeric pairs: *R (+)* enantiomeric, *S (-)* enantiomeric and the racemic mixture *RS (+ / -)*.

Drugs have three main names:

the chemical name, which reflects the chemical structure of drugs and is rarely used in medical practice, but often – in the annotations to the drugs and in the reference books. For example, 2-acetoxy-benzoic acid (acid acetylsalicylic).

international nonproprietary name (INN) of drugs. This name of drugs is offered by the WHO (World Health Organization) and is adapted for use worldwide in the academic and scientific literature for easier identification by experts and for prevention of errors in determining generic / trade names of drugs. *For example*, acid acetylsalicylic (2-acetoxy-benzoic acid).

commercial / trade name (brand names) is given by pharmaceutical companies / manufacturers of drugs and is a commercial property, protected by patents and indicated by a pictogram – an English letter "R" inside a circle. *For example*, Aspirin ® (2 -acetoxy-benzoic acid, acid acetylsalicylic). Trade name is used by the company that produces these drugs for marketing purposes, to advance it in the market and to compete with other similar drugs. After the expiration of the patent the manufacturer can sell the right to produce drugs under the INN. Such drugs are called generics (branded equivalent). Generics are usually cheaper than original drugs because their price does not include money spent on development, preclinical and clinical drug testing. *For example*, Trombo ASS (2-acetoxy-benzoic acid, acid acetylsalicylic, Aspirin).

Equal drug substances may contain the same doses of a chemical substance in one dosage form and have different trade names (synonyms). Thus, the pharmacist can make a so-called generic substitution of drugs, focusing on its INN, in the absence of drugs recommended by your doctor or the drugs required by the patient in the drugstore. *For example*, (2-acetoxy-benzoic acid, acid acetylsalicylic, Aspirin, Trombo ASS).

Peculiarities of marking of ready dosage forms

The symbol «®» *(from English "Registered trademark" – the registered mark)* is a marking which is written down on the package near a certain brand name and means the registration of the mark as a trademark for goods. In the registration certificate and other registration documents the symbol «®» is written down next to the trade name of medicinal preparation.

Tablets with a modified release are covered or uncovered tablets which contain special excipients or substances received by a special technology that allow to program the speed or location of the release of the medical substance (the modified-release tablets – MR). The name is used to mark the tablets with a controlled release, sustained-release (SR) tablets, and tablets with a gradual release, prolonged/extended release (ER). The name is not used to name the tablets that are indicated as the depot tablets, tablets that are implanted, retard-tablets, rapid-retard tablets.

There are **Drug Delivery Systems**: *Osmotic Release Oral System (OROS)* – there is the system based on the principle of osmotic pump, with which there is a constant controlled release of a drug in a unit time; *Transdermal System (TS)* of drug delivery in the form of patches; *Gastrointestinal Therapeutic System (GITS)*, which provide release of drug substances from the medicinal forms in a neutral, acidic or alkaline environment of gastrointestinal tract GIT; *Orally disintegrating tablet (ODT)*, *dry powder inhalers (DPI)*, *metered-dose inhalers (MDI)*, etc. The main merit of therapeutic systems is improvement in bioavailability as well as reduced adverse effects and limitation of high initial drug concentrations in plasma and opportunity to change the mode of taking drugs, dosing regimen on a convenient for the patients.

Retard tablets are tablets with a prolonged (periodic) release of medical substance from the stock. Usually they are in the shape of microgranules from a medical substance, surrounded by a biopolymer matrix (base), a base or microgranules are dissolve in layers releasing another portion of medical substance.

Rapid tablets contain a mixture of microgranules with an immediate release of medical substance.

Rapid retard tablets are tablets with a biphasic release that contain a mixture of microgranules with a rapid and prolonged release of the medical substance.

Tablets UNO – a recommended average dose for adults and children over 12 years is 1 tablet every 24 hours.

The tablets durules provide a gradual release of the active ingredient (iron ions) during a long time. The plastic matrix of the tablets Sorbifer Durules is completely inert in the digestive juice, but is completely dissolved under the influence of the intestinal peristalsis, when the active ingredient is completely released.

There are **international standards (International rules-standards)**, which determine the process of production of drugs: **GMP** – good manufactory practice; **GLP** – good laboratory practice – appropriate preclinical drug testing: on animals, test-systems (ex vivo), on cells, etc.; **GCP** – good clinical practice – appropriate clinical drug testing: on healthy volunteers, on patients; **GDP** – good distribution practice – appropriate practice of distribution of drugs; **GPP** – good pharmacy practice.

Despite the complexity of the creation and production of new drugs and their generics, new dosage forms, the study and specification of the action mechanisms in accordance with new knowledge in related sciences, the discovery of new pharmacological effects of the known drugs, determination of pharmacological safety, pharmacological custody and the combined use of medicine, pharmacology and pharmacy are very fast-developing sciences that require a constant monitoring and addition in teaching in the learning process.

Pharmacology includes **Pharmacokinetics** and **Pharmacodynamics.**

In order to understand and control drug action in the human body, one needs to know how a drug reaches the site(s) of drug action and when this will happen. Besides, understanding biochemical and physiological effects of the drugs and their mechanisms of action can provide the basic for the rational therapeutic use of the drugs and development of new and better therapeutic agents. More over, the adverse effects of the drugs and their toxicity can be expected by understanding a drug's mechanism(s) of action, its pharmacokinetics, and its interactions with other drugs. Thereby, both the pharmacodynamic properties of a drug and its pharmacokinetics promote the safe and successful therapy. It is necessary to remember that the effects of many drugs, both curative and maleficent, may differ widely from patient to patient due to genetic differences that alter pharmacokinetic and pharmacodynamic of a given drug.

UNIT 1. GENERAL PHARMACOLOGY

Chapter 1. Pharmacokinetics

Pharmacokinetics studies the routes of administration, the processes of absorption, distribution and metabolism (biotransformation), routes of excretion of drugs (often referred to collectively as ADME). Pharmacokinetics studies what the body does to the drugs. Realizing and applying pharmacokinetic principles can increase the probability of therapeutic success and reduce the emergence of adverse effects of the drug.

There are enteral and parenteral routes of drug administration. There are several reasons for different routes of administration of the drugs: convenience, good absorption, to avoid destruction by some enzymes, reaching of possibility to increase the drug concentration in the site of action and to decrease the drug concentration in the other places, prolongation of therapeutic effects, minimization of adverse effects, etc. But, one of reasons is to avoid the first-pass effect (in case of sublingual, transdermal, rectal routs of drug administration). Although the drugs that were administrated by inhalation bypass the hepatic first-pass effect, they may metabolize or excrete in the lung (the lung first-pass effect). More over the lung *first*-pass effect may be important for parenteral routes of drug administration.

The parenteral routes *(by-passing gastrointestinal tract)* ***of drug administration include:*** transdermal, intradermal, subcutaneous, intramuscular, intravenous, intra-arterial, intracardiac, intraperitoneal, intrapleural, intratracheal, in the joints, intrasternal, under the brain membranes (intrathecal), intranasal, inhalation, instillation, and vaginal routes.

The enteral routes *(through gastrointestinal tract)* ***of drug administration include:*** sublingual, transbuccal, per oral, per rectum, intraduodenal.

The route of drug administration is determined first of all by ***the properties of the drugs*** (medicinal form, mechanism of action, water or lipid solubility, ionization, features of metabolism, stability in acidic or alkaline environment, the type of absorption; the rate of absorption of the drug from the mucous membranes and skin) and by ***the therapeutic objectives*** (the diagnosis; the desirability of a rapid onset of action or need for long-term action; restriction to a local site or need for general action; the presence of concomitant diseases, especially liver, kidney, heart insufficiency, blood diseases, GIT diseases; vomiting; violation of swallowing; loss of consciousness; psychical diseases; the general condition of the patient; age of the patient; target organ for the drug.

The parenteral routes *(by-passing GIT)* ***of the drug administration*** introduce drugs directly across biological body's barrier defenses into the systemic circulation or other vascular tissue. Parenteral administration is used for the drugs

that are poorly absorbed from GIT, and for substances that are unstable in GIT, and for substances that irritate mucosa of GIT, and for substances that have not enteral MFs, or in patients that can't take the drugs through GIT. Parenteral administration is also used for treatment under circumstances that require a rapid onset of action. Parenteral routes have the highest bioavailability and aren't subject to first-pass metabolism (rapid metabolism in the liver) or harsh GIT environment (hydrochloric acid and digestive enzymes). Parenteral administration provides the highest possible control over the actual dose of drug delivered to the body. However, these routes are irreversible and may cause pain, fear and infections. The different parenteral routes of drug administration have advantages and limitations.

Transdermal route of drug administration is appropriated to drugs that are well absorbed through intact skin. They are used in the form of ointments, plasters. For better penetration of such drugs they may be used in combination with drugs that increase their absorption. Part of the drugs can be absorbed and enter the bloodstream, and may cause unwanted effects on the entire body.

Intradermal route of drug administration is used rarely, only in case of diagnostic tests for allergy etc.

Subcutaneous route of drug administration is like intramuscular injection, but is somewhat slower than intramuscular route.

Intramuscular route of drug administration provides the drug entrance to the systemic circulation in 10-15 minutes. The oil solutions and suspensions can be introduced intramuscularly. Substances that can cause tissue necrosis are not injected intramuscularly, subcutaneously or intradermally.

Intravenous route of drug administration is the most common parenteral route. This route is used for the drugs that aren't absorbed orally and under circumstances that require a rapid onset of action, or in the patients' conditions that can't allow introducing the drugs orally. Intravenous route of administration may cause thrombosis, thrombophlebitis and thromboembolism.

Sometimes the ***intra-arterial route of drug administration*** is used to the artery that supplies the target organ. This route can be used not only for the treatment but also for the X-ray diagnostics.

The intracardiac ***route of drug administration*** is used very rarely.

In the cavity of the body (***intraperitoneal, intrapleural, intratracheal, in the joints routes of drug administration***) the drugs are injected in case of treatment the diseases, only at special indications.

Intrasternal route of drug administration is sometimes applied to children and old people when a quick help is required and it is technically impossible to enter the drug intravenously.

Under the brain membranes – intratecal route of drug administration is used in case of the infection diseases and for local anesthesia.

Inhalation provides the rapid delivery of the drugs across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium, producing effects almost as rapidly as intravenous injection. This route is used for the drugs such as gases or aerosols and is effective and convenient for the patients

with respiratory complaints (asthma, chronic obstructive pulmonary disease, bronchospasm). In this route the drugs is delivered directly to the site of action and systemic side effects are minimized.

Instillation is the route of the drug administration by putting the drops into eyes, nose and ears.

Intranasal route of drug administration is used for the treatment of nasal mucous diseases (local action), but sometimes for the systemic action.

Vaginal route of drug administration is used for treatment of female genital organ diseases and for diagnostics – introduction of contrast agents.

Sublingual / transbuccal route of drug administration allows a drug to diffuse into the capillary network and to enter the systemic circulation directly. This route of administration has several advantages including rapid absorption, convenience of administration, low incidence of infection, avoidance of harsh GIT environment, avoidance of the first-pass metabolism.

Oral route of drug administration provides many advantages to the patient: the ease of self-administration and the limit number of systemic infections, toxicities and overdose may be overcome with antidotes such as activated charcoal. At the same time, the pathways involved in drug absorption are the most complicated, and the drug is exposed to harsh GIT environment that may limit its absorption. The drugs absorbed from the stomach or from the other site of GIT enter the portal circulation and encounter the liver before they are distributed into the general blood circulation. These drugs undergo first-pass metabolism in the liver, where they may be extensively metabolized before entering the systemic blood circulation. The first-pass metabolism in the intestine or in the liver limits efficacy of the drugs when taking orally. The dose of the drugs taking orally should be enough to reach the target organ and to provide the therapeutic or prophylactic effects. About 75% of the drugs taking orally are absorbed in 1-3 hours. In addition, ingestion of drugs with food, combination with other drugs can influence absorption. In other side, the drugs may irritate GIT mucous, hydrochloric acid and digestive enzymes may destroy drugs, but medicinal forms of the drugs may prevent gastric irritation, may protect active remedies against destruction and may prolong the period of drugs elimination providing the prolonged effect. Thus, the oral route of administration can not be applied to newborns, infants or mental patients, to patients with loss of consciousness, to patients with nausea, vomiting, to patients with impaired swallowing, insufficiency of heart (edema), to patients with violation of the absorption in GIT, or if rapid effect is required. We must remember that some of the drugs are digested in GIT (protein and polypeptide substances), some of the drugs are destroyed by hydrochloric acid and digestive enzymes and shouldn’t be taken orally too. For rapid absorption the drugs should be taken on an empty stomach. Absorption of the fat-soluble vitamins may be only in the presence of bile and fatty acids. And the administration of several drugs simultaneously should be carefully monitored and the possibility of their interaction should be taken into account.

Rectal route of drug administration provides drug absorption in lower and middle hemorrhoidal veins. In this way the drugs enter the bloodstream bypassing the liver. 50% of the drainage of the rectal region bypasses the portal circulation; thus the biotransformation of the drugs by the liver is minimized. Like the sublingual/transbuccal route of administration, the rectal route of administration has additional advantage of preventing the destruction of the drugs by intestinal enzymes or by hydrochloric acid in the stomach. The effect of the drugs introduced rectally develops rapidly as well as at intramuscular introduction. The rectal route of drug administration is useful for newborns, infants, for patients with nausea, vomiting, for patients with loss of consciousness. On the other hand, rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa.

Intraduodenal route of drug administration allows to enter the drugs in a specific area – duodenum. Duodenum is major site of entry to systemic circulation because of its large absorptive surface.

Absorption of the drugs is the transfer of the drugs from its site of administration to the bloodstream. The rate and efficiency of absorption depends on the route of administration. The total absorption means that the total dose of a drug reaches the systemic circulation. Only the direct administration of the drug in blood provides a full dose of a drug into the bloodstream (total absorption). Drug delivery by other routes may result in only partial absorption, and thus, to lower the bioavailability.

Drugs may be absorbed by ***passive diffusion***, ***facilitated diffusion*** (with carrier proteins), ***filtration, active transport, pinocytosis (endocytosis*** or ***exocytosis).***

The driving force for ***passive diffusion*** of a drug is the concentration gradient across a membrane separating two body compartments: the drug moves from region of high concentration to one of lower concentration without a carrier, isn't saturable, and shows a low structural specificity. The vast majority of drugs gain access to the body by this mechanism. Lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane bilayers. Water-soluble drugs penetrate the cell membranes through aqueous channels or pores ***(filtration)***. The capillaries of some vascular beds (e.g. in the kidney) have large pores, which permit the passage of molecules as large as proteins. Other drugs can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules ***(facilitated diffusion).*** These carrier proteins undergo conformational changes allowing the passage of drugs or endogenous molecules into the interior of cells, moving them from an area of high concentration to an area of lower concentration. This type of diffusion does not require energy, can be saturated, and may be inhibited. ***Active transport*** also involves specific carrier proteins that span the membrane. Active transport is energy-dependent and is driven by the hydrolysis or adenosine triphosphate (ATPh). These drugs are capable of moving against a concentration gradient – that

is, from a region of the lower drug concentration to one of higher drug concentration.

Pinocytosis (endocytosis or ***exocytosis)*** –is the type of delivery that transports drugs of exceptionally large size across the cell membrane. ***Endocytosis*** involves engulfment of a drug molecule by the cell membrane and transports into the cell by pinching off the drug-filled vesicle. ***Exocytosis*** is the opposite to endocytosis and is used by cells to secrete many substances by a similar vesicle formation process.

The ***passive diffusion*** is typical for lipid-soluble substances, electrolytes (potassium and sodium), weak organic acids (e.g., benzoic acid), and ethyl alcohol. ***Facilitated diffusion*** is inherent in transport of glucose, glycerol, amino acids and vitamins. The substances insoluble in lipids (e.g., water, ions of potassium and sodium) and small hydrophilic molecules (e.g., urea) are absorbed by ***filtration.*** The low molecular cations (potassium and sodium), amino acids, cardiac glycosides, vitamins of B group, corticoids are absorbed with the help of ***active transport*** The macromolecules of proteins and nucleic acids, fat acids, fat-soluble vitamins and also liposomes with drugs use ***pinocytosis*** for the absorption.

There are many factors that can influence the process of absorption: pH of environment, physiological properties of membranes, bioavailability of drugs, peculiarities of drug metabolism in the organism, including the processes of presystemic drug elimination, drug ability to dissolve in water and in lipids, drug aptitude and power to bind with plasma proteins, chemical stability in human body, features of chemical structure of drugs (molecular size, their forms, presence of a specific coating, supplemental substances, etc.), availability of specific enzymes for drug metabolism.

pH effect of drugs on drug absorption. Most of drugs are weak acids or weak bases. Acidic drugs release an H^+ causing a charged anion (A^-). Weak bases can also release an H^+. However, the protonated form of basic drugs is usually charged, and the loss of a proton produces the uncharged base. The uncharged drugs more readily pass through membranes than the charged drugs. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base. Distribution equilibrium is achieved when the permeable form of a drug achieves an equal concentration in all body water spaces.

Physical factors affecting the absorption. Absorption from the intestine is favored over than from stomach because the blood flow to the intestine is much greater than the flow to the stomach.

Absorption of the drugs across the intestine is more efficient because the intestine has a surface rich in microvilli, it has a surface area about 1000-fold that of the stomach.

If a drug moves through the GIT very quickly, it isn't well absorbed. Conversely, anything that delays the transport of the drug (the presence of food,

other drugs) from the stomach to the intestine delays the rate of absorption of the drug.

In the blood medication is usually bound to plasma proteins: the stronger such a connection, the slower developing therapeutic effect and vice versa; hypoproteinemia may lead to the increase of the drug activity and drug toxicity; drugs compete for binding to plasma proteins as a result can displace each other from the bound fraction.

Bioavailability is the fraction of administrated drug that reaches the systemic circulation in a chemically unchanged form. When the drug is given orally, only part of the administrated dose appears in the plasma. In case of intravenous administration a full dose of the drug reaches the systemic circulation and bioavailability is 100%. But not only the administrated dose of the drug and route of drug administration influence on the amount of the drug that reaches the systemic circulation, and also the fraction of the dose that is absorbed and escapes any first-pass elimination. This fraction is the drug's *bioavailability.*

By plotting plasma concentration of the drug versus time, one can measure the area under the curve (AUC). This curve reflects the extent of absorption of the drug. *Bioavailability is AUC oral/AUC injected* x *100.*

Bioavailability is the main parameter of pharmacokinetics and is used to determine the dosing regimen for different routes of administration of the drugs. Bioavailability denoted by the letter F and is expressed in %. There are: *absolute* and *relative* bioavailability. *Absolute bioavailability* is the ratio of area under the kinetic curve "concentration - time" (AUC) of the active medicinal substance in the systemic circulation after administration of the drug by other than intravenous route (peroral, rectal, subskin, under the skin, etc.) to bioavailability of the same medicinal substance, but in case of intravenous route of administration (F = 1). If the drug was introduced by other route than intravenous its bioavailability will be less than 1 (F < 1). *Relative bioavailability* – is AUC the certain drug that was compared with another medicinal form that has been accepted as a standard, or was introduced into the body by other route of administration. If a standard is the drug that was introduced by intravenous – there is *absolute bioavailability.*

Factors that influence bioavailability: first-pass hepatic metabolism, solubility of the drug, chemical instability, nature of the drug formulation, physical properties of the drug, MF of the drug, systems of delivery of the drug, dosage regime of the drug, stomach emptying rate, the presence of other drugs in the body, that can be inductors or inhibitors, interaction with certain food, transported proteins, substrate for transported proteins, condition of GIT, etc.

First-pass hepatic metabolism. When the drug is absorbed across GIT, before entering the systemic blood circulation the drug enters the portal circulation. If the drug is rapidly metabolized in the liver, the amount of unchanged drug that gains access to the systemic blood circulation is decreased (***presystemic elimination***). Many drugs undergo significant biotransformation during a single passage through the liver.

Solubility of the drug. Very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes. However, the hydrophobic drugs are also poorly absorbed because of they are totally insoluble in aqueous body fluids and, therefore, can't gain access to the surface of cells. For the drugs to be readily absorbed, it must be largely hydrophobic, yet have some solubility in aqueous solutions. This is one reason why many drugs are weak acids or weak bases. The highly lipid-soluble drugs are transported in aqueous solutions of the body on carrier proteins.

Chemical instability. Some drugs are instable in the pH of the gastric contents. Others are destroyed in the GIT by degradative enzymes.

Nature of the drug formulation. Drug absorption may be altered by factors unrelated to the chemistry of the drug, such as particle size, salt form, crystal polymorphism, enteric coating, the presence of excipients, like binders and dispersing agents, can influence the ease of dissolution and, therefore, alter the rate of absorption.

Bioequivalence. Bioequivalence matters in comparing several medications. Two relative drugs are *bioequivalent* if they show comparable bioavailability and similar times to achieve peak blood concentration. Two relative drugs with significant difference in bioavailability are said to be *bioinequivalent*. Two similar drugs are *therapeutically equivalent* if they have comparable efficacy and safety. At the same time, two drugs are bioequivalent may not be therapeutically equivalent. Thus, there are the *pharmacokinetic bioequivalence*, *pharmaceutical bioequivalence, therapeutical bioequivalence. Pharmacokinetic bioequivalence* – is a degree of similarity of pharmaceutically equivalent drug to the reference product (usually – the generic to original patented drug). Pharmacokinetic bioequivalence is determined experimentally, *in vivo*. The basic criteria of *bioequivalence* are: degree and rate of absorption of a drug, time of achievement the maximum concentration in the blood and its value, distribution pattern in tissues, type and rate of drug elimination. *Pharmaceutical bioequivalence* – is a complete reproduction by generic drug the composition and medicinal form of the original drug. *Therapeutical bioequivalence* according to FDA assumes equivalence of generic drug to the original drug by pharmaceutical, pharmacokinetic and pharmacodynamic properties.

The causes of *incomplete bioequivalence* can be: variations in the composition and structure of the drug substances for manufacturing (impurities, isomers, crystalline form, etc.); differences in the composition of excipients that were used for the production of generic; differences in production technologies of MFs.

Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and/or the cells of the tissues. The delivery of a drug from the plasma to the interstitium primarily depends on *blood flow, capillary permeability, the degree of binding of the drug to plasma and tissue proteins, and relative hydrophobicity of the drug.*

Thus, the high *blood flow* of the tissues permits drugs to rapidly move into the tissues, and poor blood flow of the tissues provides slow drug distribution.

Capillary permeability is determined by capillary structure and by the chemical nature of the drug.

The degree of binding of the drug to plasma and tissue proteins determines the degree of possibility of absorption of the drug from the vascular bed of the tissue. Both forms of the drug (free and bound to plasma proteins) are in a state of dynamic equilibrium. Major drug-binding proteins may act as a drug reservoir. The free drugs render the biological effects; bound drugs remain in the vascular bed. Macromolecular compounds which are tightly bound to plasma proteins do not penetrate through the vascular endothelium and stay in the vascular bed. Low molecular compounds can pass through the pores in the walls of capillaries into the intercellular space. In case of decreasing of plasma protein quantity the quantity of free forms of the drugs is rising and the toxic effects of the drugs may develop. Drugs may compete for the relationship to plasma proteins and replace each other from the binding, thereby increasing the free fraction of the displaced drug. High degree of connection a drug with plasma proteins contributes to the duration of drug action. Depot in fat tissue provides a gradual release of the drug and its long-term effect. The selective distribution of the drugs to specific organs and tissues determines its pharmacodynamics.

Hydrophobic drugs (fat-soluble drugs) pass all *biological barriers*: blood-brain, placental, walls of vessels, walls of intestine, membranes of cells, intracellular membranes, blood-cerebrospinal fluid, blood-testis, blood-glomerular, blood-retinal, blood-thymus and blood-lung, etc.

Drug distribution is dependent on *the ability to penetrate biological barriers, bioavailability of a drug, supply of organs and tissues with blood, accumulation: extra- and intracellular depots.*

Concentration of the drugs (C_d) – is quantity of the drug in a certain volume of blood, in a specific time after the introduction of a drug into the human body, and it is expressed in mg / l, mcg / l, mmole / l, %.

The **apparent volume distribution** (V) – is the ratio of the total amount of the drug in human body to its quantity in the blood plasma. This coefficient is very important in case of overdoses of the drug, when must remove the drug by hemodialysis. The removing of a drug by hemodialysis is effective if most of it is in the plasma.

The structural features of blood-brain and placental barriers. *Blood-brain barrier (BBB)* is the physiology barrier between blood and brain cells to protect the nervous tissue of xenobiotics and to maintain homeostasis of the brain. The main structural element of the BBB is endothelial cell. The peculiarity of the cerebral vessels is the presence of tight junctions between endothelial cells, and intercellular spaces between endothelial cells, pericytes and astrocytes, smaller than the spaces between cells in other tissues. Difficulties in passing of the drugs through blood-brain barrier connected with peculiarities of structure of brain capillaries: they haven’t pores, can’t carry out pinocytosis and they have an

additional lipid membrane. In addition, on the surface of the cell membranes of BBB endothelial cells are a series of enzymes, and in much greater quantities than in the membranes of other cells in the parenchyma. Due to the high concentration of enzymes in the endothelial cells of the BBB, many substances are metabolized during transport through the cytoplasm of these cells. Besides, BBB has a significant electrical resistance. In connection with the above, through the blood-brain barrier can be the diffusion of small polarized molecules on the concentration gradient without energy consumption. Further, BBB permeability depends on the lipophilicity of each particular substance, the molar mass of the substance. Diffusion of the substances through BBB can occur through specific channels of the cell membranes. In the cells of the brain is also the diffusion of substances by transport systems without energy consumption and active transport with energy consumption. With the help of a receptor-mediated transcytosis the large molecules are transferred into the cells of the brain through BBB. There is the cationic transport for negatively charged molecules.

Damage to the BBB in humans occurs in a wide range of diseases:

Syndrome of deficiency of protein GLUT-1, which is responsible for the BBB permeability for glucose and ascorbic acid. This is an autosomal dominant inherited disease that causes the development of microcephaly, psychomotor disturbances, ataxia, and a host of other neurological disorders:

Hereditary of folic acid malabsorption
Diabetes mellitus
Multiple sclerosis
Ischemic stroke
Bacterial infection of the central nervous system (CNS)
Viral infection of the central nervous system
Brain tumors

Table 1. BBB permeability to antibacterial drugs*

Penetrate well	**Penetrate well in inflammation**	**Poorly penetrate even in inflammation**	**Not penetrate**
Isoniazidum	Aztreonam	Gentamycin	Clindamycin
Pefloxacinum	Amikacin	Carbenicillinum	Lincomycin
Rifampicinum	Amoxicillin	Macrolides	
Chloramphenicol	Ampicillin	Norfloxacin	
Co-Trimoxazole	Vancomycin	Streptomycin	
	Meropenem	Lomefloxacin	
	Ofloxacin		
	Cephalosporins of III—IV generations		
	Ciprofloxacin		
	Levofloxacin		

* adapted from: AV Kuznetsov, O. Dreval Posttraumatic meningitis and meningoencephalitis / / Clinical guidelines in traumatic brain injury / edited by AN Konovalov, LB Likhterman, AA Potapov - M: "Antidor", 2002. - T. 3. - P. 420. - 632 p.

Placental barrier (PB) - is the physiology barrier between maternal blood and fetal blood. Placental barrier shall perform such functions as: prevents mixing of blood between mother and fetus; carries gas exchange - the diffusion of oxygen from maternal blood to fetal blood and carbon dioxide in the opposite direction; provides entry into the blood of the fetus vitamins, water, electrolytes, nutrients and minerals, as well as removal of metabolic products (urea, creatine, creatinine) by means of active and passive transport; absorbs some of the substances circulating in maternal blood, and prevents them from entering the bloodstream of the fetus. Unfortunately, however, the large number of medicines, nicotine, alcohol, drugs, pesticides and other toxic chemicals, as well as a series of infectious agents that have adverse effects on the fetus, penetrate into the bloodstream of the fetus. In addition, under the influence of pathogenic factors placental barrier function is disturbed to a greater extent. PB starts at 12 weeks of age of the fetus.

The blood-cerebrospinal fluid barrier (BCSFB) limits the central nervous system from the bloodstream and supports homeostasis of the brain. The blood-cerebrospinal fluid barrier is formed by epithelial cells with tight contacts that line the choroid plexus of brain ventricles. From the blood into surrounding brain cerebrospinal fluid received vitamins, nucleotides, and glucose through the blood-cerebrospinal fluid barrier. The overall contribution of the BCSFB in the exchange processes between the brain and the blood is low. In addition to the blood-brain, blood-cerebrospinal fluid barrier, placental barrier in humans, there are the *blood-testis, blood-glomerular, blood-retinal, blood-thymus, blood-lung barriers, etc.*

Drug metabolism (biotransformation). Biotransformation of drugs may take the form of ***metabolic transformation*** and ***conjugation.*** The drugs may undergo biotransformation in the liver, kidneys, intestines. ***Metabolic transformation*** includes oxidation, reduction, and hydrolysis. Metabolism is the main process of detoxification and elimination of drugs and other chemicals. Lipid-soluble drugs must be metabolized in the liver in two sets of reactions, called *Phase I* and *Phase II*.

In the Phase I lipophilic drugs convert into more polar metabolites by introducing or unmasking a polar functional group (-OH, -NH_2, -SH). Phase I may alter or unalter pharmacologic activity of the drugs.

Many of the enzymes that metabolize drugs, are located on lipophilic membranes of the endoplasmic reticulum of the liver, GIT and other tissues. When these membranes are isolated by homogenization and fractionation, they transform to vesicles named as ***microsomes***. Microsomes contain enzymes that play an important role in oxidation and reduction processes. The process of microsomal oxidation of the drugs requires the participation of cytochrome P450, cytochrome P450-reductase, NADP.

The cytochrome P450 system is involved in the *PhaseI* biotransformation: drug bind with cytochrome P450 system which is important for metabolism of endogenous compounds and exogenous substances ***(xenobiotics)***. Some drugs induce microsomal enzymes and other drugs inhibit microsomal enzymes are very important for pharmacokinetic drug interactions and reintroduction of drugs.

If the substances or metabolites from *PhaseI* biotransformation is sufficiently polar, they can be excreted by the kidney. Nevertheless, many Phase I metabolites are too lipophilic to be retained in the kidney tubules. The substances or metabolites from Phase I biotransformation are subjected to conjugation with endogenous substrates, such as glucuronic acid, sulfuric acid, acetic acid, or amino acid. This is *PhaseII* biotransformation. The conjugates are too polar molecules that readily excrete and very often haven't pharmacologic activity. Since, the endogenous substrates may contain in foodstuffs, nutrition plays an important role in regulation of the drug conjugation process. Conjugation is the final event of drug inactivation and reaction of "***true detoxification"***, although some these reactions of conjugation may lead to form of active conjugates, possessing hepatotoxic effect. Moreover, neonates are deficient in this conjugating system, making them vulnerable to some drugs. Drugs already possessing an -OH, -NH_2, or -COOH group may enter Phase I directly and become conjugated without Phase I metabolism. The highly polar drug conjugates may then be excreted by kidney or bile. In reality, metabolism of the drugs and/or xenobiotics is not always harmless. The toxicity of the metabolites may be higher than initially introduced substance. This phenomenon is named ***lethal synthesis.*** An example of the formation of toxic metabolites during biotransformation may be a metabolite of *acetaminophen (paracetamol) – N-acetyl-benzoquinoneimine (NAPQI)*, formed under conditions of glutathione depletion in the liver, which is required for conjugation of NAPQI. The accumulation of the active toxic metabolite of acetaminophen leading to liver necrosis. Toxic effects of *phenacetin*, namely nephrotoxic, methemoglobinemia and hemolysis, carcinogenic (formation of tumors of the urinary tract) also occur due to the formation of toxic metabolites. Lethal synthesis is inherent to *codeine*, which by a biotransformation process turns into more toxic *morphine*; to *ethyl alcohol* which is transformed into a toxic *acetaldehyde* and *methanol* is converted into *formaldehyde* and *formic acid*, *isoniazid*, which is biotransformed into *monoatsetilgidrazin* etc. However, the toxic reactions may not be apparent if alternative detoxification mechanisms aren't overloaded or exhausted and the availability of endogenous detoxifying co-substrates (glutathione, glucuronic acid, sulfate) isn't limited.

The metabolism of drugs has peculiar properties which are determined by age, gender, genetic characteristics, functions of all organs and systems of the body, environmental factors and nutrition, etc. The metabolism of the drugs is also affected by the interaction of drugs with their combined application and the interaction with endogenous compounds, as well as by the presence of diseases.

Drug elimination. The main routs of drugs elimination are through kidney and liver. There are other routs of drugs elimination: through intestine, lung, milk in nursing mother, skin, exocrine glands (lachrymal glands, salivary glands, sweat glands, sebaceous glands, stomach glands, intestinal glands, bronchial).

Filtration, channel (tubular) secretion and channel (tubular) reabsorption play the main role in the process of excretion of the drugs with urine. If the drugs have less than 90 MW and don't bind with plasma proteins they filtrate through kidney glomeruli – *glomerular filtration*. The drugs with 90-300 MW may excrete as with

urine as with bile. Process of filtration is disturbed in case of shock, collapse, decreased blood circulation, decreased hydrostatic pressure of the plasma in glomerular capillaries.

Some of drugs excrete by the way of *tubular secretion* with help of specific enzymes and with energy consumption. This process may be broken in case of hypoxia, infection, intoxication in kidney.

The *tubular reabsorption* affects the degree of drug elimination: the fat-soluble substances passively reabsorbed, ionized drugs that are weak acids or alkalis actively reabsorbed. The degree of the reabsorption can be regulated. The acid urine improves degree of the drugs ionization that lead to decreasing of their reabsorption and increasing of their excretion. And vice versa: alkalization of urine leads to increasing of degree of the drugs ionization and accelerates excretion of drugs (weak acids) with urine.

The drugs and their metabolites with more than 300 MW are excreted with *gall*. Some of them form ***gastrointestinal-hepatic/intestinal-hepatic recirculation***. In this case the drug excreted with gall to intestine, where is reabsorbed, reaches the liver and again is excreted with gall. Due to this phenomenon the drugs may cumulate and remain in the body. Intestinal-hepatic recirculation of the drugs can lead to toxic effects of these drugs *(e.g., cardiac glycosides, tetracycline, morphine, etc)*. Due to intestinal-hepatic recirculation the toxic doses of drugs are created in human body.

The gases and volatile substances are excreted through *lung*. Some substances that were directed through GIT and were not absorbed are excreted through *intestine*. Some substances can be excreted through *exocrine glands* and damage the mucous, skin and with mother's milk get into the body of the child.

There are indicators of drug elimination process such as a *constant of elimination ($C_{el.}$), half-life ($T_{1/2}$),* a *clearance (Cl)* for the quantitative evaluation of the process of removing drugs. ***Constant of elimination ($C_{el.}$)*** – is the percentage (%) of reducing of the concentration of a drug in blood per unit time. Constant of elimination is determined by the formula: $C_{el.} = 0.693/ T_{1/2}$**.. *Half-life ($T_{1/2}$)* –** is the time required to reduce the drug concentration (C_d) in the blood in twice: ***from C_d to 1/2C_d.***

Clearance (Cl)* –** is the factor that predicts the rate of elimination in relation to the drug concentration, and is expressed as the volume of plasma from which all drug appears to be removed in given time (ml/min): ***Cl = Rate of elimination/C_d. There are: renal, liver, other and systemic clearance (the last is sum of clearances from the various drug-metabolizing and drug-eliminating organs). "Other" tissues of elimination could include the lung, blood, muscles and other additional sites of metabolism.

Drug accumulation. Whenever doses of the drug are repeated, it can accumulated in the body. If the interval between an administration of the drug is shorter than its $4T_{1/2}$, the accumulation can occur. The accumulation of biologically active substances (drugs, poisons) is named a *material accumulation*. The accumulation of the effects caused by it is named a *functional accumulation*.

Chapter 2. Pharmacodynamics

Pharmacodynamics studies localization and mechanism of action, pharmacological effects of the drugs, dose-effect relationship, factors modifying drug effects and dosage, and drugs' toxicity. Pharmacodynamics studies what the drugs do to the body. The effects of most drugs result from their interaction with macromolecular components of the organism. These interactions remodel the function of the appropriate component and lay the foundation of the biochemical and physiological changes that are characteristic of the response to the drug.

Mechanism of action – is the interaction of drugs with the organism on the biomolecular level. Mechanism of drug action – is a way to achieve its pharmacological effect. *The main types of mechanism action of the drugs:*

connection with receptors
influence on ion channels
influence on the transport systems
influence on the enzymes
influence on the neurotransmitters
antimetabolic action
action in the genes level: deoxyribonucleic acid (DNA), ribonucleic acid (RNA)
chemical and physical interaction with the body fluids and mucous.

Receptors – are specialized target macromolecules that are localized on the cell surface or intracellularly. The majority of medicines exert their effects by interaction with receptors. Drugs may bind with receptors and alter biochemical and/or biophysical activity of cells. Drugs may bind with enzymes and indirectly to affect the receptors: anticholinesterase (AchE) drugs, monoaminoxydase (MAO) inhibitors (MAOIs), inhibitor of catechol-orto-methyl-transferase (COMT), etc. Drugs can exert on the neurotransmitters and change their action on the receptors: sympathomimetics, sympatholytics, etc. Most receptors are named to indicate the type of drug/chemical that interacts best with it: the receptors for serotonin are called serotonin receptors, the receptors for angiotensin are called angiotensin (AT) receptors, etc. In each case, the formation of drug-receptor complex leads to biological response. The cells have a lot of receptors.

Remedies that bind with receptors are named ***ligands***. There are the internal (natural opioid peptides, certain amino acids, etc.) and external (drugs and other xenobiotics) ligands. Interaction of receptors with their ligands follows the principle: lock-and-key. This interaction demonstrates the high degree of specificity of receptors with respect to the ligands. The size, shape, charge of the ligand molecules determines myriad binding sites of the receptors in the cells and tissues of human body. Nevertheless, in the presence of ligands the receptors can undergo a conformational change to bind with ligands. Thereby, the receptors are flexible, not rigid as implied by the lock-and-key model.

The richest sources of pharmacological receptors are proteins that are responsible for transducing extracellular signals into intercellular responses. These

receptors are divided into four families: 1) ligand-gated ion channels; 2) G protein-coupled receptors; 3) enzyme-linked receptors; 4) intracellular receptors. Hydrophilic ligands interact with receptors on the cell surface (families 1, 2, 3). As opposed, lipophilic ligands interact with receptors inside cells, because of they can enter cell through the lipid bilayers of the cell membrane.

Ligand-gated ion channels are responsible for regulation of the flow of ions across cell membranes. The concentration of second messengers is changed due to ***G protein-coupled receptors***. In turn, second messengers are responsible for actions within the cell, and stimulation of these receptors results in responses that last several second to minutes.

Second messengers are essential in conducting and amplifying signals from G protein-coupled receptors. ***Second messengers*** are molecules that relay signals from receptors on the cell surface to target molecules inside the cell, in the cytoplasm or nucleus. The types of second messengers: cAMP (cyclic adenosine monophosphate), cGMP (cyclic guanosine monophosphate), IP_3 (inositol 1,4,5-trisphosphate), Ca^{+2} ions – they are located in cytosol; DAG (diacylglycerol), phosphatidylinositol, AA (arachidonic acid) – they are membrane-associated and diffuse from the plasma membrane into the intermembrane space where they can reach and regulate membrane-associated effector proteins; NO (nitric oxide), CO (carbon monoxide), H_2S (hydrogen sulphide) – gases which can diffuse both through cytosol and across cellular membranes.

An ***effector*** is a molecule that binds to a protein and thereby alters the activity of that protein. A modulator molecule binds to a regulatory site during allosteric modulation and allosterically modulates the shape of the proteins. An effector can also be a protein that is secreted from a pathogen, which alters the host organism to enable infection, e.g. by suppressing the host's immune system capabilities.

Enzyme-linked receptors have cytosolic enzyme activity as an integral component of their structure or function. Binding of a ligand to an extracellular domain activates or inhibits this cytosolic enzyme activity. Duration of responses is on the order of minutes to hours.

Intracellular receptors significantly differ from described above receptors. Intracellular receptors are completely intracellular and resulting in the ligands must diffuse into the cell to interact with intracellular receptors. In this case the ligands must be lipid-soluble to move across cell membranes and they are transported in the body with help of the specific transport systems – plasma proteins, such as albumin. The time of activation of the intracellular receptors and time of response is much longer than other described above.

Spare receptors are present in many tissues. To achieve the maximum effect is not necessarily binding of the agonist with all its receptors. After reaching the maximal response remained free receptors, which are called spare receptors. The presence of receptor reserve ensures adequate pharmacological effects at relatively low concentrations of drugs or neurotransmitters. Pharmacological effect is not in a linear dependence on the fraction of occupied receptors.

Desensitization of receptors is reduced agonist effect when prolonged or repeated exposure. Type of acute desensitization can be explained by the conversion of the activated drug-receptor complexes in the non-activated, desensitized forms, although the receptor retains its ability to bind to the agonist, then the binding effect does not occur. Chronic desensitization usually develops slowly and is not easily reversible. It can be caused by loss or sequestration of receptors from the surface of effector cells by endocytosis (internalization), and their irreversible conformational changes or destruction. Long-term increase in the concentration of hormone or neurotransmitter can cause a decrease in the number and density of the receptors (*down-regulation*), and their destruction. Thus, the loss of receptors may occur if the effector cells are exposed to excessive concentrations of agonist. Some receptors, especially voltage-gated channels, require a rest period before can be activated again. These receptors are called "refractory" or "unresponsive".

The drugs that bind with receptors and activate them are named ***agonists/mimetics*** *(e.g., cholinergic agonists or cholinergic mimetics)*. There are the ***endogenous agonists*** *(e.g., hormones, neurotransmitters, etc.)* and ***exogenous agonists*** *(e.g., cholinomimetics, adrenomimetics, etc.)*. There are the ***full agonists*** that in case of interaction with receptors induce the effect similar to this, which cause the endogenous agonists (*e.g., isoprenaline – agonist of β -adrenergic receptors)* and ***partial agonists*** that cause less effects as compared with full agonist *(e.g., aripiprazole – atypical antipsychotic, partial agonist of dopamine receptors).* If receptor activation requires interaction with several different molecules, they are called ***co-agonists*** *(e.g., NMDA-receptors that are activated by binding both glutamate and glycine).* There are the ***competitive agonists*** *(e.g., caffeine and adenosine that bind with adenosine receptors)*. The drugs that bind with receptors and block them are named ***antagonists/blockers*** *(antagonists of adrenergic receptors, cholinergic receptors, etc.).* If drugs bind to the same receptors as endogenous ligands, they are named ***competitive antagonists*** *(e.g., naloxone – competitive antagonist of opioid receptors, losartan – competitive antagonist of adenosine)*, and if drugs bind to receptors of other sites, they are named ***noncompetitive antagonists*** *(e.g., valsartan - noncompetitive antagonist of AT1 receptors)*. It is important for clinical use of the drugs that action of competitive antagonist can be overcome by administration of high dose of full agonist, but action of noncompetitive antagonist cannot be overcome by this way. If drugs can activate a one subtype of receptor and block the other subtype of receptor, they are named ***agonists-antagonists*** *(e.g., pentazocine and nalbuphine- agonists of* δ and κ *opioid receptors)*. If drugs exert on a one type of receptors they manifest a ***selective action,*** and if drugs exert on several types of receptors they manifest a ***nonselective action*** *(e.g., prazosin – selective α1-adrenoblocker, propranolol – nonselective β1-, β2-adrenoblocker, etc.).*

Drugs can bind not only with receptors but also with other macromolecules (plasma proteins, cell proteins, enzymes) that are named ***dumb (secondary) receptors.***

With regard to ***ion channels*** drugs may also manifest ***selective*** and ***nonselective*** action, and the drugs may act as ***activators*** and ***blockers*** of ion channels *(e.g., amiodarone – nonselective blocker of K^+ channels, verapamil – selective blocker of Ca^{2+} channels, etc.).*

Drugs may be ***inductors or inhibitors*** of enzymes *(e.g., phenobarbital, carbamazepine, rifampicin – inductors of microsomal enzymes of the liver, and cimetidine, peroral contraceptives, paracetamol, chloramphenicol, chlorpromazine, isoniazid, etc. – inhibitors of microsomal enzymes of the liver).* These properties of drugs are important in their combined use: they will influence on pharmacokinetics and pharmacodynamics of the drugs that are metabolized by microsomal enzymes of the liver. At the same time the drugs can be interacted with specific enzymes *(e.g., anticholinesterase drugs with anticholinesterase in cholinergic synapse, cardiac glycosides with K^+,Na^+,ATphase, MAOIs with MAO, ACEIs with ACE, etc.).*

Some drugs due to its structure can be integrated into the metabolic processes of the organism like structure of natural ***metabolites*** *(e.g., metabolites and antimetabolites, hormones and antihormohes, sulfonamides, etc.)*.

Some drugs influence on ***DNA, RNA*** in human body or in microbial cells, viruses, funguses, protozoa *(e.g., antibiotics, antiviral drugs, antifungal drugs, antiprotozoal drugs)*.

In the base of mechanism of action of some drugs may be nonspecific changes caused by their ***physical*** and/or ***chemical properties*** *(e.g., diuretic effect of osmotic diuretics connects with their ability to increase osmotic pressure in kidney channels; antacids interact with the hydrochloric acid of the stomach and neutralize it, heparin directly interacts with its antagonist – protamine sulfate, etc.).*

Nevertheless progress of pharmacology, chemistry, physiology, and other fundamental sciences, mechanism of action of majority drugs unknown and requires further investigation.

Pharmacological effect – is the clinical manifestation of the body's reaction to the drug action. Pharmacological effect – is the manifestation of mechanism of action resulting in the change of organ functions and organisms' systems. In the base of the same pharmacological effects may be different mechanisms of action and different pharmacological effects can be provided by the similar mechanisms of action.

The principles of pharmacokinetics and pharmacodynamics form the base for understanding the time course of drug effect. In practical terms the effect isn't usually linearly proportional to the concentration of this drug in the blood because of relationship between drug concentration and its effect is not linear. Often the changes in drug effects are delayed to changes in drug concentration in the blood. The reasons of this delay may be time that required for drug to reach the site of action (delays of a few minutes, or a few hours), or slow turnover of physiologic substances that are involved in the expression of the drug effect (delays of many hours, or even days). Some of the drug effects are related to the accumulation. Very often there are negative, adverse effects of the drugs, but the positive effects may be based on the accumulation (for example, anticancer drugs that bind with DNA of cancer cells).

Thus, there are immediate effects, delayed effects and cumulative effects of the drugs.

An ***effect (action) of drugs on the body*** may be ***local, reflexive, systemic (resorptive), selective, nonselective, the main, side/adverse (both positive and negative), reversible, irreversible.***

Local action is manifested in the ways of drug introduction: skin, mucosa, vascular endothelium, muscles etc. Local action can be *astringent, enveloping (covering), absorbent, irritating, local anesthetic.*

Reflexive action is often due to irritants. In this way the irritating substance excites the ends of the sensory nerves and reflex and changes the function of internal organs.

Resorptive (systemic) action develops after absorption or direct introduction of the drug in the blood. There are direct (primary) action and indirect (secondary) action.

Selective action is seen in drugs that affect receptors, ion channels, cells, determined organ or tissues. The higher the selectivity of the drug, the fewer side effects. Some drugs are characterized by *nonspecific (nonselective) action*.

The ***main action*** the doctor tries to get by the introduction of drugs into the patient's body.

Side/adverse action/effect is usually *negative (harmful)*, but may be *positive (beneficial)* in some causes.

The effects of most drugs are ***reversible*** – they disappear after elimination of drugs, but some drugs have ***irreversible*** effects – they remains after elimination of drugs from the body. There are predictable side effects of drugs that are a consequence of the known pharmacological effects of these drugs, but there are unexpected side effects of drugs that may have an unknown mechanism of the development, remain unrecognized in clinical trials and are identified only when the drugs enter the broad consumer market.

Some of antibacterial drugs have so-called ***"postantibiotic" effect (PAE)*** of which is defined as persistent suppression of bacterial growth after a brief exposure (1 or 2 h) of bacteria to an antibiotic even in the absence of host defense mechanisms. Factors that affect the duration of the postantibiotic effect include duration of antibiotic exposure, bacterial species, culture medium and class of antibiotic. It has been suggested that an alteration of DNA function is possibly responsible for post antibiotic effect following the observation that most inhibitors of protein and nucleic acid synthesis *(e.g., aminoglycosides, fluoroquinolones, tetracyclines, clindamycin, certain newer macrolides/ketolides, and rifampicin and rifabutin)* induce long-term PAE against susceptible bacteria. Theoretically, the ability of an antibiotic to induce a PAE is an attractive property of an antibiotic since antibiotic concentrations could fall below the minimum inhibitory concentration (MIC) for the bacterium yet retain their effectiveness in their ability to suppress the growth.

The long-term adverse outcomes of drugs – there are *embryotoxic, teratogenic, fetotoxic, mutagenic, cancerogenic effects*.

The ***embryotoxic effect*** is developed in first days and weeks after fertilization (before 12 weeks of pregnancy). This is the toxic effect of the drugs on embryo. As a result, the evolution of embryo, processes of its implantation in uterus wall, placentation are disturbed. In this case, the pregnancy does not progress or there is an abortion in the early stages of embryo development *(e.g.,use of estrogens, progestins, anabolic steroids, Aspirin, Biseptol, tetracycline, isoniazid, nicotine, caffeine, ethyl alcohol, barbiturates, etc.)*.

The ***teratogenic effect*** – is the ability of the drugs to interfere in the development of the embryo and cause fetal malformations. This toxic effect is observed under the influence of drugs during the period from 3 weeks to 4 months of intrauterine development of the embryo, where the most intense is the differentiation of its tissues. Sometimes, abnormalities are developed due to violations of feto-placental blood flow, placental structure, or hormonal, fluid and electrolyte, vitamin imbalance. Teratogenic effect is typical for *antiepileptic drugs, antituberculosis drugs, oral hypoglycemic drugs, high doses of vitamins A, D, ethyl alcohol, etc.*

The ***fetotoxic effect*** is developed as a result of drug actions on the fetus (after 12 weeks of pregnancy). The use of *Acetylsalycilic acid* and other *non-opioid analgesics* in late pregnancy can lead to premature imperforation of the ductus arteriosus; the use of *reserpine* in this period can cause fetal respiratory depression, impaired sucking reflex in this newborn; *captopril* in this case can induce newborn kidney violation; *sulfonamides* that are used in third trimester of pregnancy can provoke fetus kernicterus. In addition to morphological changes in organs and tissues can occur so-called "behavioral teratogenesis", namely, behavioral disorders, memory and learning ability in the postnatal period. It is based on a violation of the neuro-mediator processes, development and the formation of neurons, the distortion of biochemical processes in the fetus. The reason of "behavioral teratogenesis" may be *ethyl alcohol, other psychoactive drugs, components of tobacco smoke.*

The ***mutagenic effect*** is the result of the influence of drugs on germ cells before fertilization and during embryo development. These disorders in organs and tissues are inherited *(e.g., use of cytostatics)*.

The ***cancerogenic effect*** is the ability of the drugs to cause the growth of tumors. But all the drugs are tested for the absence of such effect before receiving permission to use them.

Specific adverse effects of drugs are *tolerance, tachyphylaxis, euphoria, psychological and physical drug dependence, drug addiction, withdrawal syndrome, abstinence, idiosyncrasy, allergic reaction, cross allergic reaction, inhibition of immunity, chemoresistance, dysbiosis, superinfection.*

In case of repeated use of the drugs its pharmacological effect may decrease or disappear. This phenomenon is named ***tolerance***. *Mechanisms of development of tolerance may be:* changes of speed of biotransformation of the drugs, restriction of drug absorption, consolidation of body biological barriers, acceleration of drug elimination, desensitization of receptors, internalization of receptors (dawn-regulation, reducing the number of the receptors), etc. At the same time an increasing of the drug dose may restore the pharmacologic effect, but not always. It depends on the

formation mechanism of tolerance. The rapid development of tolerance is called ***tachyphylaxis*** *(e.g., naphazoline**.** ephedrine, etc.)*

Euphoria is a state of complete physical and mental well-being. If, after the discontinuation of drug use the patient has an uncontrollable craving for this drug, a violation of psychological functions, this phenomenon is called ***psychological dependence***. And, if in this case the patient has an uncontrollable craving for this drug, severe disfunction of internal organs, this phenomenon is called ***physical dependence***. ***Abstinence*** means a significant deterioration of health by reducing the number of received drug or a complete cessation of its use. The most widespread is the drug that has this specific adverse effect such as *ethyl alcohol, tobacco, opioid analgesics*.

Thereby, the *euphoria, psychological and physical dependence, abstinence* are typical for opioid analgesics, caffeine, ethyl alcohol, nicotine, etc.

Withdrawal syndrome is a complex of changes that may occur after the sudden discontinuation of the drug that the patient took a long time. This complex includes manifestation of symptoms of disease which was treated *(e.g., most of hypotensive drugs, antianginal drugs, hormones, etc.)*.

Drug ***idiosyncrasy*** is the distortion of sensitivity to drug. The basis of this side effect is genetic disorders and connections with insufficiency of certain chains of metabolism in condition of internal or external load *(e.g., use of sulfonamides, analgesics, antipyretics, primaquine, mepacrine* in people with insufficiency of glucose-6-phosphat-dehydrogenase cause hemolytic anemia; the intensified *barbiturate* induction of synthetase of aminolevulinic acid induces attack of hepatic porphyria; malignant hyperthermia in case of use of *opioid analgesics*; deficiency of methemoglobin reductase in case of treatment by *nitrates* lead to development of methemoglobinemia; deficiency of hypoxanthine-guanine-phosphoriboxil-transferase in the treatment of gout by *allopurinol* evinces by intensive renal excretion of purine, sometimes with formation of stones (lithiasis); in children of early age (infants) in the treatment by *chloramphenicol* the Grey syndrome (flatulence, diarrea, vomiting, cyanosis, circulatory disorders) may be developed that is connected with deficiency of glucuronyl transferase, disorder of chloramphenicol elimination and as a result – intoxication and death.

Allergic reactions as a response to the use of the drugs can be developed within a few days after the start of medication, or immediately after the first dose. With respect to drugs with similar chemical structure may develop ***cross-allergy*** *(e.g., sulfonamides, procaine, sulfonylurea derivatives of oral hypoglycemic drugs, β-lactam antibiotics, tetracycline, oleandomycin, promethazine, chlorpromazine etc.)*. ***Inhibition of immunity*** is elicited by *immunosuppressants, cytostatics, corticosteroids.* In these patients the bacterial, viral, fungal, and other infection can acquire a generalized character.

Chemoresistance of microorganisms is the general biological reaction of adaptation to the changed conditions of existence. There are different mechanisms of development of this condition: synthesis of specific enzymes that can destroy antibiotics *(e.g., β-lactamases, esterases)*, cell membrane sealing of microorganisms,

decrease of affinity of microorganism's structure to antibiotics, genetic mutations of microorganisms, efflux, etc.

Dysbiosis is a condition that is accompanied by a violation of the natural microflora of the skin, mucous membranes. It develops as a result of *broad-spectrum antibiotics use*, and often accompanied by a ***superinfection***, which is characterized by a population of skin and mucous membranes by resistant microorganisms to the antibiotic which is used. These microorganisms may be fungi, Pseudomonas aeruginosa, methicillin-resistant staphylococci, and others.

Types of drug doses – there are such therapeutic doses as minimal therapeutic dose, average therapeutic dose, maximal therapeutic dose, saturating dose *(e.g., for cardiac glycosides)* and loading dose *(e.g., for sulfonamides)*, maintenance dose *(e.g., for hypotensive drugs)*, toxic dose, and lethal dose. ***Therapeutic dose*** is the quantity of a drug which is used with therapeutic reason. *Minimal therapeutic dose* cases the minimal pharmacologic effect. *Average therapeutic dose* causes the average pharmacologic effect. *Maximal therapeutic dose* causes the maximal pharmacologic effect. ***Maintenance dose*** allows maintaining in human body a therapeutic dose (a target concentration) of the drug in view of its elimination. If it is necessary to reach a target concentration of a drug very quickly, it is desirable to introduce its ***loading dose. Toxic dose*** is the quantity of a drug which causes the toxic effects after use. ***Lethal dose*** is the quantity of a drug which causes death after use. ***Latitude of therapeutic action*** – is the diapason of doses between minimal therapeutic dose and minimal toxic dose. If the latitude of therapeutic action of drugs is large, the drug is safer than a drug with small latitude of therapeutic action. ***Therapeutic index (TI)*** – is the indicator which quantifies the relative safety of a drug, and it is the ratio of median lethal dose LD50 to median effective dose ED50 (ratio risk/ benefit). ***TI = LD50/ED50.*** The LD50 of a compound is determined experimentally, usually by administration of the chemical to mice or rate (orally or intraperitoneally) at a several doses in the lethal range. LD50 is the concentration of a drug at which 50% of the population will have death. ED50 is the concentration of a drug at which 50% of the population will have the desired response. Drugs with low therapeutic indexes are not safe, but the drugs with high therapeutic indexes are relatively safe.

In addition, there is a single dose, daily dose, a course dose. ***Single dose*** is a quantity of drug that was introduced at a time. ***Daily dose*** is a quantity of drug that was introduced during the day. ***Course dose*** is a quantity of drug that was introduced during the course of treatment.

Largely the effect of drug is determined by its dose, but the ***dose-effect*** relationship is not direct. The relationship of dose-effect of the drug also depends on the exposure time, ways of direction, bioavailability of the drug, etc.

Factors that affect action of the drugs (factors modifying drug effects and dosage). It is well known that all patients are different and have different reactions at the same drugs. There are endogenous and exogenous factors influencing drug effects. The *endogenous factors:* sex, age, physiologic condition (biologic rhythms of hormones and enzymes releasing, pregnancy, menstruation, climax), presence of other diseases or pathologic conditions, genetic peculiarities, ethnic and race differences in

drug effects. The *exogenous factors:* chemical structure and chemical and physical properties of drugs, drug medicinal forms, routs of drug administration, drug doses, regimes of feeding, diets (foods may be inductors or inhibitors of microsomal and other enzymes, they may contain substances that have chemical or physical action on the drugs), factors of environment such as weather, time of day, seasons, climate, etc.

Drug-Drug Interaction. Patients are commonly treated with more than one drug, have individual dietary choices, and may also be using *over-the-counter (OTC)* medications, vitamins, and other "natural" supplements. Drug-drug interaction requires the consideration because of it may cause the changes in pharmacokinetics and in pharmacodynamics such as after overdose, may lead to altered rates of absorption, altered protein binding, or different rates of biotransformation or excretion of one or both or several interacting substances.

There are the mechanisms of chemical interaction:*

Pharmacokinetic mechanism:
biotransformation
distribution
absorption
excretion
Pharmacodynamic mechanism
non-receptor
receptor

Classification of chemical interactions:*

additive
synergistic
potentiation
antagonism
a) functional
b) chemical
c) dispositional
d) receptor

* - adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12 edition. Medical. 2011. – 2084 P.

There are ***pharmaceutical, pharmacokinetic and pharmacodynamic interactions*** of the drugs. The base of ***pharmaceutical interaction*** of the drugs is the physical and chemical interactions of the substances that are in the medicinal form of the drug or in case of combine use of them. Consequences of it interaction are negative as rule *(e.g., acids can not be combined with alkalis, cardiac glycosides can not be soluble in hypertonic solution of glucose or in alkaline solution due to their inactivation in these solutios; vitamin B1 can not be introduced in the syringe together with nicotinic acid by reason of destruction of vitamin B1; vitamin B1 can not be introduced in the syringe together with penicillin because of disintegration of penicillin).* ***Pharmacokinetic interaction*** of the drugs is manifested on the stage of

drug absorption, transportation, dissemination, deport, biotransformation and excretion *(e.g., malabsorption of fluoroquinolones and tetracyclines in their joint application with antacides, calcium, iron preparations, bismuth preparations; diphenine hampers absorption of folic acid; fat-soluble vitamins are better absorbed in the presence of bile; sulfonamides reduce the connection of indirect anticoagulants with plasma proteins; disintegration of suxamethonium iodide in action of butyril-cholin-esterase of blood is impeded in concomitant use with anticholinesterase drugs; disulfiram slows metabolism of ethyl alcohol at the stage of acetaldehyde; if salicylates or barbiturates are administrated together this lead to acceleration of their elimination; amiodarone inhibits digoxine elimination through kidney; etc.)*.

Pharmacodynamic interaction of the drugs is appeared in case of the combine use of the drugs that have similar or opposite effects or mechanism of action. In this way the pharmacologic effects of the drugs may be increased (***synergism*** of the drugs) or may be decreased (***antagonism*** of the drugs). If the general effect of the drugs is higher than each effect of every drug this phenomenon is named ***potentiating*** *(e.g., concomitant use of antipsychotics, opioid analgesics and drugs for general anesthesia)*. If the drugs have similar mechanism of action and improve effect each of other this ***synergism*** of the drugs is named ***direct*** *(e.g., epinephrine and norepinephrine)*. If the drugs have different mechanism of action but improve the effect of each other, this ***synergism*** of the drugs is named ***indirect*** *(salbutamol and atropine)*. ***Antagonism*** of the drugs may be ***physical*** *(e.g., absorption of toxic substances by activated charcoal)*, ***chemical, or inactivation*** *(e.g., interaction between acids and alkalis)*, ***physiological, or functional*** *(e.g., hypotensive drugs and hypertensive drugs)*, ***direct*** *(e.g., adrenomimetics and adrenoblockers)*, ***indirect*** *(e.g., bronchspasm is caused by use of β-adrenoblockers can be obviate by use of cholinoblockers)* and ***competitive*** *(e.g., sulfonamides and para-amino-benzoic acid)*, ***one-sided*** *(e.g., atropine removes the effects of cholinomimetics, but not conversely*) and ***two-sided*** *(e.g., strychnine and chloralhydrate, sulfonamides and oral hypoglycemic drugs of sulfonylurea derivatives – they eliminate effects of some other)*. ***Dispositional antagonism*** is the alteration of the disposition of a substance (its absorption, biotransformation, distribution, or excretion) so that less of the agent reaches the target organ or its persistence in the target organ is reduced. ***Receptor antagonism*** entails the blockage of the effect of a drug with another drug that competes at the receptor site. If in case of combine use of the drugs, one effect of them is increased and other effect of them is decreased, this phenomenon is named ***synergo-antagonism*** *(on the background action of α-adrenoblockers the stimulating effect of epinephrine on the α-adrenergic receptors of the vessels is decreased and the stimulating effect of epinephrine on the β-adrenergic receptors of the vessels becomes more pronounced)*. As a result of concomitant administration of the drugs may be ***distortion of their effects*** *(e.g., introduction of phentolamine leads to distortion of pressor effect of epinephrine)*.

If drugs-antagonists are used for treatment poisonings, they are named ***antidotes***. Antidotal therapy involves antagonism or chemical inactivation of an absorbed poison. The pharmacodinamics of *morphine overdose* may be varied by

competition at a receptor, as in the antagonism provided by *naloxon* therapy; *overdose of propranolol* may be overcomed by physiological antidote *glucagon* with help a different cellular mechanism, as in stimulation an alternative to the blocked β-adrenergic receptors and increase cellular cyclic AMP; *venoms* and *chelating agents* bind and directly inactivate poisons; biotransformation of a drug can also be changed by an antidote: *fomepizole* will inhibit alcohol dehydrogenase and cease the formation of toxic acid metabolites from *ethylene glycol* and *methanol*. There are nonspecific functional antidotes that are used in supportive care of a poisoned patient *(e.g., anticonvulsants, vasoconstricting agents, drugs supporting cardiac function, respiratory center activity, etc.)*. The basis of antipoisoning therapy is a support of airway, breathing, circulation, and vital metabolic processes of the poisoned patient until the poison is eliminated from the body.

Table 2. Some common antidotes and their indications*

Antidote	Poisoning indication(s)
Acetylcysteine	Acetaminophen
Alloximum	Organophosporus and carbamate pesticides
Amyl nitrite	Cyanides (hydrogen cyanide, or prussic acid, or hydrocyanic acid and its salts)
Anticholinesterase drugs (physostigmine salicylate, neostigmine methylsufate)	Anticholinergic syndrome
Atropine sulfate	Organophosporus and carbamate pesticides
Bemegride	Barbiturates, Drug for general anesthesia
Benztropine	Drug-induced dystonia
Bicarbonate sodium (Hydrocarbonate sodium)	Na^{+} channel blocking drugs, Acetylsalicilic acid, acids, ethyl alcohol, tricyclic antidepressants, quinidine, etc.
Bromocriptine	Neuroleptic malignant syndrome
Calcium folinate	Methotrexate
Calcium gluconate or chloride	Ca^{+2} channel blocking drugs, Fluoride
Carbo activatus	Alkaloids, glycosides, salts of heavy metals except cyanides, iron, lithium, alcohols
Carbolongum	Alkaloids, glycosides, salts of heavy metals
Chloride sodium	Silver nitrate
Crotalidae polyvalent immune Fab	North American crotaline snake envenomation
Cytochrom C	Hypnotics, carbon monoxide
Dantrolene	Malignant hyperthermia
Diaethyximum	Organophosporus and carbamate pesticides
Deferoxamine	Iron

Digoxin immunew Fab	Cardiac glycosides
Dimercaprol	Lead, mercury, arsenic, gold in the presence of encephalopathy
Dipyroximum (Trimedoxime bromide)	Organophosporus and carbamate pesticides
Diphenhydramine	Drug-induced dystonia
EDTA, $CaNa_2$ (Sodium calcium edetate)	Lead, mercury, cobalt, nickel, etc., cardiac glycosides
Ethanol	Methanol, ethylene glycol
Ferrocin (Potassium-ferric hexacyanoferrit)	Radioisotopes of cesium and rubidium, the decay products of uranium
Flumazenil	Benzodiazepines
Fomepizole	Methanol, ethylene glycol
Glucagon hydrochloride	B-adrenergic antagonists
Hydroxocobalamin hydrochloride	Cyanide
Insulin (high dose)	Ca^{+2} channel blockers
Leucovorin calcium	Methotrexate
Menadione sodium bisulfite (Vicasol)	Indirect anticoagulants (phenindione, ethyl biscoumacetate, etc.)
Methylene blue	Methemoglobinemia
Naloxone hydrochloride	Opioids
Naltrexone	Opioids
Octreotide acetate	Sulfonylurea-unduced hypoglycemia
Oxygen, hyperbaric	Carbon monoxide, hydrocyanic acid, chrome, phosgene, etc.
Penicillamine	Lead, mercury, copper, arsenic, gold
Pralidoxime chloride	Organophosporus pesticides
Protamine sulfate	Heparin
Pyridoxine hydrochloride	Isoniazid seizures
Succimer (DMSA)	Lead, mercury, arsenic
Thiosulfate sodium	Cyanide, mercury, arsenic, lead, iodine
Trimephacinum	Uranium, beryllium, radionuclides
Unitiolum	Arsenic, mercury, bismuth, and other heavy metals, cardiac glycosides, propranolol, amitriptyline, etc.
Vitamin K_1	Coumarin, indanedione
Vitamin A, C, B group	Vitamin D

* adapted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12 edition. Medical. 2011. – 2084 P.; M.P.Skakun, K.A.Posochova Pharmacology. Ternopil. Ukrmedkniga. 2003. – 740P.

UNIT 2: DRUGS AFFECTING MEDIATORY PROCESSES

Chapter 3. Intermediants: adenosinergic, dopaminergic, serotoninergic, histaminergic, eicosanoids: prostaglandins, leucotriens, thromboxans

Substances that specifically interact with certain systems of neurotransmitters / modulators are called substances of intermediated type.

These are mainly agonists or antagonists of the receptors. The action of others are mediated by endogenous ligands due to altering their metabolism, release, capture and deposit.

Adenosine is a purine nucleoside comprising a molecule of adenine attached to ribofuranose via β-N9-glycosidic bond. Adenosine plays an important role in biochemical processes, such as energy transfer (adenosine triphosphate – ATP and adenosine diphosphate – ADP), signal transduction (cyclic adenosine monophosphate – cAMP). Adenosine is also an inhibitory neurotransmitter, believed to play a role in promoting sleep and suppressing arousal, because its concentration is increased in the body during the sleep.

Metabolism of adenosine: Adenosine used as a second messenger can be the result of *de novo* purine biosynthesis via adenosine monophosphate; though the existence of other pathways is possible.. When adenosine enters the circulation, it is broken down by adenosine deaminase, which is present in red blood cells (erythrocytes) and the vessel wall. So, inhibitors of adenosine deaminase, allow adenosine to accumulate in the blood stream. This causes an increase in coronary vasodilatation. Adenosine deaminase deficiency is a known cause of immunodeficiency.

Adenosine is an endogenous purine nucleoside that modulates many physiological processes. Cellular signaling by adenosine occurs through four known adenosine receptor subtypes (A1, A2A, A2B, and A3). The adenosine **receptors** (or **P receptors**) are a class of purinergic receptors, G-protein-coupled receptors with adenosine as endogenous ligand. In regard to stress or injury, the function of *adenosine* is primarily that of cytoprotection preventing tissue damage during instances of hypoxia, ischemia, and seizure activity. Activation of A2A receptors produces a constellation of responses that in general can be classified as anti-inflammatory. Different adenosine receptor subtypes (A1, A2A, A2B, and A3) are all seven transmembrane spanning G-protein-coupled receptors. These four receptor subtypes are further classified on the basis of their ability to either stimulate or inhibit adenylate cyclase activity. The A2A and A2B receptors mediate the stimulation of adenylate cyclase, while the A1 and A3 adenosine receptors inhibit adenylate cyclase activity. Additionally, A1 receptors have been

reported to mediate adenosine inhibition of Ca^{2+} conductance, whereas A2B and A3 receptors stimulate phospholipase activity. Both A1 receptors and A2A play roles in the heart, regulating myocardial oxygen consumption and coronary blood flow, while the A2A receptor also has broader anti-inflammatory effects throughout the body. These two receptors also have an important role in the brain, regulating the release of other neurotransmitters such as dopamine and glutamine, while the A2B and A3 receptors are located mainly peripherally and are involved in processes such as inflammation and immune responses.

Most *older compounds acting on adenosine receptors* are nonselective, with the endogenous agonist adenosine being used in hospitals as treatment for severe tachycardia, and acting directly to slow the heart through action on all four adenosine receptors in heart tissue, as well as producing a sedative effect through action on A1 and A2A receptors in the brain.

Xantines derivatives such as caffeine and theophylline act as non-selective antagonists at A1 and A2A receptors in both heart and brain and so have the opposite effect to adenosine, producing a stimulant effect and rapid heart rate. These compounds also act as phosphodiesterase inhibitors, which produces additional anti-inflammatory effects, and makes them medically useful for the treatment of conditions such as asthma, but less suitable for use in scientific research.

By nature of caffeine's purine structure it binds to some of the same receptors as adenosine. Caffeine's principal mode of action is as an antagonist of adenosine receptors in the brain.

With the proviso that theophylline and theobromine cross the blood brain barrier very poorly (thus a low *CNS* effects on the heart), the pharmacological effects of *adenosine* may therefore be blunted in individuals who are taking large quantities of methylxanthines (e.g., caffeine, found in coffee, or theophylline in tea, or theobromine, as found in chocolate). Generalized, *adenosine* has an inhibitory effect in the CNS. Caffeine's stimulatory effects, on the other hand, are primarily (although not entirely) credited to its inhibition of adenosine by binding to the same receptors, and therefore effectively blocking adenosine receptors in the CNS. This reduction in adenosine activity leads to increased activity of the neurotransmitters dopamine and glutamate.

Adenosine antagonists are widely used in neonatal medicine, because a reduction in A1 expression appears to prevent hypoxia-induced ventriculomegaly and loss of white matter and therefore raise the possibility that pharmacological blockade of A1 may have clinical utility. Theophylline and caffeine are nonselective adenosine antagonists that are used to stimulate respiration in premature infants.

Newer adenosine receptor agonists and antagonists are much more potent and subtype-selective, and have allowed extensive research into the effects of blocking or stimulating the individual adenosine receptor subtypes, which is now resulting in a new generation of more selective drugs with many potential medical uses. Some of these compounds are still derived from adenosine or from the

xanthine family, but researchers in this area have also discovered many selective adenosine receptor ligands that are entirely structurally distinct, giving a wide range of possible directions for future research.

Adenosine is believed to be an anti-inflamatory agent at the A2A receptor. Topical treatment of adenosine to foot wounds in diabetes mellitus has been shown in lab animals to drastically increase tissue repair and reconstruction. Topical administration of adenosine for use in wound healing deficiencies and diabetes mellitus in humans is currently under clinical investigation. Methotrexate's anti-inflammatory effect may be due to its stimulation of adenosine release.

When administered intravenously, adenosine causes transient heart block in the atrioventricular (AV) node. This is mediated via the A1 receptor, inhibiting adenylyl cyclase, reducing cAMP and so causing cell hyperpolarization by increasing outward K^+ flux. It also causes endothelial dependent relaxation of smooth muscle as it is found inside the artery walls. This causes dilation of the "normal" segments of arteries; i.e. where the endotelium is not separated from the tunica media by atherosclerotic plaque. This feature allows physicians to use adenosine to test for blockages in the coronary arteries, by exaggerating the difference between the normal and abnormal segments. In individuals suspected of suffering from a supraventricular tachycardia, adenosine is used to help identify the rhythm. Certain supraventricular tachycardias (SVTs) can be successfully terminated with adenosine. This includes any re-entrant arrhythmias that require the AV node for the re-entry, e.g., AV re-entrant tachycardia, AV nodal re-entrant tachycardia. In addition, atrial tachycardia can sometimes be terminated with adenosine. Adenosine has an indirect effect on atrial tissue causing a shortening of the refractory period. When administered via a central lumen catheter, adenosine has been shown to initiate atrial fibrillation because of its effect on atrial tissue. In individuals with accessory pathways, the onset of atrial fibrillation can lead to a life-threatening ventricular febrilation. Fast rhythms of the heart that are confined to the atria (e.g., atrial fibrillation, atrial flutter) or ventricles (e.g., monomorphic ventricular tachycardia) and do not involve the AV node as part of the re-entrant circuit is not typically converted by adenosine. However, the ventricular response rate is temporarily slowed with adenosine in such cases. Because of the effects of adenosine on AV node-dependent supraventricular tachycardias, adenosine is considered as a class IV antiarrhythmic agent. When adenosine is used to cardiovert an abnormal rhythm, it is normal for the heart to enter ventricular asystole for a few seconds. This can be disconcerting to a normally conscious patient, and is associated with angina-like sensations in the chest. Thereby, there are:

Parmacologic effects of adenosine are:

antiarrhythmic
vasodilatation
improvement of microcirculation
decreasing of platelet aggregation

improvement of methabolic and reparative processes in eye lens and for deceleration of its degeneration
antiphlogistic
negative inotropic, negative chronotropic, negative dromotropic associated with inhibition of transport of calcium ions into the cell

Indications for adenosine use:

supraventricular tachyarrhythmias
arrhythmia re-entry
Wolff-Parkinson-White (WPW) syndrome (adenosine can be administered only when available equipment for cardioversion)
in ophthalmology - for improvement of methabolic and reparative processes in eye lens and for deceleration of its degeneration
inflammatory eye diseases
cataracta

Side effects of adenosine:

facial flushing
rash on the chest
bradycardia
arterial hypotension
lightheadedness
diaphoresis
nausea after administration of adenosine due to its vasodilatory effects

Contraindications for adenosine use:

sick sinus syndrome (without a pacemaker)
2^{nd} and 3^{rd} degree of heart block (without a pacemaker)
long QT syndrome
severe arterial hypotension
decompensated heart failure
asthma (in nowadays the selective adenosine antagonists are being investigated for the use in the treatment of asthma)
poisoning-induced tachycardia
in WPW syndrome, adenosine may be administered if equipment for cardioversion is immediately available as a backup.

These symptoms are transitory, usually lasting less than one minute. This lasts a few seconds after administration of a bolus dose, during transient asystole induced by intravenous administration. In some cases adenosine can make patients' limbs feel numb for about 2–5 minutes after administration intravenously depending on the dosage (usually above 12 mg).

Caution! The recommended dose may be increased in patients on *theophylline* since *methylxanthines* prevent binding of *adenosine* at receptor sites. The dose is often decreased in patients on *dipyridamole* (Persantine) and *diazepam* (Valium) because *adenosine* potentiates the effects of these drugs. The recommended dose is also reduced by half in patients who are presenting congestive heart failure, myocardial infarction, shock, hypoxia, and/or hepatic or

renal insufficiency, and in elderly patients. *Dopamine* may precipitate toxicity in the patient. *Carbamazepine* may increase heart block. *Theophylline* and *caffeine* (*methylxanthines*) competitively antagonize adenosine's effects; an increased dose of adenosine may be required. *Dipyridamole* potentiates the action of adenosine, requiring the use of lower doses.

The ***adenosine analog***, *NITD008* has been reported to directly inhibit the recombinant an RNA-dependent RNA polymerase of the dengue virus by terminating its RNA chain synthesis. This suppresses peak viremia, rise in cytokines and prevented infected animal from death raising the possibility of a new treatment for this flavivirus. The 7-deaza-adenosine analog has been shown to inhibit the replication of the hepatic C virus. Such adenosine analogs are potentially clinically useful since they can be taken orally.

Table 3. Places of location, mechanism and effects of activation of adenosine receptors in human body

Receptor	Mechanism	Places of location	Effects of activation*
A1	This receptor has an inhibitory function on most of the tissues in which it is expressed. In the brain, it slows metabolic activity by a combination of actions. Presynaptically, it reduces synaptic vesicle release while post synaptically it has been found to stabilize the magnesium on the N-methyl-D-aspartate receptor.	Ubiquitous throughout the entire body: brain > heart, kidney, lung; spermatozoa; adipocytes; brain (cerebral cortex, hippocampus), spinal cord and trigeminal ganglia	negative chronotropic; antinociception; role in spermatozoa capacitation; chemotaxis in immature plasmacytoid dendritic cells
A2A	The activity of A2A adenosine receptor, a G-protein coupled receptor family member, is mediated by G proteins that activate adenylyl cyclase.	It is abundant in basal ganglia, vasculature and platelets and it is a major target of caffeine. Jejunum, ileum, colon; Heart, lung > kidney, brain; Thymus gland > heart, lung > spleen, leukocytes	coronary artery vasodilatation; increases blood flow to the myocardium; causes arterial hypotension; decreases in neurotransmission activity such as norepinephrine, dopamine and acetylcholine; inhibition of platelet aggregation;

			down-regulation of chemokine receptor function, that is very important in case of infectious diseases and inflammatory processes; regulation of cytokine production
A2B	This integral membrane protein stimulates adenylate cyclase activity in the presence of adenosine. It stimulate release calcium → activate calmodulin → activate myosin light chain kinase → phosphrylate myosin light chain → myosin light chain plus actin → bronchoconstriction. This protein also interacts with netrin-1, which is involved in axon elongation. Stimulation of Phospholipase C activity.	Jejunum, ileum, colon; Brain, heart, kidney and lung; Bronchial smooth muscle cells; Large intestine, cecum, urinary bladder	bronchospasm; inhibition of cell proliferation; vasodilation of small coronary arteries; vasoconstriction of chorionic vessels
A3	It has been shown in studies to inhibit some specific signal pathways of adenosine. It allows for the inhibition of growth in human melanoma cells.	Liver, lung > brain, aorta; CNS: corpus callosum, substantia nigra, thalamus, subthalamic nucleus, spinal cord; hippocampus; adrenal cortex, adrenal medulla > spleen, small intestine; jejunum, ileum, colon; kidney, heart; placenta	cardioprotective in cardiac ischemia; inhibition of neutrophil degranulation

* - there are pharmacologic effects of adenosine agonists.

Table 4*. Agonists and antagonists of adenosine receptors

Receptor	Agonists	Antagonists
A1	adenosine; cyclopentyladenosine; 2-chloroadenosine	theophylline; caffeine; flavanone; galangin; sakuranetin; morin
A2A	adenosine; cyclopentyladenosine; 2-chloroadenosine; N(6)-cyclohexyladenosine; metrifudil	theophylline; caffeine; flavone; galangin; sakuranetin; morin; visnagin
A2B	adenosine; cyclopentyladenosine; 2-chloroadenosine	alloxazine; theophylline
A3	adenosine; cyclopentyladenosine	(R)-niguldipine; galangin; nicardipine; sakuranetin; flavanone; flavone; visnagin; theophylline

* - adopted from IUPHR Database. International Union of Pharmacology. 2012. http://www.iuphar-db.org/DATABASE

An adenosine reuptake inhibitor is a type of drug which acts as a reuptake inhibitor for the purine nucleoside and neurotransmitter adenosine by blocking the action of one or more of the equilibrative nucleoside transporters. This in turn leads to increased extracellular concentrations of adenosine and therefore an increase in adenosinergic neurotransmission.

List of the adenosine reuptake inhibitors:
Acadesine, Acetate, Barbiturates, Benzodiazepines, Calcium Channel Blockers, Carbamazepine, Carisoprodol, Cilostazol, Cyclobenzaprine, Dilazep, Dipyridamole, Estradiol, Ethanol (Alcohol), Flumazenil, Hexobendine, Hydroxyzine, Indomethacin, Inosine, Meprobamate, Nitrobenzylthioguanosine, Nitrobenzylthioinosine, Papaverine, Pentoxifylline, Phenothiazines, Phenytoin, Progesterone, Propentofylline, Propofol, Puromycin, Soluflazine, Toyocamycin, Tracazolate, Tricyclic antidepressants.

Dopamine a simple organic chemical in the catecholamine family is a monoamine neurotransmitter which plays a number of important physiological roles in the bodies of animals. In addition to being a catecholamine and a monoamine, dopamine may be classified as a substituted phenethylamine. Its name derives from its chemical structure, which consists of an amine group (NH_2) linked to a catechol structure called dihydroxyphenethylamine, the decarboxylated form of dihydroxyphenylalanine (acronym DOPA). In the brain, dopamine functions as a neurotransmitter – a chemical agent released by nerve cells to send signals to other nerve cells. The human brain uses five known types of dopamine receptors, labeled D1, D2, D3, D4, and D5. Dopamine is produced in several areas of the brain, including the substancia nigra and the ventral tegmental area.

Dopamine is a neurotransmitter produced in the brains of humans and animals. Also, it is a hormone produced by the adrenal medulla and other tissues (eg kidneys). *Dopamine* is a biochemical precursor of norepinephrine (and epinephrine). *Dopamine* has synthetic analogs and stimulatirs of its release in the brain. In particular, *amphetamine* stimulates dopamine release directly by influence of its transport, *cocaine* and *psychostimulators* block the dopamine reuptake and increase of its

concentration in synaptic and that allows people who use them, get a sense of fun artificially. *Morphine* and *nicotine* mimic the action of natural neuromediators, but alcohol blocks action of dopamine antagonists. A long-term drug stimulation of dopamine release lead to decline of natural dopamine production and reduction of quantity of dopamine receptors in the brain that encourages addicts to increase the dose to get the same effect.

Currently some *dopamine agonists* are used for treatment of Parkinson's disease, and some *antidepressants* have dopaminergic activity. Simultaneously, *reserpine* blocks the presynaptic dopamine pumping into vesicles. Drugs that reduce dopamine level cause inability to experience pleasure.

Biosynthesis (scheme 1). *Dopamine* is synthesized in the body from within cells (mainly by neurons and cells in the medulla of the adrenal glands) and can be created from any one of the following three amino acids:

L-Phenylalanine (PHE)
L-Tyrosine (L-4-hydroxyphenylalanine; TYR)
L-DOPA (L-3,4-dihydroxyphenylalanine; DOPA)

These amino acids are provided from natural sources such as the ingestion of various kinds of food, with L-tyrosine being the most common of the three. Although dopamine itself is also commonly found in many types of food, unlike the amino acids that form it, it is incapable of crossing the protective blood-brain-barrier (BBB), which severely restricts its functionality upon consumption. It must be formed from within the walls of the BBB to properly perform its cognitive duties, though not its peripheral actions. Dopamine itself is also used in the synthesis of the following related catecholamine neurotransmitters:

Norepinephrine (β,3,4-trihydroxyphenethylamine; Noradrenaline; NE, NA)
Epinephrine (β,3-dihydroxy-*N*-methylphenethylamine; Adrenaline; EPI, ADR)

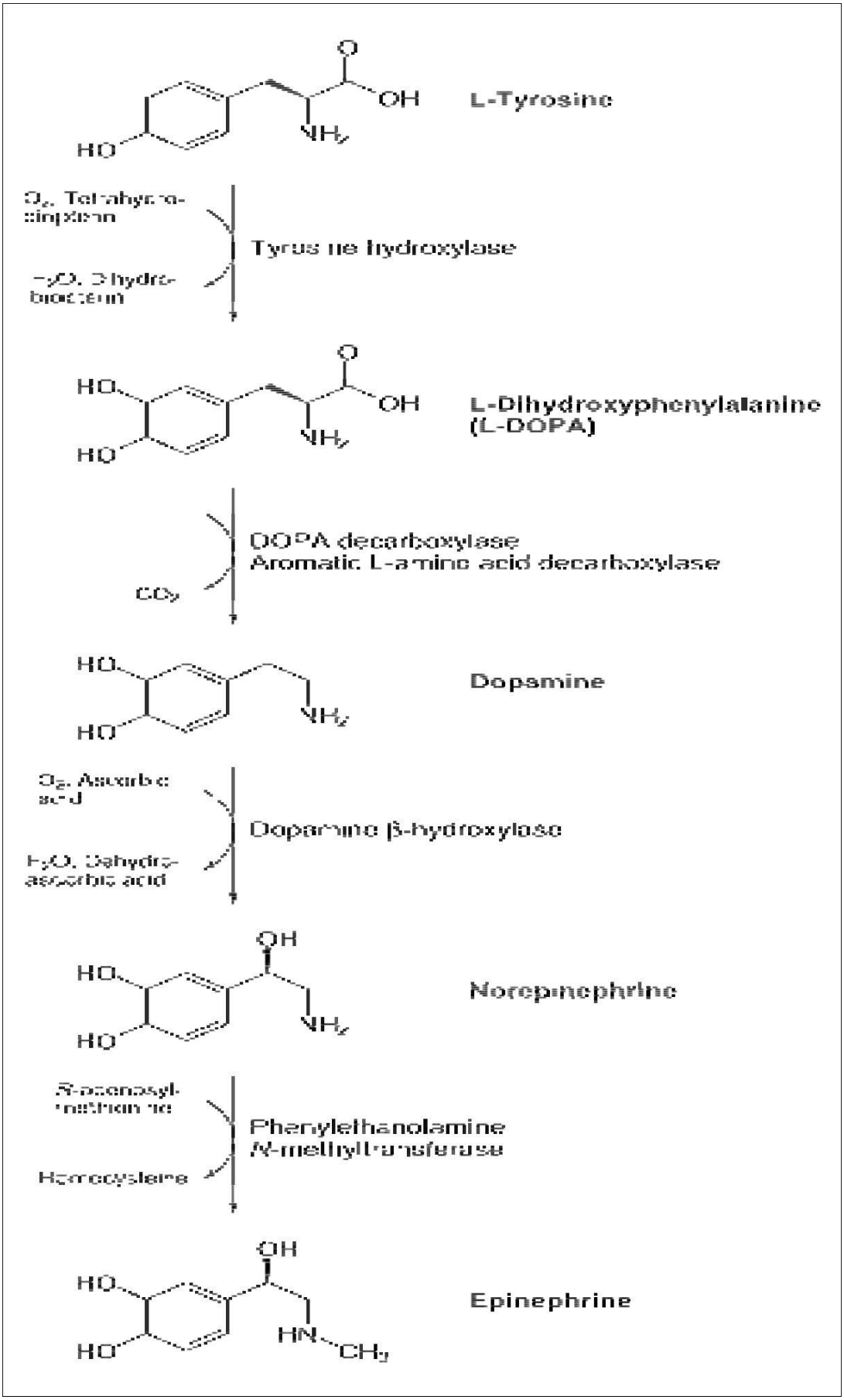
This is the complete metabolic pathway:

- L-Phenylalanine → L-Tyrosine → L-DOPA → Dopamine → Norepinephrine → Epinephrine

L-Phenylalanine is converted into L-tyrosine by the enzyme phenylalanine hydroxylase (PAH) with molecular oxygen (O_2) and tetrahydrobiopterin (THB) as cofactors. L-Tyrosine is converted into L-DOPA by the enzyme tyrosine hydroxylase (TH) with tetrahydrofolic acid (THFA), O_2, and ferrous iron (Fe^{2+}) as cofactors. L-DOPA is converted into dopamine by the enzyme aromatic L-amino acid decarboxylase (AAAD; also known as DOPA decarboxylase – DDC) with pyridoxal phosphate (PLP) as the cofactor. The reactions are illustrated as follows:

PAH: L-Phenylalanine + THB + O_2 → L-Tyrosine + DHB + H_2O
TH: L-Tyrosine + THFA + O_2 + Fe^{2+} → L-DOPA + DHFA + H_2O + Fe^{2+}
AAAD: L-DOPA + PLP → Dopamine + PLP + CO_2

Dopamine is converted into norepinephrine by the enzyme dopamine β-hydroxylase (DBH) with O_2 and L-ascorbic acid as cofactors. Finally, norepinephrine is converted into epinephrine by the enzyme phenylethanolamine



Scheme 1. Catecholamine biosynthesis (adopted from http://en.wikipedia.org).

N-methyltransferase (PNMT) with S-adenosyl-L-methionine (SAMe) as the cofactor. The reactions are illustrated as follows:

DBH: Dopamine + Ascorbic Acid + O_2 → Norepinephrine + DHA + H2O

PNMT: Norepinephrine + SAMe → Epinephrine + Homocysteine

It should be noted that some of the cofactors also require their own synthesis.

Guanine → Guanosine → Guanosine Monophosphate (GMP) → Guanosine Diphosphate (GDP) → Guanosine Triphosphate (GTP)

GTP Cyclohydrolase I (GTPCH, GCH): GTP → 7,8-Dihydroneopterin Triphosphate (DHNTP)

6-Pyruvoyltetrahydropterin Synthase (PTS, PTPS): DHNTP → 6-Pyruvoyltetrahydropterin (Dyspropterin)

Sepiapterin Reductase (SPR): Dyspropterin → Tetrahydrobiopterin (THB)

Folic Acid → DHFA → THFA

Pyridoxine → Pyridoxamine → Pyridoxal → PLP (requires Zn^{2+} as a cofactor)

Niacin → Nicotinamide → NMN → NAD+ → NADH / NADP+ → NADPH

Deficiency in any required amino acid or cofactor will result in subsequent dopamine, norepinephrine, and epinephrine biosynthesis impairment and deficiency as well. Conversely, supplementation with L-phenylalanine, L-tyrosine, L-DOPA, or any of the cofactors will increase their respective concentrations.

Storage, release, and reuptake. Upon synthesis, dopamine is transported from the cell cytosol into synaptic vesicles by the vesicular monoamine transporter 2 (VMAT2). Dopamine is stored in and remains in these vesicles until an action potential occurs and forces them to merge with the cell membrane via a process known as exocytosis, thereby dumping dopamine into synapses.

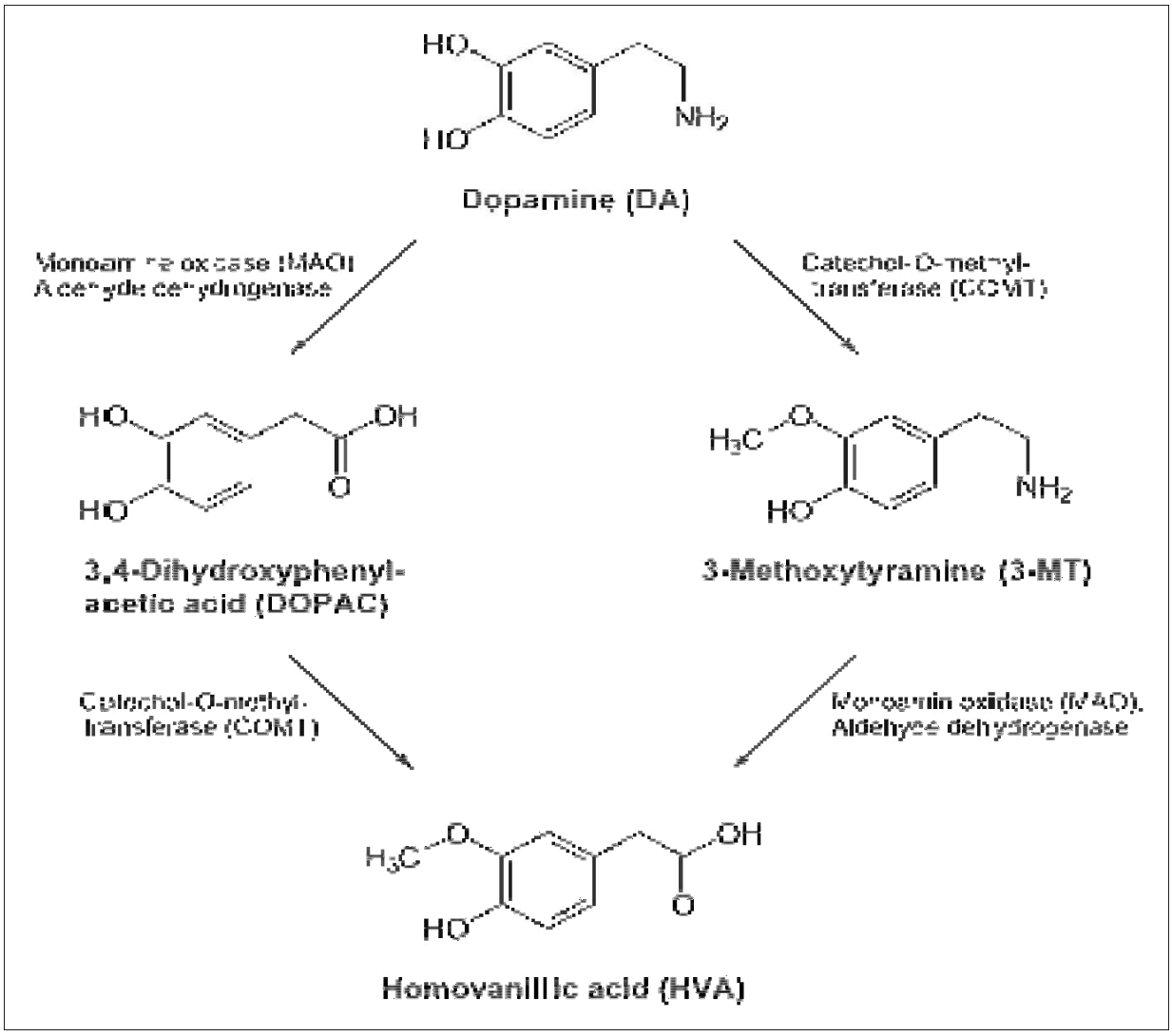
Once in the synapse, dopamine binds to and activates postsynaptic dopamine receptors, resulting in the signal of the presynaptic cell being propagated to the postsynaptic neuron. Dopamine also binds to presynaptic dopamine receptors, which can either excite the presynaptic cell or inhibit it depending on their electrical potential. Presynaptic receptors with an inhibitory potential are called autoreceptors and inhibit neurotransmitter synthesis and release. They serve to keep dopamine levels normalized in certain pathways when release is acutely disrupted and becomes too high or too low.

After dopamine has performed its synaptic duties, it is taken up via reuptake back into the presynaptic cell by either the high-affinity dopamine transporter (DAT) or the low-affinity plasma membrane monoamine transporter (PMAT). Once back in the cytosol, it is subsequently repackaged into vesicles by VMAT2.

Degradation (scheme 2). *Dopamine* is directly broken down into inactive metabolites by two enzymes, monoamine oxidase (MAO), and catechol-O-methyl transferase (COMT). It is equally metabolized by the two respective isoforms of MAO, MAO-A and MAO-B. *Dopamine* is metabolized by MAO into 3,4-dihydroxyphenylacetaldehyde (DOPAL). DOPAL is further metabolized into 3,4-dihydroxyphenylacetic acid (DOPAC) by the enzyme aldehyde dehydrogenase

(ALDH). DOPAL can also be reduced to 3,4-dihydroxyphenylethanol (DOPET; also known as hydroxytyrosol) by aldose reductase (AR) to a lesser extent. Finally, COMT reduces DOPAC and DOPET to homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylethanol (MOPET), respectively, which are then excreted in the urine. COMT can also directly metabolize dopamine into 3-methoxytyramine (3-MT), which is then subsequently metabolized to HVA by MAO and is excreted in the urine as well. The reactions are illustrated and summarized here:

Dopamine → DOPAL → DOPAC → HVA
Dopamine → DOPAL → DOPET → MOPET
Dopamine → 3-MT → HVA



Scheme 2. Dopamine degradation (adopted from http://en.wikipedia.org/).

In most areas of the brain, including the striatum and basal ganglia, *dopamine* is inactivated by reuptake via the DAT, then enzymatic breakdown by MAO into DOPAC. In the prefrontal cortex, however, there are very few DAT proteins, and dopamine is inactivated instead by reuptake via the norepinephrine transporter (NET), presumably on neighboring norepinephrine neurons, then

enzymatic breakdown by COMT into 3-MT. The DAT pathway is roughly an order of agnitude faster than the NET pathway. *Dopamine* that is not broken down by enzymes is repackaged into vesicles for reuse by VMAT2.

Dopamine receptors. *Dopamine* binds and activates a group of called the dopamine receptors to cause its physiological effects in the body. The dopamine receptors are a series of five G protein-coupled receptors (GPCRs), which consist of the D1, D2, D3, D4, and D5 receptors. As GPCRs, they work by modulating the cyclic adenosine monophosphate (cAMP) second messenger system to produce a cellular response. The five receptors are individually categorized into two distinctive groups based on their varying properties and effects, the D1-like and D2-like subfamilies. The D1 and D5 receptors belong to the D1-like subfamily. They are coupled to Gs and increase the cellular concentrations of cAMP by the activation of the enzyme adenylate cyclase. The D2, D3, and D4 receptors belong to the D2-like subfamily. They are coupled to Gi/Go and decrease the cellular concentrations of cAMP by inhibition of adenylate cyclase. Ultimately, the cAMP second messenger system, through several downstream mechanisms, works by facilitating the opening of plasmalemmal ion channels which allow extracellular positively charged ions such as Na+ and K+ to enter the cytoplasm of the cell in excess quantities, thereby generating an action potential. The D1-like receptors enhance the activity of the system and are therefore excitatory, while the D2-like receptors in contrast do the opposite and are therefore inhibitory. The D1 receptor is the most widespread dopamine receptor in the central nervous system. The D3, D4, and D5 receptors are present in significantly lower levels than are the D1 and D2 receptors. In fact, the D1 receptors are approximately 100x more common than the D5 receptors. However, dopamine binds to the D3, D4, and D5 receptors with nanomolar or submicromolar affinity constants, while its corresponding constants for D1 and D2 receptors are in the micromolar ranges. As an example, dopamine has 20-fold higher binding affinity for the D3 receptor in comparison to the D2 receptor, and 10-fold higher binding affinity for the D5 receptor over the D1 receptor. Hence, overall activation of the system seems to be more or less well-balanced.

Table 5*. Dopamine receptors: family, gene, type, mechanism and potential in human body

Family	Receptor	Gene	Type	Mechanism	Potential
D1-like	D1	DRD1	Gs-coupled.	Increasing intracellular levels of cAMP by activating adenylate cyclase.	Excitatory
	D5	DRD5			
D2-like	D2	DRD2	Gi/Go-coupled.	Decreasing intracellular levels of cAMP by inhibiting adenylate cyclase.	Inhibitory
	D3	DRD3			
	D4	DRD4			

* - adopted from IUPHR Database. International Union of Pharmacology. 2012. http://www.iuphar-db.org/DATABASE

Table 6. Places of location, mechanism and effects of activation of dopamine receptors in human body

Receptor	Mechanism	Places of location	Effects of activation**
D1	Adenylate cyclase stimulation; Calcium channel	Adrenal cortex, heart, kidney; Leukocytes*; Immune cells in the spleen, bone marrow, and blood circulation	Contribution to pathophysiology and/or maintenance of increased blood pressure in essential hypertension; D1 receptors are responsible for the cognitive-enhancing effects of dopamine; Analgesic
D2	Adenylate cyclase inhibition; Potassium channel	Adrenal cortex; Leukocytes*; Immune cells in the spleen, bone marrow, and blood circulation	Stimulation of accumulation of cAMP in membrane particles of the kidney medulla; Control of renal blood flow; D2 receptors are more specific for motor actions; Low D2 receptor-binding is found in people with social anxiety; Analgesic
D3	Adenylate cyclase inhibition; Potassium channel	Ventral striatum/nucleus accumbens > neostriatum, cerebral cortex, cerebellar cortex; Brain: nucleus accumbens and islands of Calleja; Leukocytes*; Immune cells in the spleen, bone marrow, and blood circulation	
D4	Adenylate cyclase inhibition	Brain: Pre-frontal cortex, temporal neocortex > occipital cortex; Pulmonary artery; Aortic endothelium, umbilical vein endothelium;	Modulation of von Willebrand factor secretion in endothelial cells; D4 receptors are responsible for the cognitive-enhancing

		Brain: Occipital lobe, cerebellum, hippocampus, middle frontal gyrus of temporal lobe, cingulate gyrus of frontal lobe, amygdala > superior temporal gyrus of temporal lobe, superior frontal gyrus of frontal lobe, thalamus, septal nuclei, hypothalamus > substantia nigra, caudate nucleus, globus pallidus, superior parietal lobe; Leukocytes*; Immune cells in the spleen, bone marrow, and blood circulation	effects of dopamine
D5	Adenylate cyclase stimulation	Pulmonary artery; Brain: striatum, hippocampus, dentate gyrus, subiculum, frontal cortex, limbic cortex, occipital cortex, cerebellum; Leukocytes*; Immune cells in the spleen, bone marrow, and blood circulation	

* - there is low expression of receptors on T lymphocytes and monocytes, moderate expression on neutrophils and eosinophils, and high expression on B cells and natural killer cells.
** - there are pharmacologic effects of dopamine agonists.

Biological role. *Dopamine* has many functions in the *brain*, including important roles in behavior (inhibits the tendency to make unwanted actions) and cognition, voluntary movement, motivation, punishment and reward, inhibition of prolactin production (involved in lactation and sexual gratification), sleep, mood, attention, working memory, and learning. Sociability is also closely tied to *dopamine* neurotransmission. Dopaminergic neurons (i.e., neurons whose primary neurotransmitter is dopamine) are present chiefly in the ventral tegmental area (VTA) of the midbrain, the substantia nigra pars compacta, and the arcuate nucleus of the hypothalamus. Dopaminergic neurons of the midbrain are the main source of dopamine in the brain.

Dopamine is commonly associated with the reward system of the brain, providing feelings of enjoyment and reinforcement to motivate a person to perform certain activities. *Dopamine* is released (particularly in areas such as the nucleus accumbens and prefrontal cortex) by rewarding experiences such as food, sex,

drugs, and neutral stimuli that become associated with them. Recent studies indicate that aggression may also stimulate the release of dopamine in this way. *Dopamine* may also have a role in the salience of potentially important stimuli, such as sources of reward or of danger, and *dopamine* assists decision-making, increases the creative drive of idea generation.

Other pathological states have also been associated with *dopamine* dysfunction, such as schizophrenia, psychosis, autism, and attention deficit, hyperactivity disorder, as well as drug abuse, whereas hyperdopaminergic state is related with hypersociality, hypersexuality. Libido can be increased by drugs that affect dopamine, but not by drugs that affect opioid peptides or other neurotransmitters. Insufficient dopamine biosynthesis in the dopaminergic neurons can cause Parkinson's disease, a condition in which one loses the ability to execute smooth, controlled *movements*. Decreased levels of *dopamine* have been associated with painful symptoms that frequently occur in Parkinson's disease: painful clinical conditions, including burning mouth syndrome, fibromyalgia, and restless legs syndrome.

Dopamine is the primary neuroendocrine inhibitor of the secretion of prolactin from the anterior pituitary gland. Thus, in the context of regulating prolactin secretion, dopamine is occasionally called *prolactin-inhibiting factor (PIF), prolactin-inhibiting hormone (PIH), or prolactostatin*.

In the frontal lobes, *dopamine* controls the *flow of information* from other areas of the brain.

The analgesic capacity of *dopamine* occurs as a result of dopamine D2 and D3 receptor activation.

Dopamine is one of the neurotransmitters implicated in the control of nausea and vomiting via interactions in the chemoreceptor trigger zone.

Dopamine acts upon receptors present on immune cells, with all subtypes of dopamine receptors found on leukocytes: T lymphocytes, monocytes, neutrophils, eosinophils, B cells and natural killer cells.The sympathetic innervation of lymphoid tissues is dopaminergic, and increases during stress. Dopamine can also affect immune cells in the spleen, bone marrow, and blood circulation. In addition, dopamine can be synthesized and released by the immune cells themselves. The effects of dopamine on immune cells depend upon their physiological state. While dopamine activates resting T cells, it inhibits them when they are activated. Disorders such as schizophrenia and Parkinson's disease, in which there are changes in brain dopamine receptors and dopamine signaling pathways, are also associated with altered immune functioning.

Dopamine as a hormone has some physiological properties: increases the peripheral vascular resistance, systolic blood pressure, increases the force of heart contractions, cardiac output, heart rate, increases myocardial oxygen demand and myocardial oxygen delivery by increased coronary blood flow, reduces renal vascular resistance, increases blood flow in them, and kidney filtration, increases natriuresis, extends the mesenteric vessels, in contrast to other catecholamines, inhibits the synthesis of aldosterone in the adrenal cortex, decreases the secretion

of renin by the kidneys, increases the secretion of prostaglandins by kidney tissue, inhibits the motility of the stomach and intestines, causes relaxation of the lower esophageal sphincter and strengthens gastro-esophageal and duodeno-gastric reflux, in the CNS dopamine stimulates chemoreceptors trigger zone and vomiting center and thus participates in the act of vomiting.

Should be noted that increased levels of *dopamine* in the blood plasma has little effect on the central nervous system functions because it was a bad passes through the blood-brain barrier, except on the outside of the blood-brain barrier sites, such as the trigger zone.

Increased levels of *dopamine* in the blood plasma is in shock, trauma, burns, blood loss, stress states, with different pain syndromes, anxiety, fear. Thereby, dopamine plays a role in adaptation of the organism to stressful situations, trauma, blood loss, etc.

Also, *dopamine* levels in the blood are increased with deterioration of renal blood flow or increased content of sodium ions, as well as angiotensin or aldosterone in plasma. Apparently, this is due to increased synthesis of dopamine from DOPA in kidney tissue in case of renal ischemia, or when they are under the influence of angiotensin and aldosterone. Perhaps this is a physiological mechanism for the correction of renal ischemia, and to counteract hyperaldosteronemia and hypernatremia. According to researches, aging process manifests a decrease in the number and density of dopamine D2-receptor striatum, reduced concentration of dopamine in the subcortical brain.

Clinical symptoms of these changes are impoverishment facial expressions, some general slowness, stooped, old man's posture, a shortening of stride length, changes are also noted in the cognitive sphere: decreased with age, speed of reaction, it becomes harder to acquire and implement a new program of action, reduced the level of attention and the volume of memory.

As a drug *dopamine* cannot cross the BBB and it does not directly affect CNS, but its precursors cross the BBB relatively easily. Pharmacologic effects of *dopamine* are dependent from dose (Chapter 6., p. 121).

Table 7**. Agonists and antagonists of dopamine receptors

Receptor	Agonists	Antagonists
D1	dopamine, norepinephrine, lisuride, cabergoline, bromocriptine, pergolide, quinogolide, apomorphine, rotigotine	flupentixol, fluphenazine, haloperidol, butaclamol, flupentixol, chlorpromazine, thioridazine, clozapine, ketanserin, spiperone
D2*	dopamine, aripiprazole, lisuride, cabergoline, terguride, roxindole, N-porphynorapomorphine, bromocriptine, apomorphine, pergolide, bromocriptine, piribedil, apomorphine, quinpirole, pramipexole, quinelorane, quinpirole	domperidone, nemonapride, *N*-methylspiperone, raclopride, eticlopride, spiperone, terguride, nafadotride, roxindole, nafadotride, haloperidol, raclopride, amisulpiride, flupentixol, pimozide, amisulpiride, raclopride, chlorpromazine, sulpiride, clozapine, flupenthixol

D3	dopamine, lisuride, cabergoline, terguride, roxindole, N-porphynorapomorphine, pramipexole, pergolide, apomorphine, bromocriptine, quinpirole, quinelorane, quinpirole, apomorphine, piribedil	nemonapride, spiperone, eticlopride, nafadotride, flupentixol, raclopride, pimozide, haloperidol, raclopride, amisulpiride, butaclamol, chlorpromazine, domperidone, haloperidol, risperidone, sulpiride, clozapine
D4	dopamine, apomorphine, lisuride, roxindole, quinpirole, cabergoline, pergolide	nemonapride, *N*-methylspiperone, spiperone, haloperidol, terguride, chlorpromazine, clozapine, aripiprazole, eticlopride, piribedil, bromocriptine, nafadotride, butaclamol, raclopride, sulpiride
D5	dopamine, lisuride, cabergoline, apomorphine, beta-ergocriptine, norepinephrine, pergolide, bromocriptine, rotigotine	flupentixol, fluphenazine, butaclamol, chlorpromazine, clozapine, haloperidol, ketanserin, thioridazine, spiperone

* - *terguride* is a partial agonist at the D2S receptor and an antagonist at the D2L receptor; *roxindole* is a partial agonist at the D2S receptor and an antagonist at the D2L receptor.
** - adopted from IUPHR Database. International Union of Pharmacology. 2012. http://www.iuphar-db.org/DATABASE

Serotonin or **5-hydroxytryptamine (5-HT)** is a monoamine neurotransmitter, derived from tryptophan. Approximately 90% of human's serotonin is located in the enterochromaffin cells in the GIT. The remainder is synthesized in serotonergic neurons of the CNS and regulates mood, appetite, sleep, cognitive functions, including memory and learning.

Biosynthesis (scheme 3). Serotonin is synthesized from the amino acid L-tryptophan by a short metabolic pathway consisting of two enzymes: tryptophan hydroxylase (TPH) and amino acid decarboxylase (DDC). The TPH-mediated reaction is the rate-limiting step in the pathway. TPH has been shown to exist in two forms: TPH1, found in several tissues, and TPH2, which is a brain-specific isoform. Tryptophan hydroxylase is synthesized only in the soma of serotonergic neurons, hydroxylation occurs in the presence of iron ions and the cofactor of pteridine.

A prerequisite for the synthesis of serotonin is the presence of sunlight. In the dark hormone melatonin is synthesized from serotonin in the pineal gland.

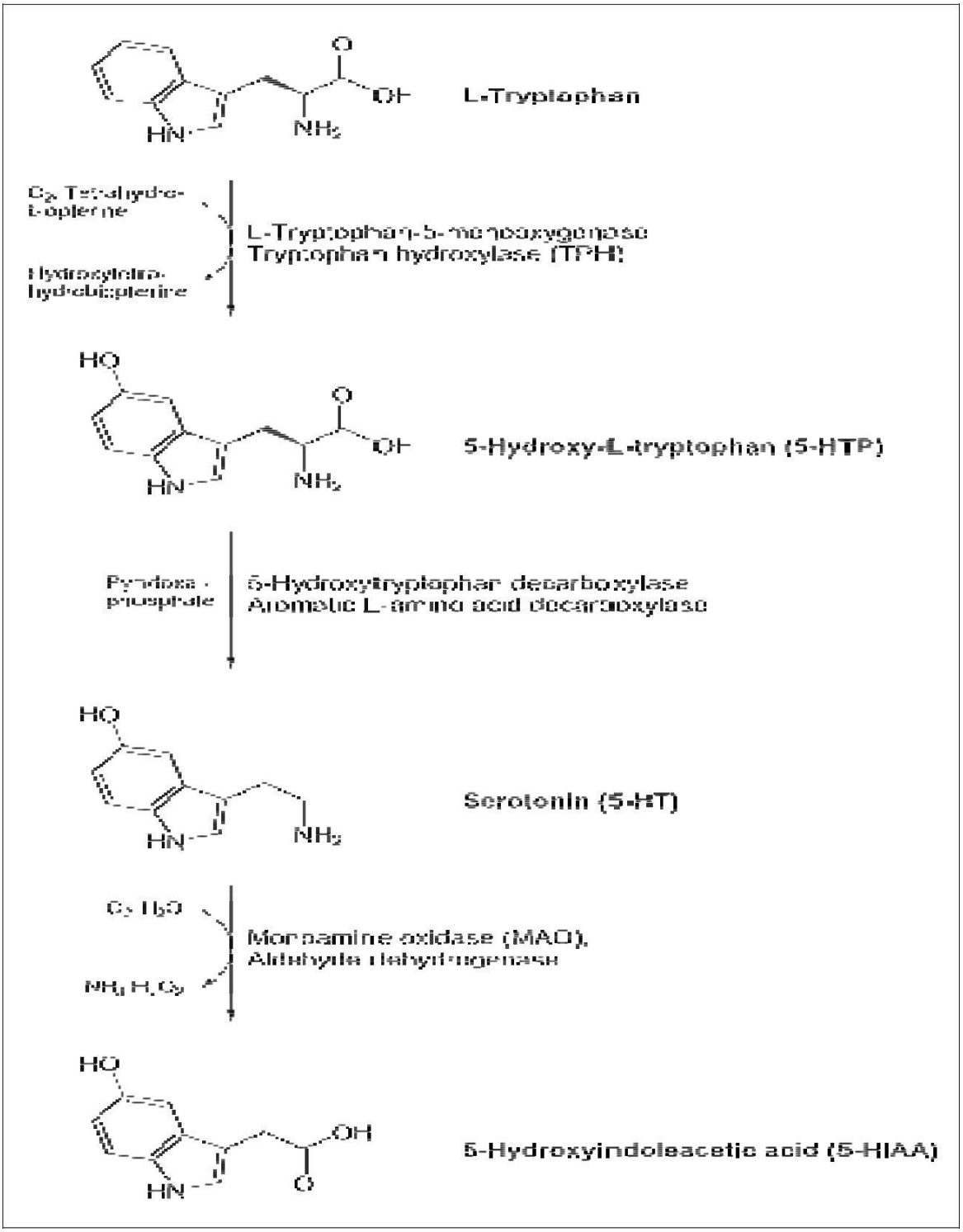
Methabolism of Serotonin. Under the action of the enzyme monoamine oxidase (MAO), serotonin is converted to 5-hydroxyindolaldehyd which, in turn, can be reversibly transformed into a 5-hydroxytriptophol under the influence of alcohol dehydrogenase. 5 hydroxyindolaldehyd irreversibly under the influence of acetat dehydrogenase converted into 5-hydroxyindoleacetic acid, which is then excreted in the urine and feces.

Serotonin is a precursor of melatonin, which is formed by the pineal gland's enzyme arylalkylamine N-acetyltransferase (AANAT) in the pineal gland.

Also, turning with a MAO into 5-hydroxyindol-3-acetaldehyde, *serotonin* can be under the influence of aldehydreductase become tryptophol, and under the

influence of acetaldehydrogenase-2 – into 5-hydroxyindoleacetic acid (5-HIAA) chiefly by the liver.

Serotonin may be involved in the formation of endogenous opiates, reacts with acetaldehyde to form a harmalol. *Norepinephrine* inhibits *serotonin* release.



Scheme 3. The pathway for the synthesis of serotonin from tryptophan (adopted from http://en.wikipedia.org/).

Circulation of serotonin. *Serotonin* which was synthesized by neuron is pumped into vesicles. This process is a proton-conjugate transport. In the vesicle

ions H^+ are pumped with the proton-dependent ATPase. On leaving the protons the molecules of serotonin enter the vesicle on a gradient. Further, in response to depolarization of terminals, serotonin output in the synaptic cleft.

Part of it is involved in the transmission of nerve impulses, acting on the postsynaptic membrane of cell receptors, and the other part returns to the presynaptic neuron with reuptake. Autoregulation of serotonin release is achieved by activation of presynaptic 5-HT receptors, triggering a cascade of reactions that regulate the entry of calcium ions into presynaptic terminals. Calcium ions, in turn, activate the phosphorylation of the enzyme 5-tryptophan hydroxylase, which provides the conversion of tryptophan into serotonin, which leads to increased synthesis of serotonin.

Reuptake of serotonin is produced by the transporter which is the specific protein, which produces sodium-potassium-coupled transport. Returning in the cell mediator splits with MAO to 5-HIAA.

The chemistry of *serotonin* transport systems is also similar to those of *norepinephrine*.

Biological role. The physiological functions of *serotonin* are extremely diverse. Reduction of the *serotonin* level leads to increase of sensitivity of pain in the human organism.

Serotonin secreted from the enterochromaffin cells and releases eventually into the blood. There, it is actively taken up by blood platelets, which store it. When the platelets bind to a clot, they disgorge serotonin, where it serves as a vasoconstrictor and helps to regulate hemostasis and blood clotting. Serotonin also is a growth factor for some types of cells, which may give it a role in wound healing.

One type of tumor, called carcinoid, sometimes secretes large amounts of *serotonin* into the blood, which causes various forms of the carcinoid syndrome of flushing, diarrhea, and heart problems. Because of serotonin's growth-promoting effect on cardiac myocytes, persons with serotonin-secreting carcinoid may suffer a right heart (tricuspid) valve disease syndrome, caused by proliferation of myocytes onto the valve.

Serotonin is also found in fungi and plants. Serotonin's presence in insect venoms and plant spines serves to cause pain, which is a side effect of serotonin injection. Serotonin is produced by pathogenic amoebas, and its effect on the gut causes diarrhea. Its widespread presence in many seeds and fruits may serve to stimulate the digestive tract into expelling the seeds.

Serotonin functions as a neurotransmitter in the nervous systems of human organism. Serotonergic neurons are grouped in the brain stem (truncus encephali) where are descending projections in spinal marrow and ascending projections in cerebellum, limbic system, basal ganglia and cortex. At the same time neurons are distinguished morphologically, electrophysiologically, target innervation and sensitivity to certain neurotoxic agents.

Ultimately, the *functions of serotonin* are: to facilitate motor activity; to play an important role in the mechanisms of hypothalamic regulation of hormonal

pituitary function; to cause an increase in the secretion of prolactin and other hormones of the anterior pituitary. These effects are opposite to the effects of stimulation of dopaminergic pathways.

Serotonin as a hormone. *Serotonin* plays an important role in *blood clotting*. Blood platelets contain significant amounts of serotonin and have the ability to capture and accumulate serotonin from blood plasma. Serotonin increases the functional activity of platelets and their tendency to aggregation and thrombus formation. Besides, serotonin causes an increase of synthesis of clotting factors by the liver. Serotonin excretion from damaged tissue is one of the mechanisms of blood clotting at the place of injury, the more so that serotonin causes *vasoconstriction*.

Serotonin is involved in the processes of *allergy* and *inflammation*. It increases vascular permeability, enhances chemotaxis and migration of leukocytes to inflammatory, increases levels of eosinophils in the blood, enhances mast cell degranulation and release of other mediators of allergy and inflammation.

Local (eg, intramuscular) administration of exogenous *serotonin* causes intense pain at the injection site. Presumably serotonin along with histamine and prostaglandins, stimulating receptors in the tissues, plays a role in the occurrence of pain impulses from the site of injury or inflammation.

Large amount of serotonin is produced in the intestine. *Serotonin* enhances motility and secretory activity of GIT, more over, it increases bacterial metabolism in the colon. Colon bacteria themselves have the ability to decarboxylate tryptophan and thereby increase the secretion of serotonin by intestine. In dysbiosis and several other diseases of the colon intestinal serotonin production is greatly reduced.

The massive release of serotonin from the dying cells of the stomach and intestine mucous when exposed to cytotoxic chemotherapy is one of the causes of ausea and vomiting, diarrhea during chemotherapy of malignant tumors. A similar condition is in some malignant tumors, ectopically producing serotonin.

A high quantity of *serotonin* is also observed in the uterus. Serotonin plays a role in paracrine regulation of contractility of the uterus and fallopian tubes, and to coordinate delivery. Production of serotonin in the myometrium increases in a few hours or days before birth and increases even more directly in the process of childbirth.

Also, *serotonin* is involved in the process of ovulation - the serotonin concentration (and other biologically active substances) in the follicular fluid is increased just before the rupture of the follicle, which apparently leads to an increase pressure within the follicle. Serotonin has a significant influence on the processes of excitation and inhibition in the sexual organs. Thus, the increase in the concentration of serotonin in males delays the onset of ejaculation.

In humans, though insulin regulates blood sugar and insulin-like growth factors (IGF) regulates growth, *serotonin* controls the release of both hormones, so *serotonin* suppresses insulin release from the beta cells in the pancreas, and

exposure to selective serotonin re-uptake inhibitors reduces fetal growth. Human *serotonin* can also act as a growth factor directly. Liver damage increases cellular expression of 5-HT2A and 5-HT2B receptors. Serotonin present in the blood then stimulates cellular growth to repair liver damage. 5HT2B receptors also activate osteocytes, which build up bone. However, serotonin also inhibits osteoblasts, through 5-HT1B receptors.

In summary, we can say that *serotonin* has the main

Biologic/Pharmacologic effects:

increases tone of smooth muscles
causes vasoconctrictin except the vessels of skeleton muscles and heart
increases blood pressure
activates platelet aggregation and clot formation
enhances tone and motility of GIT and myometrium
stimulates pain
stimulates nausea and vomiting
stimulates cellular growth to repair liver damage
suppresses insulin release from the beta cells in the pancreas
regulates the bone formation
causes fibrosis anywhere in the body, especially retroperitoneal fibrosis, cardiac fibrosis.

Pathologies associated with serotonin. Reduced level of serotonin in the brain is one of the factors in the formation of *depressions* and *severe migraines*. Hyperactivation of serotonin receptors may lead to *hallucinations*. Elevated levels of activity may be associated with *schizophrenia*.

Several classes of drugs target the 5-HT system, including some antidepressants, antipsychotics, anxiolytics, antiemetics, and antimigraine drugs, as well as the psychedelic drugs and empathogens. Some serotonergic agonist drugs also cause *fibrosis* anywhere in the body, particularly the syndrome of retroperitoneal fibrosis, as well as cardiac valve fibrosis. In the past, three groups of serotonergic drugs have been epidemiologically linked with these syndromes. They are the serotonergic vasoconstrictive antimigraine drugs (ergotamine and methysergide), the serotonergic *appetite suppressant* drugs (fenfluramine, chlorphentermine, and aminorex), and certain anti-Parkinsonian dopaminergic agonists, which also stimulate serotonergic 5-HT2B receptors. These include pergolide and cabergoline, but not the more dopamine-specific lisuride.

Some 5-HT3 antagonists, such as ondansetron, granisetron, and tropisetron, are important antiemetic agents. They are particularly important in treating the nausea and vomiting that occur during anticancer chemotherapy using cytotoxic drugs. Another application is in the treatment of postoperative nausea and vomiting.

In humans defective signaling of serotonin in the brain may be the root cause of sudden infant death syndrome. Researchers now believe that low levels

of serotonin in the animals' brainstem, which control heartbeat and breathing, may have caused sudden death.

Serotonin syndrome. Extremely high levels of serotonin can cause a condition known as serotonin syndrome, with toxic and potentially fatal effects. This is a rare but potentially deadly reaction to taking drugs (psychostimulators, antidepressants, opiates, tranquilisers and the like) or drugs that increase serotonergic transmission including the recreational use of them. The clinical symptoms include disorientation, confusion, agitation, hypomania, restlessness, fever, chills, tremors, sweating, diarrhea, nausea, vomiting, ataxia, hyperreflexia, myoclonia (sudden brief jerks of the muscles), abdominal cramping pain, hyperpyrexia (fever above 41,1° C), hypertension, tachycardia, etc., ranging from barely noticeable to the deadly. The intensity of the symptoms of serotonin syndrome varies over a wide spectrum, and the milder forms are seen even at nontoxic levels.

At the initial stage of the serotonin syndrome manifested primarily by the gastrointestinal and nervous system disorders characterized by dyspeptic symptoms (wildness, abdominal cramps, bloating, diarrhea, nausea, and rarely vomiting, etc.), extrapyramidal disorder (tremor, dysarthria, restlessness, muscle hypertonicity), hyperreflexia, myoclonic twitches, usually beginning in the feet and spreading throughout the body. At its last stages, with extremely rarely observed in the malignant form of flow, serotonin syndrome similar to neuroleptic malignant syndrome clinic: sudden onset of fever, profuse sweating, mask ike face, greasiness of the face, acute cardiovascular disorders leading to death.

Serotonin is found in mushrooms, fruits and vegetables, in nuts of the walnut (*Juglans*) and hickory (*Carya*) genera, in plantains, pineapples, bananas, kiwifruit, plums, and tomatoes. Foods with a high content of tryptophan (an amino acid from which serotonin is produced): dates, bananas, plums, figs, tomatoes, milk, soybeans, dark chocolate, contribute to the biosynthesis of serotonin and often improves mood. They can cause acute toxic effects (serotonin syndrome), if they used in large quantities during treatment with certain groups of antidepressants. Unlike its precursors, 5- HTP and tryptophan, serotonin does not cross the BBB, which means ingesting serotonin in the diet has no effect on brain serotonin levels.

Wasps and deathstalker scorpions have *serotonin* in their venom that allow to increase the pain of their stings on large animals, and also to cause lethal vasoconstriction in smaller prey. Serotonin is one compound of the poison contained in stinging nettles (*Urtica dioica*), where it causes pain on injection in the same manner as its presence in insect venoms. Several plants contain serotonin; examples are plants from the Anadenanthera genus that are used in the hallucinogenic yopo snuff.

Table 8. Places of location, mechanism and effects of activation of serotonin receptors in human body

Receptor	Mechanism	Places of location	Effects of activation*
5-HT1A	Adenylate cyclase inhibition; Stimulates cAMP accumulation	Benign and malignant prostate tissue; Poorly expressed in coronary arteries, atrium, ventricle and epicardium; Spinal cord: dorsal horn > ventral horn; CNS: dentate gyrus, hippocampus, subiculum, parahippocampal gyrus and neocortical regions (superficial and middle laminae), raphe of the brainstem; Kidney: medullary and cortical thick ascending limbs, distal convoluted tubules, connecting tubule cells, principal cells of the initial collecting tubule	Stimulation of cell proliferation
5-HT1B	Adenylate cyclase inhibition	Cortical cerebral arteries (smooth muscle cell layer > endothelial cell layer); Coronary artery > atrium > ventricle, epicardium; Benign and malignant prostate tissue; Brain: substantia nigra, globus pallidus > striatum > amygdala, hippocampus, septa region, hypothalamus; Trigeminal ganglion; Brain: substantia nigra, globus pallidus > caudate nucleus, putamen, nucleus accumbens, central gray, hippocampal formation > various cortical regions; Brain: striatum, cortex, lateral geniculate nucleus, raphe nucleus	Vasoconstriction

5-HT1D	Adenylate cyclase inhibition	Benign and malignant prostate tissue; Globus pallidus > frontal cortex > putamen; Spinal cord: dorsal horn > ventral horn; Poorly expressed in coronary arteries, atrium, ventricle and epicardium; Trigeminal ganglion	Growth hormone release
5-ht1e	Adenylate cyclase inhibition	Putamen > frontal cortex, globus pallidus; Cortical areas, caudate nucleus, putamen, amygdala	
5-HT1F	Adenylate cyclase inhibition	Brain, uterus (endometrium and myometrium), mesentery; Ventricle wall > atrium, epicardium, coronary artery; Brain: lamina V of the frontal cortex in large pyramidal cells, hippocampal pyramidal cells, thalamic nuclei and dorsal raphe	
5-HT2A	Phospholipase C stimulation	Atrium, coronary artery > ventricle wall, epicardium; CNS: parahippocampal gyrus and neocortical regions (superficial and middle laminae) > dentate gyrus, hippocampus (all fields), subiculum; Spinal cord: dorsal horn	Contraction of coronary arteries; Enhancement of platelet activation induced by ADP (adenosine-diphosphate) and thrombin
5-HT2B		Uterus, trachea, small intestine > liver, heart, ovary, skeletal muscle, brain, kidney, testis, placenta, prostate, pancreas	
5-HT2C	Phospholipase C stimulation; Adenylate cyclase inhibition	Resting lymphocytes	

5-HT4	Adenylate cyclase stimulation Calcium channel; Following cAMP production activation of Ca^{2+} channels and inhibition of K^{+} channels have been described in atrial myocytes and neurons respectively	Brain: caudate nucleus > lenticular nucleus, substantia nigra, hippocampus, frontal cortex; Heart: atria, ventricles; Brain: striato-nigral system > hippocampus, neocortex and colliculus; Brain: basal ganglia (caudate nucleus, putamen, nucleus accumbens), hippocampal formation (CA1, CA2, CA3 fields, subiculum, dentate gyrus, entorhinal cortex); Brain: basal ganglia (caudate nucleus, putamen, nucleus accumbens, globus pallidus, substantia nigra) > amygdala, hippocampal formation, cortex; Smooth muscle of the rectum; Myenteric plexus and smooth muscle of the colon; Myenteric plexus of the stomach; Esophagus, atrium, sinoatrial node, adrenal gland, frontal cortex; Brain: Frontal cortex, hippocampus > caudate, putamen > globus palidus, substantia nigra	Potentiation of neurally-mediated contraction of the detrusor muscle; Stimulation of aldosterone secretion from the adrenal cortex; Stimulation of gastric emptying; Relaxation of colon; Stimulation of peristaltic reflex (ascending contraction and descending relaxation); Atrial arrhythmic contractions
5-ht5a	Adenylate cyclase inhibition; Phospholipase C stimulation; It should be noted that as well as reports showing that the receptor couples to many different	Resting lymphocytes; Brain: amygdala, caudate nucleus, cerebellum, hypothalamus, substantia nigra, thalamus; Expression not seen in any peripheral tissues; Brain: neocortical regions (mainly layers II-III and V-VI), hippocampus (dentate gyrus and	

	signalling pathways, there are also reports showing that the receptor has difficulty coupling to any intracellular pathways	pyramidal cell layer of CA1 and CA3 fields), cerebellum (Purkinje cells, dentate nucleus and granule cells)	
5-ht5b			
5-HT6	Adenylate cyclase stimulation; Phospholipase C stimulation	A truncated, nonfunctional 5-HT6 receptor with a 289 bp deletion of the region coding for transmembrane IV and third intracellular loop has been identified in the caudate and substantia nigra of the human brain	
5-HT7	Adenylate cyclase stimulation	Heart: ventricle wall > epicardium > atrium, coronary artery; Coronary artery > brain > descending colon, ileum; Amygdala, aorta, cerebral cortex, hippocampus, thalamus, small intestine > spleen, pancreas, stomach, kidney; CNS: trigeminal ganglia; CNS: suprachiasmatic nucleus	

* - there are pharmacologic effects of serotonin agonists.

Table 9**. Agonists and antagonists of serotonin receptors

Receptor	Agonists	Antagonists
5-HT1A	lisuride, roxindole, flesinoxan, spiroxatrine, ipsapirone, pergolide, terguride, ziprasidone, aripiprazole, tandospirone, zalospirone, naphthylpiperazine, ocaperidone, bromocriptine, buspirone, cabergoline, donitriptan, eletriptan, naratriptan, nafadotride, xanomeline, apomorphine, clozapine, fluparoxan, zolmitriptan, quetiapine, piribedil, rizatriptan, sumatriptan, quinpirole, olanzapine, urapidil	repinotan, tiospirone, tertatolol, pindolol, methiothepin, spiperone, propranolol, flurocarazolol, pizotifen, yohimbine, fluspirilene, thioridazine, iloperidone, pimozide, flurocarazolol, sertindole, zotepine, risperidone, butaclamol, cyamemazine, chlorpromazine, haloperidol, pipamperone, raclopride, ketanserin, ritanserin

5-HT1B	alniditan, eletriptan, sumatriptan, donitriptan, oxymetazoline, donitriptan, alniditan, 7-methoxy-1-naphthylpiperazine, dihydroergotamine, ziprasidone, 5-(nonyloxy)-tryptamine, lysergol, naratriptan, eletriptan, 1-naphthylpiperazine, lisuride, zolmitriptan, sumatriptan, xanomeline, rizatriptan, pergolide, terguride, bromocriptine, cabergoline, olanzapine, tryptamine, clozapine, aripiprazole, roxindole	ketanserin, mianserin, spiperone, yohimbine, cyanopindolol, pindolol, methiothepin, metergoline, zotepine, methysergide, sertindole, rauwolscine, risperidone, flurocarazolol, pipamperone, ocaperidone, ritanserin
5-HT1D	eletriptan, alniditan, sumatriptan, donitriptan, dihydroergotamine, oxymetazoline, donitriptan, 7-methoxy-1-naphthylpiperazine, lysergol, alniditan, lisuride, ziprasidone, eletriptan, lysergic acid, zolmitriptan, naratriptan, sumatriptan, xanomeline, 1-naphthylpiperazine, cabergoline, bromocriptine, pergolide, rizatriptan, terguride, aripiprazole, dimethyltryptamine, tryptamine, roxindole, clozapine, olanzapine, quetiapine,	zotepine, metergoline, ocaperidone, methysergide, risperidone, bufotenine, rauwolscine, methiothepin, ritanserin, ketanserin, yohimbine, sertindole, cyanopindolol, pipamperone, haloperidol, fluspirilene, spiperone
5-ht1e	naratriptan, zolmitriptan, lysergol, ergonovine, eletriptan, rizatriptan, clozapine, ziprasidone, 5-fluorotryptamine, ergotamine, tryptamine, donitriptan, quetiapine, olanzapine, sumatriptan, dihydroergotamine, xanomeline	methylergonovine, 1-naphthylpiperazine, methiothepin, methysergide, zotepine, sertindole, risperidone, yohimbine, metergoline, fluspirilene, rauwolscine
5-HT1F	naratriptan, eletriptan, sumatriptan, zolmitriptan, clozapine, dihydroergotamine, ergotamine, rizatriptan, olanzapine, xanomeline, quetiapine, tryptamine, donitriptan, ergotamine, sumatriptan,	methysergide, methylergonovine, 1-naphthylpiperazine, yohimbine, metergoline, sertindole, methiothepin, risperidone, metergoline
5-HT2A	methylergonovine, ergotamine, lisuride, ergonovine, terguride, cabergoline, pergolide, aripiprazole, methysergide, tryptamine, bromocriptine, quetiapine, quipazine, lorcaserin, donitriptan, quinpirole, pindolol	altanserin, ketanserin, methylspiperone, risperidone, ritanserin, sertindole, ziprasidone, spiperone, amoxapine, methysergide, clozapine, cyamemazine, chlorpromazine, mianserin, olanzapine, butaclamol,mesulergine, metergoline, zotepine, amesergide, methiothepin, risperidone, sarpogrelate, amitriptyline, methysergide, sergolexole, clozapine, pipamperone, ritanserin, perphenazine, roxindole, loxapine, fluspirilene,

		trazodone, trifluoperazine, thioridazine, fluphenazine, haloperidol, trazodone, pimozide, thiothixene, mesulergine, apomorphine, xanomeline, bufotenine, quetiapine, fluoxetine, molindone, duloxetine, norfluoxetine, agomelatine, pindolol
5-HT2B*	methylergonovine, cabergoline, ergotamine, methysergide, pergolide, norfenfluramine, quipazine, tryptamine, quipazine, lorcaserin, quinpirole, pindolol, lorcaserin	rauwolscine, methiothepin, ritanserin, lisuride, metergoline, 1-naphthylpiperazine, mesulergine, clozapine, tegaserod, mianserin, terguride, amesergide, xanomeline, yohimbine, roxindole, bromocriptine, mianserin, trazodone, apomorphine, agomelatine, piboserod, sarpogrelate, spiroxatrine, ketanserin, piboserod, spiperone, haloperidol, piribedil, pindolol, fluoxetine, norfluoxetine, melatonin
5-HT2C	ergotamine, methysergide, methylergonovine, lisuride, lorcaserin, aripiprazole, quipazine, oxymetazoline, pergolide, tryptamine, cabergoline, bromocriptine, quinpirole	methysergide, mesulergine, mianserin, sertindole, ritanserin, metergoline, amoxapine, zotepine, amitriptyline, methiothepin, tiospirone, olanzapine, ziprasidone, clozapine, cyamemazine, loxapine, chlorpromazine, risperidone, sarpogrelate, xanomeline, fluoxetine, terguride, thioridazine, ketanserin, apomorphine, perphenazine, trazodone, norfluoxetine, roxindole, trifluoperazine, agomelatine, duloxetine, spiperone
5-HT4	tegaserod, prucalopride, cisapride, renzapride, zacopride, mosapride, metoclopramide	piboserod, tropisetron,
5-ht5a	donitriptan, lysergic acid, sumatriptan	methiothepin, ergotamine, ritanserin, methysergide, clozapine, metergoline, bufotenine, yohimbine, clozapine, propranolol, ketanserin
5-ht5b		
5-HT6	ergotamine, lisuride, bromocriptine, pergolide, lergotrile, dimethyltryptamine, 1-naphthylpiperazine, 5-benzyloxytryptamine, aripiprazole, tryptamine, xanomeline, donitriptan	zotepine, methiothepin, chlorpromazine, thioridazine, dihydroergotamine, olanzapine, amoxapine, clozapine, fluperlapine, perphenazine, bufotenine, loxapine, fluperlapine, iloperidone, fluphenazine, α-ergocryptine, dihydroergocristine, pimozide, ritanserin, thioridazine, mianserin, perphenazine, tiospirone, amitriptyline, metergoline, cyproheptadine, methysergide, duloxetine, risperidone, tiospirone,

		fluoxetine, spiperone, risperidone, sumatriptan, mesulergine
5-HT7	lisuride, pergolide, aripiprazole, bromocriptine, tryptamine, 1-naphthylpiperazine, bufotenine, xanomeline, tryptamine, buspirone, cisapride	risperidone, pimozide, methiothepin, tiospirone, zotepine, metergoline, ziprasidone, pirenperone, fluperlapine, fluphenazine, dihydroergotamine, mesulergine, methysergide, spiperone, ritanserin, clozapine, iloperidone, chlorpromazine, perphenazine, butaclamol, mianserin, amoxapine, cyproheptadine, ergotamine, cyamemazine, thioridazine, loxapine, ritanserin, dihydroergocryptine, amitriptyline, olanzapine, ketanserin, haloperidol, buspirone, sumatriptan, yohimbine

* - methysergide is a low intrinsic efficacy partial agonist, although in some functional assays it may behave as an antagonist.

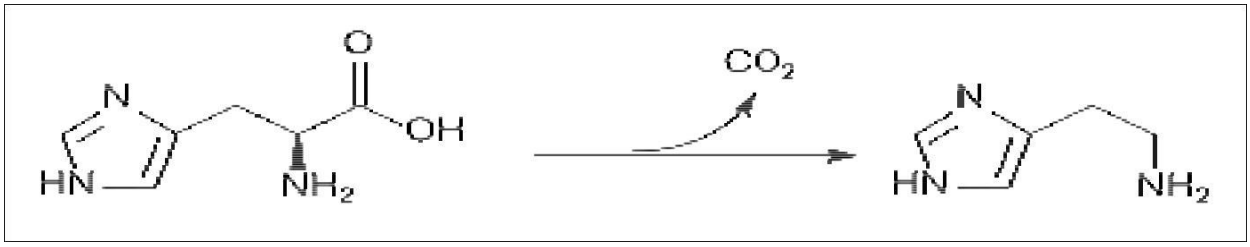
**- adopted from IUPHR Database. International Union of Pharmacology. 2012. http://www.iuphar-db.org/DATABASE

At present, the physiological significance of serotonin has been insufficiently studied. In clinical practice, serotonin and its synthetic analogues, substances similar to it in chemical structure, agonists and antagonists of serotonin receptors are not used widely. Among them were used in the clinic, highly anti-emetics (ondansetron, tropisetron, granisetron), drugs stimulating GIT motility (metoclopramide), haemostatic drugs (serotonin adipinate), antialergic drugs (cyproheptadine, fenspiride, etc.), antihypertensives (ketanserin, urapidil, indoramin) and as the drugs for treatment and prophylactic of migraine (dihydroergotamine, ergotamine, sumatriptan, naratriptan, pizotifen, etc.) as an adaptogen (mexaminum, melatonin, etc.) to improve sleep (mexaminum, melatonin, etc.) as antipsychotics (olanzapine, clozapine, chlorpromazine, perphenazine, fluphenazine, etc.). For more details, these drugs will be discussed in the relevant chapters.

Histamine is an organic nitrogen compound involved in local immune responses as well as regulating physiological function in the GIT and acting as a neurotransmitter.

Synthesis and methabolism (scheme 4). Histamine is derived from the decarboxylation of the amino acid histidine, a reaction catalyzed by the enzyme L-histidine decarboxylase. It is a hydrophilic vasoactive amine. Once formed, histamine is either stored or rapidly inactivated by its primary degradative enzymes, histamine-N-methyltransferase or diamine oxidase. In the central nervous system, histamine released into the synapses is primarily broken down by histamine-N-methyltransferase, while in other tissues both enzymes may play a role. Several enzymes, including MAO-B and aldehyde dehydrogenase 2 family (mitochondrial) (ALDH2), further process the immediate metabolites of histamine for excretion or recycling.

Bacteria also are capable of producing histamine using histidine decarboxylase enzymes unrelated to those found in animals. A non-infectious form of foodborne disease, scombroid poisoning (is a foodborne illness that results from eating spoiled/decayed fish), is due to histamine production by bacteria in spoiled food, particularly fish. Fermented foods and beverages naturally contain small quantities of histamine due to a similar conversion performed by fermenting bacteria or yeasts. Sake contains histamine in the 20– 40 mg/L range; wines contain it in the 2–10 mg/L range.



Scheme 4. Conversion of histidine to histamine by histidine decarboxylase (adopted from http://en.wikipedia.org/).

Storage and release. *Histamine* is a ubiquitous chemical messenger that can be released from a variety of cells (e.g. mast cells, enterochromaffin-like cells, neurons) to act on one of four *histamine receptors: H1, H2, H3 and H4*.

Most *histamine* in the body is generated in granules in mast cells or in white blood cells called basophils. Mast cells are especially numerous at sites of potential injury - the nose, mouth, and feet, internal body surfaces, and blood vessels. Non-mast cell histamine is found in several tissues, including the brain, where it functions as a neurotransmitter. Another important site of histamine storage and release is the enterochromaffin-like (ECL) cell of the stomach.

The most important pathophysiologic mechanism of mast cell and basophil histamine release is immunologic. These cells, if sensitized by IgE antibodies attached to their membranes, degranulate when exposed to the appropriate antigen. Certain amines and alkaloids, including such drugs as morphine, and curare alkaloids, can displace histamine in granules and cause its release. Antibiotics like polymyxin are also found to stimulate histamine release.

Histamine release occurs when allergens bind to mast-cell-bound IgE antibodies. Reduction of IgE overproduction may lower the likelihood of allergens finding sufficient free IgE to trigger a mast-cell-release of histamine.

Mechanism of action. *Histamine* exerts its actions by combining with specific cellular histamine receptors. The four *histamine receptors* that have been discovered in humans are designated H1 through H4, and are all G protein-coupled receptors (GPCR).

Table 10. Places of location, mechanism and effects of activation of histamine receptors in human body

Receptor	Mechanism	Places of location	Effects of activation*
H1	Adenylate cyclase stimulation; Phospholipase C stimulation; Ca2+ mobilisation	Smooth muscle; Myometrium; Endothelium; Cranial arteries; Central nervous system; GIT; Myocardium (ventricle > atrium)	Bronchoconstriction, bronchial smooth muscle contraction; Vasodilation; Separation of endothelial cells (responsible for hives); Pain and itching due to insect stings; The primary receptors involved in allergic rhinitis symptoms and motion sickness; Sleep/wake regulation; Mediation of hypersensitivity reactions and allergic response (release of proinflammatory mediators, interleukins, cytokines, cell adhesion, chemotaxis, and others); Regulation of food intake and cognitive functions in the CNS
H2	Phospholipase C stimulation; Adenylate cyclase stimulation leading to the formation of cAMP	GIT, parietal cells; Mast cells; Vascular smooth muscle cells; Brain (cerebrum, caudate and putamen nuclei, external layers of cerebral cortex > hippocampal formation > dentate nucleus of cerebellum); Myocardium (atrium and ventricle)	Relaxation of smooth muscle; Primarily involved in vasodilation; Stimulate gastric acid secretion; Inhibition of neutrophil activation; Inhibition of neutrophil chemotaxis and T-lymphocyte proliferation
H3	Adenylate cyclase inhibition	Central nervous system - brain: thalamus, caudate nucleus, putamen, cerebellum, amygdala, substantia nigra, hippocampus, hypothalamus, cerebral cortex; to a lesser extent peripheral nervous system	Decreased neurotransmitter release: histamine, acetylcholine, norepinephrine, serotonin; Vasoconstriction; Activation of spinal H_3 receptors inhibits mechanical nociception Regulation of activity of

		tissue; Presynaptic receptors are located in adrenergic and cholinergic nerve endings	histamine and other neurotransmitters in CNS; Regulation of sleep/wake; cognitive functions in CNS; Inhibition of nociception;
H4	Phospholipase C stimulation; Inhibition of adenylyl cyclase; Mobilisation of calcium from intracellular stores; Stimulation of mitogen-activated protein (MAP) kinase in both heterologous expression systems and native immune cells	Basophils; Monocytes; Eosinophils and dendritic cells; Mast cells; Leukocytes, spleen, lung, liver > heart, skeletal muscle; Brain: cerebellum, hippocampus, bone marrow; thymus, small intestine, spleen, colon	Plays a role in chemotaxis, eosinophil shape change; Upregulation of cell surface adhesion molecules; Activation of chemotaxic, acummulation of eosinophils in place of inflammation

* - there are pharmacologic effects of histamine agonists.

Physiologic functions. *Histamine* is one of the endogenous factors (mediators) involved in the regulation of vital body functions and plays an important role in the pathogenesis of several disease states. Under normal circumstances, *histamine* is in the body mostly in the bound, inactive state. In various pathological processes (anaphylactic shock, burns, frostbite, hay fever, urticaria and allergic diseases), as well as when certain chemicals are increased in the body, the amount of free histamine is enhanced. *Liberatores of histamine* are d-tubocurarine, morphine, iodine-containing radiocontrast agents, macromolecular compounds (dextran, etc.) and other drugs.

Free histamine has high activity: it causes spasm of smooth muscles (including muscles of the bronchi), the expansion of the capillaries and a decrease in blood pressure, blood stasis in the capillaries and increased permeability of their walls, causes swelling of surrounding tissue and blood clots.

Histamine causes increased secretion of gastric juice. In CNS *histamine* plays the role of mediator, regulates sleep, and controls the mechanisms of memories and learning. It also affects erection and sexual functions. While *histamine* has stimulatory effects upon neurons, it also has suppressive ones that protect against the susceptibility to convulsion, drug sensitization, denervation supersensitivity, ischemic lesions and stress. Metabolites of *histamine* are increased in the cerebrospinal fluid of people with schizophrenia, while the efficiency of H1 receptor binding sites is decreased.

Histamine plays a role in angiogenesis. As an integral part of the immune system, *histamine* may be involved in immune system disorders and allergies.

Effects on nasal mucous membrane: Increased vascular permeability causes fluid to escape from capillaries into the tissues, which leads to the classic symptoms of an allergic reaction: a runny nose and watery eyes. Allergens can bind to IgE-loaded mast cells in the nasal cavity's mucous membranes. This can lead to three clinical responses: sneezing due to histamine-associated sensory neural stimulation; hyper-secretion from glandular tissue; nasal congestion due to vascular engorgement associated with vasodilation and increased capillary permeability.

Table 11*. Agonists and antagonists of histamine receptors

Receptor	Agonists	Antagonists
H1	dimethylhistaprodifen, histamine, 2-pyridylethylamine	cyproheptadine, doxepin, clozapine, zotepine, olanzapine, pyrilamine, triprolidine, thiothixene, quetiapine, cetirizine, chlorpromazine, chlorpheniramine, loxapine, perphenazine, diphenhydramine, fluspirilene, fluphenazine, risperidone, thioridazine, ziprasidone, aripiprazole, trifluoperazine, sertindole, cetirizine, chlorpheniramine, arpromidine, pimozide, haloperidol, molindone, clobenpropit, pipamperone, impromidine
H2	impromidine, arpromidine, histamine, burimamide	aminopotentidine, iodoaminopotentidine, tiotidine, ranitidine, cimetidine, metiamide, burimamide, clobenpropit
H3	methylhistamine, histamine, iodoproxyfan, immepip, perceptin, imetit, imbutamine, proxyfan, impentamine, impromidine, dimaprit	iodoproxyfan, clobenpropit, ciproxifan, iodophenpropit, clobenpropit, thioperamide, proxyfan, impentamine, burimamide, clozapine
H4	histamine, methylhistamine, imetit, immepip, impromidine, ethylhistamine, dimethylhistamine, dimaprit, methimepip, improgan	pyrilamine, clobenpropit, iodophenpropit, thioperamide, burimamide, clozapine, ciproxifan

* - adopted from IUPHR Database. International Union of Pharmacology. 2012. http://www.iuphar-db.org/DATABASE .

The use of histamine, its analogs and histamine receptors activators is restricted by their advers effects and specific biological and pharmaceutical activities. Of all the known histamine receptor blockers in clinical practice primarily the blockers H_1 and H_2 histamine receptors are used, mostly, as the drugs that reduce gastric mucosa secretion, and as the antiallergic drugs.

Classification of H_1 histamine blockers

- ***I generation:***
  - diphenhydramine (Alledryl, Allergan, Allergin, Allergival, Amidryl, Benadryl, Benzhydraminum, Diabenyl, Dimedrolum, Dimedryl, Dimidril, Restamin, etc.).
  - clemastine (Alagyl, Anhistan, Fenistil, Fumartin, Lecasol, Meclastin, Mecloprodine fumarate, Rekonin, Rivtagil, Tavegil, Tavist, etc.).
  - promethazine (Allergan, Antiallersin, Atosil, Diprazinum, Fargan, Phenergan, Pipolphen, etc.).
  - sequifenadine (Sequifenadine hydrochloride, Bicarphenum, Histafen).
  - chloropyramine (Allergan S, Chlorneoantergan, Chloropyribenzamine h/cl., Chlortripelenamine h/cl., Halopyramine, Sinopen, Suprastin, Synopen).
- ***II generation:***
  - astemizole (Alermizol, Asmoval, Astelong, Astemisan, Hismanal, Histalong, Histamanal, Ifirab, Lembil, Mibiron, Stelert, Stemiz, Vagran).
  - azelastine (Allergodil).
  - acrivastatine (Semprex).
  - dimetindene (Fenistil).
  - loratadine (Claritin, Clarotadinum, Klarisens, Lomilan, Loratin, Loridin).
  - mebhydrolin (Dialin, Diazolinum, Incidal, Mebhydrolini Napadisylas, Omeril).
  - qiufenadine (Phencarolum).
  - terfenadine (Bronal, Caradonel, Daylert, Histadine, Rapidal, Riter, Seldane, Tamagon, Teridine, Termenadin, Thelladadan, Triludan, Tofrin, Toldan, Teridine, Termenadin, Thelldan, Triludan, Tofrin, Toldan, Trexyl, etc.)
  - cyproheptadine (Adekin, Apetigen, Astonin, Cipractin, Cyprodin, Istabin, Pariactin, Peritol, Supersan, Vieldrin, Vinorex, etc.).
  - ebastine (Kestine).
  - fenspiride (Eurespal)
- ***III generation:***
  - desloratadine (NeoClarityn, Claramax, Clarinex, Larinex, Aerius, Dazit, Azomyr, Deselex and Delot.).
  - levocetirizine (Allear, Alcet , Seasonix, Teczine, T-Day Syrup, Vozet, Zyxem, Zilola, Xaltec, Xozal, Xusal, Xuzal, Xyzal).
  - fexofenadine (Allegra, Telfast).
  - cetirizine (Alerza, Allertec, Cetirinax, Cetrine, Letizen, Parlazin, Reactine, Zetrinal, Zodac, Zyncet, Zyrtec, etc.).

H_1 histamine blockers for local use:

- levocabastyine (Gistimet)
- bamipine (Soventol)

Classification of H_2 histamine blockers

- ***I generation:*** cimetidine (Altramet, Belomet, Benomet, Cigamet, Cimesan, Histodyl, Primamet, Tagamet, Ulcometine, Ulcuzal, Zagastrol, etc.) – it is deleted preparation (deregistered), not manufactured and is not used nowadays because of the many side effects.

II generation: ranitidine (Acidex, Aciloc-E, Anistal, Gertocalm, Histac, Raniberl, Ranigast, Ranisan, Ranital, Ranitin, Rantac, Renx, Zantac, Zantin, Zoran, Ulcodin, Ulcosan, Ulran, etc.).

III generation: famotidine (Acipep, Amifatidine, Antodine, Blokacid, Famocid, Famodar, Femocin, Fudon, Fluxid, Gaster, Gasterogen, Lecedil, Novafam, Pepcidine, Pepcid, Pepdul, Quamatel, Topcid, Ulceran, Ulfamid, etc.).

IV generation: nizatidine (Axid)

V generation: roxatidine (Roxane).

Miscellaneous H2 blockers

lafutidine (Stogar, Protecadin)

ebrotidine (Ebrocit)

Eicosanoids. *Prostaglandines* and others arachidonate metabolites, such as *prostacyclin* (PGI2), *thromboxane* A_2 (TxA_2), *leukotroenes* (LTs), *lipoxins*, *hepoxilins* belong to the class of *eicosanoids*. Membrane lipids supply the substrate for the synthesis of *eicosanoids* and *platelet-activating factor* (PAF). Eicosanoids are not stored but are produced by most cells. PGs, PGI2, TxA_2 are known as *prostanoids*. The eicosanoids act through activation of specific cell surface receptors that couple to intracellular second-messenger systems to modulate cellular activity.

This table (tabl. 12) lists the major classes of eicosanoid receptors and their signaling characteristics. Splice variants for EP_3, TP, and FP are indicated. Major phenotypes in knockout mouse models are listed. $Ca^{2+}{}_i$ – cytosolic Ca^{2+}; cAMP – cyclic AMP; PLC - phospholipase C (activation leads to increased cellular inositol phosphate and diacylglycerol generation and increased $Ca^{2+}{}_i$); IsoPs – isoprostanes;

Table 12*. Eicosanoid receptors

Receptor	Primary ligand	Secondary ligand	Primary coupling	Major phenotype in knockout mice**
DP_1	PGD_2		cAMP (G_s)	↓Allergic asthma
DP_2/$CHRT_2$	PGD_2	15d-PGJ_2	↓cAMP, Ca^{2+} (G_i)	or ↓Allergic airway inflammation
EP_1	PGE_2	PGI_2	$Ca^{2+}{}_i$ (Gq)	↓Response of colon carcinogens
EP_2	PGE_2		cAMP (G_s)	Impaired ovulation and fertilization Salt-sensitive hypertension
EP_3 I-VI, e,f	PGE_2		↓cAMP, $Ca^{2+}{}_i$ (G_i); cAMP (G_s); PLC, $Ca^{2+}{}_i$ (Gq)	Resistance to pyrogens ↓Acute cutaneous inflammation
EP_4	PGE_2		cAMP (G_s)	Patent ductus arteriosus ↓Bone mass/density in

				aged mice Bowel inflammatory response ↓Colon carcinogenesis
$FP_{A,B}$	$PGF_{2\alpha}$	IsoPs	PLC, $Ca^{2+}{}_i$ (Gq)	Failure of parturition
IP	PGI_2	PGE_2	cAMP (G_s)	Thrombotic response ↓Response to vascular injury Atherosclerosis Cardiac fibrosis Salt-sensitive hypertension ↓Joint inflammation
$TP_{\alpha,\beta}$	TxA_2	IsoPs	PLC, $Ca^{2+}{}_i$ (Gq, G_i, $G_{12/13}$, G_{16}); Rho, ERK activation (Gq, $G_{12/13}$, G_{16})	Bleeding time ↓Response to vascular injury ↓Atherosclerosis Survival after cardiac allograft
BLT_1	LTB_4		$Ca^{2+}{}_I$, ↓cAMP (G_{16}, G_i)	Some suppression of inflammatory response
BLT_2	LTB_4	12*(S)*-HETE	$Ca^{2+}{}_I$ (Gq-like, G_i-like, G_z-like)	?
$CysLT_1$	LTD_4	LTC_4/LTE_4	PLC, $Ca^{2+}{}_i$ (Gq)	↓Innate and adaptive immune vascular permeability response Pulmonary inflammatory and fibrotic response
$CysLT_2$	LTC_4/ LTD_4	LTE_4	PLC, $Ca^{2+}{}_i$ (Gq)	↓Pulmonary inflammatory and fibrotic response

- adopted from Goodman & Gilman's The Pharmacological Basis of Therapeutics. 12th Edition, 2011.

** - A knockout mouse is a genetically engineered mouse in which researchers have inactivated, or "knocked out," an existing gene by replacing it or disrupting it with an artificial piece of DNA. The loss of gene activity often causes changes in a mouse's phenotype, which includes appearance, behavior and other observable physical and biochemical characteristics. Knockout mice are important animal models for studying the role of genes which have been sequenced but whose functions have not been determined. By causing a specific gene to be inactive in the mouse, and observing any differences from normal behaviour or physiology, researchers can infer its probable function. Mice are currently the most closely related laboratory animal species to humans for which the knockout technique can easily be applied. They are widely used in knockout experiments, especially those investigating genetic questions that relate to human physiology. Gene knockout in rats is much harder and has only been possible since 2003. The first recorded knockout mouse was created by Mario R. Capecchi, Martin Evans and Oliver Smithies in 1989, for which they were awarded the Nobel Prize for Medicine in 2007 (adopted from http://en.wikipedia.org/wiki/Knockout_mouse).

ERK – extracellular signal regulated protein kinase; Rho – a family of small signaling G proteins; 15d-PGJ_2 – 15-deoxy-$\Delta^{12, 14}$- PGJ_2; DP_2 – is a member of the fMLP-receptor superfamily; fMLP – formyl-methionyl-leucyl-phenylalanine; CysLT – Cysteinyl leukotriene receptor; HETE – hydroxyeicosatetraenoic acid.

A **prostaglandin (PG)** is any member of a group of lipid compounds that are derived enzymatically from fatty acids and have important functions in the animal body. Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring.

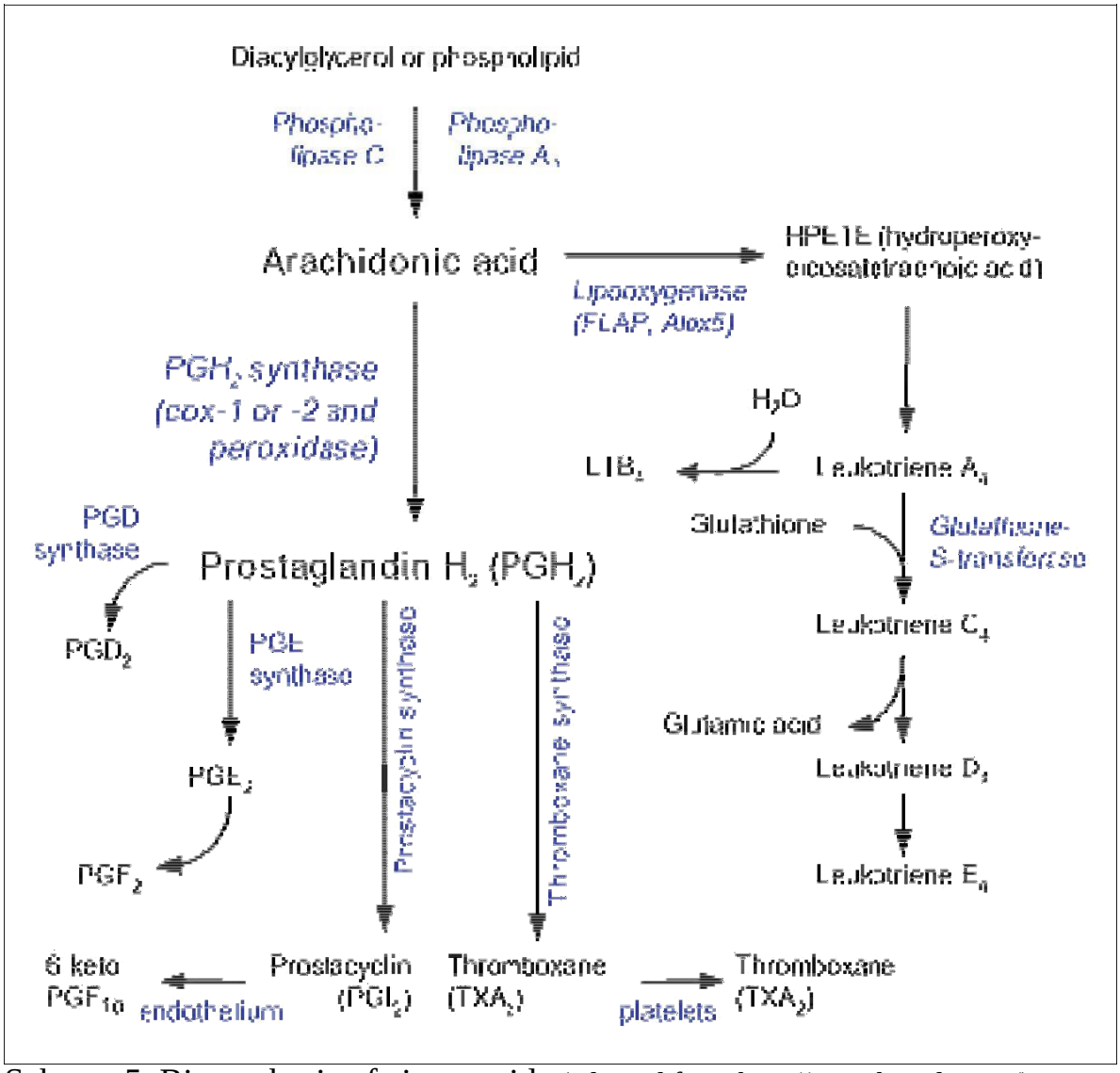
They are mediators and have a variety of strong physiological effects, such as regulating the contraction and relaxation of smooth muscle tissue. *Prostaglandins* are not endocrine hormones, but autocrine or paracrine, which are locally acting messenger molecules. They differ from hormones in that they are not produced at a discrete site but in many places throughout the human body. Also, their target cells are present in the immediate vicinity of the site of their secretion (of which there are many).

Biosynthesis (scheme 5). PGs are synthesized in almost all nucleated cells except erythrocytes and lymphocytes. They are autocrine and paracrine lipid mediators that act upon platelets, endothelium, uterine and mast cells. They are synthesized in the cell from the essential fatty acids. An intermediate arachidonic acid (AA) is created from diacylglycerol via phospholipase-A2 (PLA_2), and then brought to either the cyclooxygenase pathway or the lipoxygenase pathway to form either prostaglandin and thromboxane (Tx) or leukotriene (LT), respectively. The cyclooxygenase pathway produces thromboxane, prostacyclin and prostaglandin D, E and F. Alternatively, the lipoxygenase enzyme pathway is active in leukocytes and in macrophages and synthesizes leukotrienes. Tx defines the formation of blood clot. Prostacyclin prevents blood coagulation and it is a potent stimulator of myometrial contractility, and it is derived at first from COX-2. The prostacyclin formation and release is regulated by vasoconstrictor and vasodilator autacoids. It became apparent that the oppression of Tx and stimulation of prostacyclin provides a good therapeutic effect in cardiovascular diseases.Thereby, *eicosanoids affect platelet function.*

It is known that the eicosanoids have short $T_{1/2}$ and do not circulate and are considered not to impact on systemic vascular tone directly. However, they may modulate vascular tone locally or through renal or other indirect effects.

Inhibitors of Eicosanoid biosynthesis. There are the drugs that reduce the availability of Ca^{2+}, because PLA_2 is activated by Ca^{2+} and calmodulin, and inhibition of PLA_2 decreases the release of the precursor fatty acid and thus the synthesis of all its metabolites; glucocorticoids that also inhibit PLA_2 and glucocorticoids also downregulate induced expression of COX-2, but not COX-1; traditional non-steroid anti-inflammatory drugs (tNSAIDs) that inhibit the COX.

Release from the cells. Prostaglandins were originally believed to leave the cells via passive diffusion because of their high lipophilicity. The discovery of the prostaglandin transporter, which mediates the cellular uptake of prostaglandin,



Scheme 5. Biosynthesis of eicosanoids (adopted from http://en.wikipedia.org/).

demonstrated that diffusion alone cannot explain the penetration of prostaglandin through the cellular membrane. The release of prostaglandin has now also been shown to be mediated by a specific transporter, namely the multidrug resistance protein 4 (MRP4, ABCC4), a member of the ATP-binding cassette transporter superfamily. Whether MRP4 is the only transporter releasing prostaglandins from the cells is still unclear.

Cyclooxygenases (COX). Prostaglandins are produced following the sequential oxidation of arachidonic acid (AA), dihomo-γ-linolenic acid (DGLA) or eicosapentaenoic acid (EPA) by cyclooxygenases (COX-1 and COX-2) and terminal prostaglandin synthases. The classic dogma is as follows: COX-1 is responsible for the baseline levels of prostaglandins; COX-2 produces prostaglandins through stimulation. COX-2 is the predominant COX at the sites of inflammation, whereas COX-1 is the major sourse of cytoprotective PGs in the gastrointestinal tract (GIT). However, while COX-1 and COX-2 are both located in

the blood vessels, stomach and the kidneys, prostaglandin levels are increased by COX-2 in scenarios of inflammation.

Endogenous PGs, TXs, LTs function in physiological and pathological processes. PGs activate membrane receptors locally near their sites of formation. There are currently ten known prostaglandin receptors on various cell types. Prostaglandins ligate a sub-family of cell surface seven-transmembrane receptors, G-protein-coupled receptors. These receptors are termed DP_{1-2}, EP_{1-4}, FP, IP_{1-2}, and TP, corresponding to the receptor that ligates the corresponding prostaglandin (e.g., DP_{1-2} receptors bind to PGD2). The diversity of receptors means that prostaglandins act on an array of cells and have a wide variety of effects such as: cause constriction or dilation in vascular smooth muscle cells; cause aggregation or disaggregation of platelets; sensitize spinal neurons to pain; induce labor ($PGF_{2\alpha}$ and TxA_2 are important in final stage of delivery); may play a role in the maintenance of placenral blood flow; decrease intraocular pressure; regulate inflammatory mediation; regulate calcium movement; control hormone regulation; control cell growth; act on thermoregulatory center of hypothalamus to produce fever; act on mesangial cells in the glomerulus of the kidney to increase glomerular filtration rate; regulation of blood pressure in response to high-salt diet; support the renal blood flow and salt excretion; act on parietal cells in the stomach wall to inhibit acid secretion. Furthermore polymorphisms in the genes for PGD_2 synthase and TP receptor have been associated in asthma in humans.

Considering the role of both COX-1 and COX-2 in the syntesis of PGs and role of COX-2 in protection against oxidative injury in cardiac tissue, it can be assumed connection between inhibitors of COX-2 and myocardial ischemia/reperfusion injury, violation of cardiac function. Moreover, COX-2 derivated TxA_2 facilitated to oxidant stress, isoprostane generation, and activation of TP and feasibly the FP to increase cardiomyocite apoptosis and fibrosis. Selective reduction of COX-2 in cardiomyocites leads to mild heart failure and tendency to arrhythmogenesis.

Pharmacological inhibition or genetic removal of COX-2 hampers tumor formation, such as colon, breast, lung and other cancers. Large human epidemiological investigations demonstrated link between use of NSAIDs and considerable descension in relative risks for cancer development, whereas polymorphism in COX-2 have been associated with heightened risk of colon and other cancers. Whereas aspirin use is associated with reduced risk of a breast cancer in women. Besides, the pro- and anti-oncogenic roles of both COX, not only COX-2, and LT inhibitors and LT receptors are studied. Moreover, an increased interest is the use of LT antagonists/ihibitors for prevention/therapy of various types of cancer. Thereby the pro- and anti-oncogenic roles of prostanoids not yet fully explored and are under research.

Prostaglandins are potent but have a short half-life before being inactivated and excreted. Therefore, they send only paracrine (locally active) or autocrine (acting on the same cell from which it is synthesized) signals. LTs are potent mediatios of inflammation.

The following (tabl. 13) is a comparison of different types of prostaglandin, prostacyclin I2 (PGI_2), prostaglandin E2 (PGE_2), and prostaglandin F2α ($PGF_{2\alpha}$).

Table 13*. Prostaglandine receptors: type and functions

Type	Receptor	Functions
PGI2	IP	vasodilation inhibit platelet aggregation bronchodilatation
PGE2	EP_1	bronchoconstriction GI tract smooth muscle contraction
	EP_2	bronchodilatation GI tract smooth muscle relaxation vasodilatation
	EP_3	decrease gastric acid secretion increase gastric mucus secretion uterus contraction (when pregnant) GI tract smooth muscle contraction lipolysis inhibition increase autonomic neurotransmitters increase platelet response to their agonists and increase atherothrombosis in vivo
	Unspecified	hyperalgesia pyrogenic
PGF2α	FP	uterus contraction bronchoconstriction

* - adopted from http://en.wikipedia.org/

Fatty acid cyclo-oxygenase (COX) converts arachidonic acid to prostaglandin H_2 (PGH_2), from which further prostanoids, PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 (prostacyclin) and TxA_2 (thromboxane A_2), may be derived. Eicosanoid receptors interact with G_s, G_i, G_q to modulate the activities of adenyl cyclase and phospholipase C.

Five prostanoid receptors were recognized and correspondingly named DP, EP, FP, IP and TP receptors. Additionally, EP receptors have been subdivided into four groups, termed EP_1, EP_2, EP_3 and EP_4; the DP receptor also has two subtypes – DP_1 and DP_2; TP receptor has isoforms α and β; FP receptor has isoforms A, B.

DP_1 receptors are coupled to adenylate cyclase via a G_s protein. Activation of DP_1 receptors leads to inhibition of platelet activation and vasodilatation. DP_1 receptors are expressed in the brain, where they may be involved in the regulation of sleep.

The *DP_2 receptor* is structurally distinct from all of the other known prostanoid receptors. Indeed this receptor was originally termed $CRTH_2$ to indicate

both its activity and the cell type in which it was initially identified. Unlike the DP_1 receptor, it is activated by prostanoids with an unnatural configuration at C-15 and also by 15-oxo analogues (potential products of 15-hydroxy prostaglandin dehydrogenase). Furthermore, the COX inhibitor indomethacin is an agonist at the DP_2 receptor. Activation of DP_2 receptors leads to eosinophil, basophil and Th2 (T helper) cell activation, while DP_1 receptor activation may oppose these events. Ramatroban, originally developed as a TP antagonist, also blocks DP_2 receptors. DP_2 receptor is an exception and is unrelated to the other prostanoid receptors; rather, it is a member of the formyl-methionyl-leucyl-phenylalanine (fMLP) receptor superfamily.

As a broad generalization, *EP_1 and EP_3 receptors* mediate excitatory effects, while *EP_2 and EP_4 receptors* mediate inhibitory effects. EP_1 receptors are believed to be coupled via regulatory G proteins to (PLC-independent) influx of extracellular Ca^{2+}; phosphatidylinositol hydrolysis ensues as a consequence of this influx. EP_3 receptors are subject to splice variance at the C-terminus and, to date, ten isoforms have been identified across species, six of these being expressed in man . These isoforms differ in their G-protein coupling thereby contributing to the wide spectrum of EP_3 actions: contraction of smooth muscle, enhancement of platelet aggregation, inhibition of autonomic neurotransmitter release, inhibition of gastric acid secretion, and inhibition of fat cell lipolysis. EP_2 and EP_4 receptors are believed to be coupled through a G_s protein to stimulation of adenylate cyclase. Both EP subtypes may be present on smooth muscle cells with the latter usually showing considerably higher sensitivity to PGE_2. Selective agonists exist for all four EP subtypes. Selective antagonists for EP_1 receptors have been known for some time and several have progressed into clinical trials as analgesic/anti-inflammatory agents. EP_1 and EP_2 receptors have limited distribution compared with the distribution of EP_3 and EP_4 receptors.

FP receptors are believed to be coupled via a regulatory G protein to stimulation of PI (phosphatidylinositol) hydrolysis. FP receptors are expressed in kidney, heart, lung, stomach, and eye; they are abundant in the corpus luteum, where their expression pattern varies during the estrus cycle. They are found in smooth muscle, being particularly widely distributed in cats and dogs, where they mediate contraction. Fluprostenol is a highly selective FP agonist. FP receptors present in the corpus luteum of many species mediate luteolysis, and $PGF_{2\alpha}$ analogues (fluprostenol, cloprostenol) have been used in animal husbandry to synchronize oestrus and induce parturition. FP receptor-stimulation also profoundly lowers intraocular pressure in laboratory animal species and man and FP agonists applied topically as C1-ester pro-drugs (latanoprost, travoprost) are increasingly used as anti-glaucoma drugs. FP receptor antagonists have been slow to emerge; the $PGF_{2\alpha}$ analogue appears to be a partial agonist at the FP receptor.

IP receptors are coupled via a G_s protein to stimulation of adenylate cyclase. IP receptors are expressed in many tissues and cells, including human kidney, lung, spine, liver, vasculature, and heart. IP receptors relax vascular smooth muscle and inhibit platelet aggregation. They appear to contribute to cardiovascular health

by counteracting vasoconstriction and platelet activation mediated via TP receptors. Prostacyclin and a few of its stable analogues are used to treat pulmonary hypertension, with careful attention to dosage to avoid excessive lowering of arterial blood pressure. Cicaprost is the most selective IP agonist; other commonly used agonists (carbacyclin, iloprost) have sufficient EP_1 and/or EP_3 agonism to oppose their IP-receptor-mediated actions. A large range of non-prostanoid prostacyclin mimetics exists; while some of these agents appear to be IP partial agonists, analysis is hampered by the their ability to inhibit PLC-driven events via a non-prostanoid mechanism. Selective IP receptor antagonists that competitively block the vasodilator platelet-inhibitory actions of IP agonists have recently been described. These agents suppress hyperalgesia and oedema in animal models of inflammation, indicating that PGI_2 may not always have beneficial actions in the body.

TP receptors are expressed in platelets, vasculature, lung, kidney, heart, thymus, and spleen. TP receptors are present in nearly all mammalian blood vessels, airways and blood platelets, where they mediate smooth muscle contraction and platelet aggregation. Signal transduction occurs via regulatory G proteins linking to stimulation of PI hydrolysis. Both PGH_2 and TxA_2 are potent agonists for the TP receptor, but are rarely used in characterization studies owing to the instability of their bicyclic ring systems. A number of highly potent TP agonists have been synthesized, but their utility is compromised by their slow onset / slow offset on isolated tissue preparations. There are many TP receptor antagonists, some of which are obviously analogues of PGH_2 / TxA_2, while others bear little structural resemblance to prostanoids. Heterogeneity in the affinities of TP antagonists has stimulated much debate about the existence of subtypes of TP receptor; however, species differences may account for much of the variation. On the other hand, there is now evidence for splice variance within TP receptors, and a resulting C-terminus extended form of the TP receptor has been shown to be particularly highly expressed in vascular endothelial cells. Simple TP receptor antagonists have found little use in cardiovascular disease; preventative treatment with low-dosage aspirin is sufficient to tip the balance away from thromboxane. Agents combining TP antagonism and Tx synthase inhibition (ridogrel) have shown more promise.

There is interest in the *isoprostanes*, a class of prostanoids that are not products of the enzyme cyclo-oxygenase, but are rather formed by direct oxidation of membrane phospholipids. The isoprostanes exhibit a wide range of biological actions, and most evidence suggests that they act at the same receptors as the 'classical' prostanoids. There is evidence, however, that 8-epi $PGF_{2\alpha}$ may act at a receptor that, although similar to a TP receptor, is not identical.

It has been proposed that *C1-ethanolamides of PGE2 and PGF2&alpha* and their analogues (e.g. bimatoprost) can activate prostamide receptors, which are distinct from the known prostanoid receptors.

Leucotriene (LT) and Lipoxin (ALX) receptors. Two receptors exist for both LTB_4 (BLT_1 and BLT_2) and the cysteinyl leukotrienes ($CysLT_1$ and $CysLT_2$). A

receptor that binds lipoxin, ALX, is identical to the fMLP-1 receptor; the nomenclature now reflects LXA_4, as a natural and potent ligand. The BLT_1 is expressed predominantly in leukocytes, thymus, and spleen, whereas BLT_2 (the low-affinity receptor for LTB_4) is found in spleen, leukocytes, ovary, liver, and intestine.

$CysLT_1$ is expressed in lung and intestinal smooth muscle, spleen, and peripheral blood leukocytes, wheares $CysLT_2$ is found in heart, spleen, peripheral blood leukocytes, adrenal medulla, and brain.

The CysLTs apparently prevail during allergic constriction of the airway. 5-LOX (lipoxygenase) influence on the level of eosinophils in airway and bronchial smooth muscle tone. From this it follows that the CysLTs receptors antagonists and inhibitors of 5-LOX are effective in the treatment in human asthma. As a rule, prostanoids promote acute inflammation notwithstanding the exceptions, such as PGE_2 which is an inhibitor of mast cells activation.

The ALX receptors are expressed in lung, peripheral blood leukocytes, and spleen. Responses to ALX receptor activation vary with cell type. AA release is stimulated in human neutrophils, whilst Ca^{2+} mobilization is blocked; in monocytes, LXA_4 stimulates Ca^{2+} mobilization.

Pharmacological effects. Prostanoids may *modulate local vascular smoth muscle tone* at the site of their formation and influence the systemic blood pressure through their renal function and tone of efferent arteriole. Reduction of the systemic blood pressure may cause reflex tachycardia. So, PGE_2, PGI_1, PGD_2 cause vasodilatation and reduce systemic blood pressure, whereas PGE_2 can elicit vasoconstriction via activation of EP_1 and EP_2. $PGF_{2\alpha}$ is a powerful constrictor of both pulmonary arteries and veins in humans.

TxA_2 is a powerful constrictor also. Infusion of PGs of E and F series increases cardiac output.

LTs can constrict or relax vascular smooth muscle tone, particularly in renal autoregulation, decrease the vascular volume and decrease cardiac contractility, reduce the coronary blood flow. At higher concentrations LTs can constrict arterioles and reduce exudation of plasma, and may promote the vascular smooth muscle proliferation. Epoxyeicosatrienoic acids (EET) elicit vasodilatation, especially in coronary circulation. Isoprostanes may constrict or dilate the vessels.

PGs also act on *smooth muscles in human internal organs* outside the vasculature. They can contract or relax the smooth muscles. LTs contract majority of smooth muscle and act predominantly on smooth muscles in the airways and are a thousand times more potent that histamine. LTs also stimulate bronchial mucus secretion and elicit mucosal edema. TxA_2, $PGF_{2\alpha}$, PGD_2 contract bronchial and tracheal muscles, in contrary, PGE_2, PGI_2 relax them. Approximately 10% of people have bronchospasm as a result of treatment with aspirin or others NSAIDs, but only non-selective inhibitors of COX and never - with selective inhibitors of COX-2, which indicates the involvement of COX-1 in this pathological process.

Action of PGs, prostacyclins on the *uterus muscles* depends on physiological conditions of women, so that phases of menstrual cycle, pregnancy and its absence,

and duration of gestation. So, the response of uterus muscles on PGs action increases with pregnancy progresses; sensitivity to the contractile response is the most apparent before menstruation, while relaxation - at the midcycle.

Longitudinal *muscles of GIT* are contracted by PGEs and PGFs. They also stimulate the movement of water and electrolytes into the intestinal lumen, that is the basis of watery diarrhea in case of their use, as well as oral and parenteral. As opposed PGI_2 does not cause this effect, moreover prevents that provoked by other PGEs. PG endoperoxides, TxA_2, PGI_2 have the same action, but less potent. Circular muscles of GIT are relaxed by PGE_2 and are contracted by $PGF_{2\alpha}$. LTs contract muscles of GIT. PGEs decrease transit time in the small intestine and colon. PGs induce diarrhea, cramps, reflux of bile, nausea and vomiting in oral introduction.

PGE_2 and PGI_2 manifest the *cytoprotective effect in the stomach*: reduce acid secretion and pepsin content, enchance mucus secretion, inhibit gastric damage and promote healing of duodenal and gastric ulcers.

The impact of PGE_2 on the *platelet aggregation* depends on its concentration: low concentration of PGE_2 increases platelet aggregation, and vice versa - high concentration of PGE_2 decreases platelet aggregation. Both PGI_2 and PGD_2 reduce platelet aggregation. Mature platelets express only COX-1, but immature platelet forms also express COX-2, although its role in platelet development and function has yet to be clarified. TxA2 is a major product of COX-1 in platelets, it induces platelet shape change and aggregation, but TxA2 action is restricted by its short T1/2 and by endogenuos inhibitors of platalet function, such as NO, PGI2 and others.

On the whole eicosanoids are involved in the *inflammatory and immune responses* in humans, as reflected by clinical use of the NSAIDs. Besides, LTs induce inflammation, lipoxins have anti-inflammatory effect, and prostanoids can cause both kind of activity. So, PGE_2 and PGI_2 are the prevalent pro-inflammatory prostanoids; TxA_2 can enhance platelet-leukocyte interaction; PGD_2 also promotes inflammation; PGE_2 and TxA_2 regulate apoptosis of immature thymocytes.

The *renal* prostanoids such as PGE_2, PGI_2, $PGF_{2\alpha}$, TxA_2 are synthesized largely in renal medulla, but in cortex layer too. PGE_2 and PGI_2 (COX-2-derivatives) increase medullary blood flow, renal blood flow, glomerular filtration due to their local vasodilatative effects, and inhibit sodium reabsorption. COX-1 derivatives promote salt excretion in the collecting ducts. On the other hand, the action of PGE_2 and PGI_2 lead to increased renin release, and, as a result, to sodium retention and increased blood pressure.

$PGF_{2\alpha}$ contracts the iris sphincter muscle and reduces intraocular pressure by increasing the aqueous humor outflow of the *eye* through the uveoscleral and trabecular meshwork pathway.

PGE_2 can cross BBB and act on thermosensitivity neurons in *CNS*. PGE_2 obviously is a mediator for endogenous and exogenous pyrogens into separate brain areas. Exogenous $PGF_{2\alpha}$ and PGI_2 promote fever but do not facilitate the pyretic response. PGD_2 and TxA_2 do not induce fever, besides PGD_2 also appears

to mediate an increase in extracellular adenosine that, in turn, facilitates induction of sleep. There is evidence that COX-2-derivative prostanoids are involved in several CNS degenerative disorders, however therapeutic effect of blocking their synthesis or action has to be studied.

PGs and LTs increase the sensitivity of nociceptors and potentiate *pain* receptors. PGE_2 and PGI_2 reduce the threshold to stimulation of nociceptors, causing so called "peripheral sensitization". Centrally, in the response to peripheral pain, COX-1 and COX-2 are expressed in the spinal cord and release PGs. PGs and LTs induce hyperalgesia and allodynia via increasing in pain transmission neuronal pathway in the spinal cord.

PGs also act on *endocrine tissues*. So, PGE_2 elevates the concentration of ACTH, GH, prolactin, gonadotropins, stimulates steroid production, insulin release, thyrotropin-like effects on the thyroid. PGE_2 induces oocyte maturation required for fertilization during and after ovulation.

PGs are powerful modulators of *bone metabolism*. The COX-1 is expressed in normal bone, whereas the COX-2 is expressed in inflammation and mechanical stress. PGE_2 induces bone formation due to increasing osteoblastogenesis, and PGE_2 activates bone resorption via activation of osteoclasts.

Eicosanoids, their inhibitors, agonists and antagonists of eicosanoid receptors have broad therapeutic applications. Inhibitors of eicosanoid biosynthesis and COX inhibitors are widely used as anti-inflammatory drugs. Low-dose aspirin is used for cardioprotection, LT antagonists are employed for treatment of asthma and aspirin-induced asthma, FP agonists are used in treatment of open-angle glaucoma, EP agonists are used to stimulate delivery and alleviate gastric irritation owing to application of tNSAIDs. In general, the therapeutic use of eicosanoids and their derivatives is limited because of the frequent and significant adverse effects and their short $T_{1/2}$. Notwithstanding these limitations, prostanoids are used in following conditions: therapeutic abortion (PGEs and PGFs: dinoprostone, carboprost tromethamine), for gastric cytoprotection (misoprostol), impotence (alprostadil), maintenance of patent ductus arteriosus (alprostadil), pulmonary hypertension (prostacyclin, epoprostenol, iloprost, treprostinil), glaucoma (latanoprost, bimatoprost, travoprost).

Table 14. Medicinal forms of the drugs of intermediated type

INN	Trade names	Medicinal forms	
Adenosine,	Adenocor	Parenteral solution for i/m, i/v injections in flacons;	0.006 g in 2 ml;
		in ampoules	1% -1 ml; 2 ml; 2% - 1 ml
Adenosine phosphate,	Phosphaden solution for injections Phosphaden Phosphaden tablets	Powder-substance; Tablets;	0.5; 0.25
Cytochrome C +	Oftan Catachrom	Eye drops in flacons;	0.675 mg + 1 mg +

Sodium succinate + Adenosine + Nicotinamide + Benzalkonium chloride,			2 mg + 20 mg + 40 mg - 10 ml
Calcium chloride + Magnesium chloride + Nicotinic acid + Adenosine	Vita-Iodunol	Eye drops in flacons-droppers	20 mg + 30 mg + 3 mg + 10 mg - 10 ml
Caffeine	Guaranin, Theinum	Powder; Parenteral solution for s/c injections in ampoules; Parenteral solution for subconjunctival injection;	 200 mg/1 ml; 100 mg/1 ml
	Coffein-benzoate sodium	Tablets;	0.1; 0.2;
Caffeine + ergotamine tartrat	Coffetaminum, Cofergot, Ergofein, Ergoffin	Tablets;	0.1 + 0.001
Theobromine	Theostene, Thesal	Powder; Tablets	 0.25
Theophylline	Afonylum, Aqualin, Asmafil, Diffumal, Durofilin, Uniler, Euphylong, Lanophyllin, Neotheopecum, Optiphyllin, Oralphyllin, Retafil, Slow-bid, Slow-Phylline, Ventax, Spophylline retard, Teo, Teodil, Teolix, Theobiolongum, Theocin, Theofin, Theopecum, Theophylline, Theostat, Theotard, Uni-dur, etc.	Powder; Suppositories	 0.2
Dopamine	Допамін, Допмін, Aprical, Cardiosteril, Dopamex, Dopastat, Dophan, Dopmin, Dynatra, Giludop, Hydroxytyra-Min, Inovan, Intropan, Intropin, Revivan, Rivimine, Dynatra	Parenteral solution for i/v injections in ampoules	0.5%, 1% - 2 ml; 2% - 10 ml; 4% - 5 ml

Ibopamine	Escandin	Tablets	0.05; 0.1
Bromocriptine	Aberginum, Bromergon, Bromocriptinum mesilat, Lactodel, Parlodel, Pravidel, Serocriptine	Tablets; Capsules	0.0025; 0.004; 0.01; 0.005; 0.01
Cabergolin	Dostinex	Tablets	0.0005
Quinagolide	Norprolac	Tablets	0.025 mg; 0.05 mg; 0.075 mg; 0.15 mg
Apomorphine	Apokyn, Ixense, Spontane, Uprima	Parenteral solution for s/c injections in ampoules; Gelatin capsules	1% - 1 ml; 0.01; 0.02; 0.03; 0.04; 0.06
Levodopa	Avodopa, Bendopa, Bio-dopa, Brocadopa, Caldopa, Madopan, Cicandopa, Dalutrin, Deadopa, Dopacin, Dopaflex, Dopal, Doparkin, Dopastral, Doprin, Eldopar, Eurodopa, Larodopa, L-Dopa, Levopa, Levopar, Medidopa, Oridopa, Pardopa, Parkidopa, Parmidin, Veldopa Speciadopa, Tonodopa, etc.	Tablets; Capsules	0.25; 0.5
Pergolide	Permax	Tablets	0.00005; 0.000025; 0.001
Ropinirole	Requip Modutab	Tablets	0.25 mg; 1 mg; 2 mg; 5 mg
Domperidone	Cilroton, Euciton, Motilak, Motilium, Nauseline, Nauzelin, Passagix, Peridal, etc.	Tablets; Suspension for per oral use in flacons	0.01; 0.1% - 200 ml
Pimozide	Opaп, Antalon, Norofen, Opiran, Oralep, Orap, Pimotid, Pirium	Tablets	0.001; 0.004
Metoclopramide	Apo-Metoclop, Cerucal, Cerulan, Clometol, Clopan, Comportan, Dibertil, Emetisan, Gastrobids, Gastrosil, Imperal, Klometol, Legir, Maxeran, Maxolon,	Tablets; Peroral solution in flacons; Aerosol for intranasal administration in vials; Parenteral solution for i/m, i/v injections in ampoules	0.005; 0.01; 0.1% - 30ml, 100ml, 200 ml; 20% - 2 ml; 40% - 4 ml; 0.5% - 2 ml

	Metoclol, Moriperan, Nausifar, Paspertin, Peraprin, Perinorm, Plastil, Pramin, Primperan, Primperil, Reglan, Regastrol, Rimetin, Reliverin, Terperan, Viscal, etc.		
Thiethylperazine	Thiethylperazini maleas, Thiethylperazine maleate, Torecan, Toresten, Tresten	Dragee; Rectal suppositories; Parenteral solution for i/m injections in ampoules	6.5 mg; 6.5 mg; 6.5 mg/1 ml - 0,65% - 1 ml
Haloperidol	Haldol, Aloperidin, Apo-Haloperidol, Halidol, Haloper, Halophen, Halopidol, Senorm, Seranase, Serenace, Trancodol, etc.	Tablets; Tablets-forte; Peroral solution; Parenteral solution for i/m, i/v injections in ampoules; Parenteral oil solution for i/m injections in ampoules	0.0005; 0.001; 0.0015; 0.002; 0.005; 0.01; 0.005; 0.2% - 10 ml; 0.5% - 1 ml; 5% - 1 ml
Perphenazine	Chlorpiprazin, Chlorpiprozine, Decentan, Fentazin, Neuropax, Trilifan, Perphenan, Trilafon, etc.	Tablets	0.004; 0.006; 0.01
Fluphenazine	Fluphenazine decanoate: Modecate, Prolixin Decanoate, Dapotum D, Anatensol, Fludecate, Sinqualone Deconoate; Fluphenazine enanthate: Dapotum Injektion, Flunanthate, Moditen Enanthate Injection, Sinqualone Enanthate; Fluphenazine hydrochloride: Prolixin, Permitil, Dapotum, Lyogen, Moditen, Omca, Sediten, Selecten, Sevinol, Sinqualone, Trancin flucate	Tablets; Dragee; Parenteral solution for i/m injections in ampoules	0.001; 0.0025; 0.005; 0.00025; 0.001; 0.0025; 0.005; 0.25% - 1 ml

Chlorpromazine	Thorazine, Ларгактил, Ampliactil, Amplictil, Chlorazin, Chlorpromanyl, Chlorpromazine, Contomin, Fenactil, Hibanil, Hibernal, Kloproman, Largactil, Megaphen, Promactil, Plegomazin, Propaphenin, etc.	Coated tablets for children; Dragee; Parenteral solution for i/m, i/v injections in ampoules	0.01; 0.025; 0.05; 2.5% - 1.0 ml, 2.0 ml, 5.0 ml, 10ml
Clozapine	Clazaril, Iprox, Lapenax, Lepotex, Fazaclo Leponex, Alemoxan	Tablets; Granules for peroral solution preparation in packages (for children); Parenteral solution for i/m, i/v injections in ampoules; Tablets	0.025; 0.1; 0.5; 1.0 2.5% - 2 ml 0.05
Aripiprazole	Abilify, Amdoal, Zylaksera	Tablets	0.005; 0.01; 0.015; 0.02; 0.03
Serotonin	Serotonin adipinate	Powder-substance; Parenteral solution for i/m, i/v injections in ampoules	 1% - 1 ml; 0.5% - 10 ml
Mexaminum	Mexaminum	Tablets	0.05
Melatonin	Eucalin, Melapur, Melatonum, Melaton, Melaxen, etc.	Tablets; Capsules; Powder-substance	0.003
Sumatriptan	Sumatriptan succinate Amigrenin, Imigran, Imitrex	Powder-substance Tablets Solution for i/m, i/v injections in syringes Aerosol for intranasal introduction	 0.05; 0.1; 1.2% - 0.5 ml; 10 mg, 20 mg/1 dose
Dihydroergotamine	Agit, Angionorm, Clavigrenin, Cornhidral; DH-Ergotamin, Diergotan, Dihydergot, Dihydroergotamine mesilate, Dihytamin, Ditamin, Migretil, Ergomimet, Ikaran, Ergovasan, Vasogin, Migrifen, Tonopress, Verteblan, etc.	Peroral solution in flacons; Peroral solution in flacons; Tablets; Aerosol for intranasal introduction	0,2% (2 mg in 1 ml - 20 drops) - 10 ml, 30 ml; 0,1% (1 mg) - 1 ml; 0.0025; 0.4%; 1%
Dihydroergotoxinum	Alkergot, Circanol, Clavor, DH-	Tablets; Peroral solution in	0.0015; 0.1% - 50 ml

	Ergotoxin, Erginemin, Ergocomb, Ergodibat, Ergohydrin, Ergoloid mesylat, Ergomed, Ergoxyl, Hyderan, Hydergin, Optamine, Trigot, Redergin, Redergot, Secamin, Secatoxin, Vasolax,etc.	flacons; Parenteral solution for i/m, i/v injections in ampoules	(50 mg); 0.03% - 1ml (0.3 mg)
Tropisetron	Navoban	Capsules; Parenteral solution for i/v injections in ampoules	0.005; 1 mg/1 ml - 5 ml
Naratriptan	Naramig	Tablets	0.0025
Pizotifen	Litec, Pizotylin, Sandolitec, Sandomigran, Sandomigrin, Sanmigran, Sanomigran	Tablets; Dragee	0.0005
Ketanserin	Perketal, Serefrex, Sufrexal, Sufroxal, Taseron	Tablets; Parenteral solution for i/m, i/v injections in ampoules	20 mg, 40 mg; 0.5 % - 2 ml, 10 ml
Urapidil	Ebrantil, Eupressyl	Capsules; Parenteral solution for i/v injections in ampoules	30 mg, 60 mg, 90 mg; 0,5% - 5 ml, 10 ml
Indoramin	Baratol, Doralese	Tablets	20 mg, 25 mg
Histamine	Eramin, Ergamine, Histalgine, Histamyl, Histapon, Imadyl, Imido, Istal, Peremin, etc.	Powder-substance; Parenteral solution for s/c injections in ampoules	0.1% - 1 ml
Diphenhydramine	Alledryl, Allergan, Allergin, Allergival, Amidryl, Benadryl, Benzhydraminum, Diabenyl, Dimedrolum, Dimedryl, Dimidril, Restamin, etc.	Tablets; Parenteral solution for i/m, i/v injections in ampoules; Rectal suppositories; Eye drops; Intranasal solution; Ointment	0.02; 0.025; 0.03; 0.05; 0.1; 1% - 1 ml; 0.01 0.5%; 3%-10%
Clemastine	Alagyl, Anhistan, Fenistil, Fumartin, Lecasol, Meclastin, Mecloprodine fumarate, Rekonin, Rivtagil, Tavegil,	Tablets; Parenteral solution for i/m, i/v injections in ampoules; Syrup in flacons	1 mg; 1 mg/1 ml - 2 ml; 0.67 mg/1 ml - 5 ml

	Tavist, etc.		
Promethazine	Allergan, Antiallersin, Atosil, Diprazinum, Fargan, Phenergan, Pipolphen, etc.	Parenteral solution for i/m, i/v injections in ampoules; Dragee; Tablets; Powder for injections in ampoules;	2.5% - 2 ml; 0.025; 0.05; 0.005; 0.01 0.05;
Paracetamol/ promethazine/ dextromethorphan;	Coldrex Nite	Syrup	1.0 + 20 mg + 15 mg - 20ml;
Pethidine/ promethazine;		Capsules; Parenteral solution for i/m injections in ampoules;	1 ml;
Guaifenesin + Ipecacuanha + promethazine	Prothiazine Expectorant	Syrup	5 mg + 45 mg + 10 mg - 5 ml
Sequifenadine	Sequifenadine hydrochloride, Bicarphen, Histafen	Tablets	0.05
Chloropyramine	Allergan S, Chlorneoantergan, Chloropyribenzamine h/cl., Chlortripelenamine h/cl., Halopyramine, Sinopen, Suprastin, Synopen	Tablets; Parenteral solution for i/m, i/v injections in ampoules	0.025; 2% - 1ml
Astemizole	Alermizol, Asmoval, Astelong, Astemisan, Hismanal, Histalong, Histamanal, Ifirab, Lembil, Mibiron, Stelert, Stemiz, Vagran	Tablets; Peroral suspension in flacons	0.01; 0.005; 0.001/1 ml - 50 ml, 100 ml
Acrivastatine	Semprex	Capsules	0.008
Dimetindene	Fenistil	Tablets retard; Peroral solution in flacons; Gel in tubes	0.0025, 0.004; 0.1% - 10 ml, 20 ml; 0.1% - 20.0, 30.0
Loratadine	Claritin, Clarotadinum, Klarisens, Lomilan, Loratin, Loridin	Tablets; Syrup in flacons; Peroral suspension in flacons	0.01; 0.001/1 ml -100 ml, 120 ml; 0.1% - 30 ml, 100ml
Mebhydrolin	Dialin, Diazolinum, Incidal, Mebhydrolinum Napadisylas, Omeril	Tablets; Dragee	0.1; 0.05, 0.1
Azelastine	Allergodil	Tablets; Intranasal spray in	0.002; 0.14 mg/1 dose -

		flacons Eye drops in flacons	10 ml; 0.05% - 6 ml, 10 ml
Qiufenadine	Phencarolum	Tablets	0.025
Terfenadine	Bronal, Caradonel, Daylert, Histadine, Rapidal, Riter, Seldane, Tamagon, Teridine, Termenadin, Thelladadan, Triludan, Tofrin, Toldan, Teridine, Termenadin, Thelldan, Triludan, Tofrin, Toldan, Trexyl, etc.	Tablets; Peroral suspension in flacons	0.06, 0.12; 0.6% - 30 mg/5 ml
Cyproheptadine	Adekin, Apetigen, Astonin, Cipractin, Cyprodin, Istabin, Pariactin, Peritol, Supersan, Vieldrin, Vinorex, etc.	Tablets; Syrup in flacons	0.004; 0.04% - 0.4 mg/1 ml – 100 ml
Fenspiride	Eurespal	Tablets; Syrup in flacons	0.08; 0.2% - 150 ml
Ebastine	Kestine	Tablets	0.01
Cetirizine	Alerza, Allertec, Cetirinax, Cetrine, Letizen, Parlazin, Reactine, Zetrinal, Zodac, Zyncet, Zyrtec, etc.	Tablets; Peroral solution in flacons	0.01; 1% - 10 ml, 20 ml
Desloratadine	NeoClarityn, Claramax, Clarinex, Larinex, Aerius, Dazit, Azomyr, Deselex, Delot	Powder-substance; Tablets; Syrup	0.005, 0.0025; 0.5 mg/1 ml - 60 ml, 120 ml;
Levocetirizine	Allear, Alcet , Cezera, Glencet, Seasonix, Suprastinex, Teczine, T-Day Syrup, Vozet, Zyxem, Zilola, Xaltec, Xozal, Xusal, Xyzal	Tablets; Peroral solution in flacons; Syrup	0.005; 5 mg/1 ml – 10 ml, 20 ml; 2.5 mg/5 ml
Fexofenadine	Allegra, Allerfex, Beksist-sanovel, Gifast, Dinox, Fexadin, Fexofast, Rapido, Telfast	Tablets; Capsules	0.03, 0.06, 0.12, 0.18; 0.12, 0.18;
Bamipine	Soventol	Gel in tubes	2% - 20.0
Cimetidine	Altramet, Belomet, Benomet, Cigamet, Cimesan, Histodyl, Primamet, Tagamet, Ulcometine, Ulcuzal,	Tablets; Tablets retard; Capsules; Syrup; Parenteral solution for	0.2, 0.3, 0.4; 0.35; 0.2, 0.3; 4% - 5 ml; 10% - 2 ml

	Zagastrol, etc.	i/m, i/v injections in ampoules	
Ranitidine	Acidex, Aciloc-E, Anistal, Gertocalm, Histac, Raniberl, Ranigast, Ranisan, Ranital, Ranitin, Rantac, Renx, Zantac, Zantin, Zoran, Ulcodin, Ulcosan, Ulran, etc.	Tablets; Parenteral solution for i/m, i/v injections in ampoules	0.075, 0.15, 0.2, 0.3; 1% - 5 ml, 10% - 2 ml
Famotidine	Acipep, Amifatidine, Antodine, Blokacid, Famocid, Famodar, Femocin, Fudon, Fluxid, Gaster, Gasterogen, Lecedil, Novafam, Pepcidine, Pepcid, Pepdul, Quamatel, Topcid, Ulceran, Ulfamid, etc.	Tablets; Powder for i/v injections in ampoules	0.02, 0.04; 0.02
Nizatidine	Axid	Capsules; Parenteral solution for i/v injections in ampoules	0.15, 0.3; 2.5% - 4ml
Roxatidine	Roxane	Tablets retard; Tablets forte	0.075; 0.15
Lafutidine	Stogar, Protecadin	Tablets	0.005
Ebrotidine	Ebrocit, Ebrodin, Ulsanic	Tablets	0.4
Dinoprost	Amoglandin, Enzaprost F, Minprostin $F_{2\alpha}$, Panacelan F, Prostaglan, Prostarmon, Prostarmon F, Prostin $F_{2\alpha}$	Parenteral solution in ampoules for i/v, intraamnial, extraamnial, intravaginal injections	0.5% - 1ml, 5 ml, 8 ml
Dinoprostone	Cerviprost, Enzaprost E, Medullin, Predinil, Prepidil, Prostarmon E, Prostin E_2	Parenteral solution for i/v injections in ampoules Vaginal gel Powder for injections in syringe	0.1%, 0.5% - 1ml 0.017%, 0.034%, 0.07% - 3ml 0.0005
Carboprost tromethamine	Hemabate, Tham	Parenteral solution in ampoules for i/m, intraamnial injections	250 mcg - 1 ml
Misoprostol Misoprostol + diclophenac sodium	Cytotec Artrotec	Tablets Tablets	0.2 mg 0.2 mg + 200 mg

Alprostadil	Alprostane, Caverject, Edex, Mews, Minprog, Prostadin, Prostavasin, Prostin VR, Vazaprostan	Powder for injections in ampoules (i/m, i/v) Powder for injections in flacons (i/m, i/v) Concentrate in ampoules (i/m, i/v) Urethral suppositories	0.01 mg, 0.02 mg 0.01 mg, 0.02 mg 0.05% - 0.2 ml 0.125 mg, 0.25 mg, 0.5 mg, 1mg
Epoprostenol	Flolan	Powder for injection in flacons (i/v)	500 mcg; 1.5 mg
Iloprost	Ventavis	By inhalation of nebulised solution	10 mcg/1 ml (initial dose 2.5 mcg)
Treprostinil	Remodulin, Tyvaso	Parenteral solution in flacons for s/c, i/v Solution for inhalations in ampoules	1.0 mg/1 ml -20 ml; 2.5 mg/1 ml - 20 ml; 5 mg/1 ml - 20 ml; 10 mg/1 ml - 20 ml; 2.9 ml (0.6 mg/1ml) - initial dose - 3 breaths of Tyvaso (18 mcg of treprostinil)
Latanoprost	Xalatan	Eye drops in flacons	0.005% - 2.5ml
Bimatoprost	Lumigan, Allergan, Ganfort	Eye drops in flacons Eye drops in flacons	100 mcg/1ml - 3ml; bimatoprost 300 mcg/1mL + timolol (as maleate) 5 mg/1ml
Travoprost	Travatan, Alcon DuoTrav	Eye drops in flacons Eye drops in flacons	40mcg/1ml; travoprost 40 mcg + timolol (as maleate) 5 mg/1 ml
Montelucast	Singular	Chewable tablets	5 mg
Zafirlucast	Accolate	Tablets	20 mg
Zileuton	Syflo	Tablets	0.3; 0.6
Ozagrel	Domenan	Tablets	0.1; 0.2

UNIT 3: DRUGS AFFECTING the AUTONOMIC NERVOUS SYSTEM

Chapter 4. Cholinergic agonists

Drugs that act on the cholinergic receptors are named **cholinergic drugs**. Mediator (neurotransmitter) of cholinergic nervous system is ***Acetylcholine (Ach).*** Synapse – is the place of primary pharmacological reaction ("butt") of synapse tropic drugs. Cholinergic synapse is constructed of presynaptic and postsynaptic structures between which is a synaptic cleft.There are cholinergic receptors on the postsynaptic membrane that are specific proteins with the spatial construction. Form of this complex complies with the principle of structural complementarity.

The *first step* of ***neurotransmission process in cholinergic neurons*** is synthesis of acetylcholine: choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form Ach. The *second step* of neurotransmission process in cholinergic neurons is storage of Ach in vesicles: Ach is contained in presynaptic vesicles together with adenosine triphosphate (ATP) and proteoglycan. The *third step* is release of Ach into the synaptic space. The *fourth step* is binding of Ach (after its diffusion across the synaptic space) to the postsynaptic receptors on the target cells or presynaptic receptors in the membrane of the neuron. This process leads to a biologic response within the cells like initiation of nerve impulse in a postganglionic fiber, activation of specific enzymes in effector cells as mediated by second-messenger molecules. The *fifth step* of neurotransmission process in cholinergic neurons is degradation of Ach: acetylcholinesterase (AchE) destroys Ach to choline and acetate in synaptic gap. The *sixth step* is recycling of choline: in the neuron choline is acetylated into Ach and is stored until released by a subsequent action potential.

There are postsynaptic Muscarinic (M-cholinoreceptors) and Nicotinic (N-cholinoreceptors) ***cholinergic receptors*** on the surface of the effector organs.

According to ***mechanism of action*** all agonists of cholinergic receptors (also called **cholinomimetics**) are divided into several groups: M-N-cholinomimetics, M-cholinomimetics, N-cholinomimetics, Anticholinesterases (reversible and irreversible).

Table 15. Places of location and effects* of activation of M-cholinoreceptors

Places of location	Effects of activation
CNS	excitement
Vegetative ganglions	improvement of nervous impulses transmission
Eye	-miosis, -reduction of intraocular pressure,

	-spasm of accommodation (the vision is established on proximate visibility)
Bronchi	increase of bronchial muscle tonus and bronchial glands secretion that lead to bronchospasm
Heart	cardiodepressive effect: reduction of heart contractility (negative inotropic effect); reduction of heart conductivity (negative dromotropic effect); bradycardia (negative chronotropic effect)
GIT	increase of smooth muscle tonus of walls and reducing of sphincter tonus that lead to diarrhea, abdominal pain
Gall bladder	increase of smooth muscle tonus of walls and reducing of sphincter tonus
Urinary bladder	increase of smooth muscle tonus of walls and reducing of sphincter tonus that lead to frequent uresis/urinary incontinence
Uterus	increase of smooth muscle tonus
Smooth muscle of vessels	reducing of smooth muscle tonus of vessels that lead to vasodilatation
Exocrine glands: salivary, gastric, intestinal, lachrymal, sweat, bronchial	increase of glands secretion

* - effects of activation of M-cholinoreceptors there are pharmacologic effects of M-cholinergic agonists, both direct and indirect action.

Table 16. Places of location and effects* of activation of N-cholinoreceptors

Places of location	**Effects of activation**
Posterior lobe of pituitary	increase of secretion of antidiuretic hormone (ADH) that lead to edema (anasarca)
Vegetative ganglions	improvement of nervous impulses transmission
Carotid sinus	stimulation of chemoreceptors and in this way stimulation of respiratory center and vasomotor center that lead to intensification of breathing and blood circulation
Cerebral layer of adrenal gland	increase of epinephrine secretion, as a result increase of the blood pressure and acceleration of the heart rate
Skeletal muscles	improvement of neuromuscular transmission

* - effects of activation ofN-cholinoreceptors are pharmacologic effects of N-cholinergic agonists.

Classification of Cholinergic agonists: Cholinomimetics, Anticholinesterases and Reactivators of cholinesterase

M-, N- cholinomimetics

Acetylcholine
Carbachol

M- cholinomimetics

Pilocarpine
Aceclidine
Cisapride

N- cholinomimetics

Lobeline
Cytisin

Anticholinesterases

reversible:

tertiary amines:

Physostigmine
Galanthamine

quaternary amines:

Neostigmine methylsulfate
Pyridostigmine bromide
Ambenonium chloride
Distigmine bromide

- irreversible:

Arminum

- ***Reactivators of Cholinesterase***

Trimedoxime bromide
Alloximum
Izonitrozinum
Diaethyximum

Mechanism of action of direct cholinergic agonists (also called **cholinomimetics).** Cholinergic agonists mimic the effects of Ach by binding directly to cholinergic receptors. The direct-action cholinergic drugs have longer duration of action than acetylcholine.

Mechanism of action of indirect cholinergic agonists (reversible anticholinesterases). Indirect cholinergic agonists (reversible anticholinesterases) are inhibitors of AchE that prolong lifetime of Ach, improve the accumulation of Ach in the synaptic space and cause cholinomimetic effects in the body. As a result these drugs provoke stimulation of both muscarinic and nicotinic receptors in the effector organs. In accordance with the chemical structure there are *tertiary amines* and *quaternary amines.* The tertiary amines overcome the BBB and they are

effective in patients with patology of CNS. The quaternary amines can not get over the BBB and are used in case of violations of peripheral cholinergic innervation.

Mechanism of action of indirect cholinergic agonists (irreversible anticholinesterases). The indirect cholinergic agonists (irreversible anticholinesterases) are the organophosphate compounds. It can bind covalently to AchE that lead to long-term increase in Ach in cholinergic synapses. Many of these remedies are extremely toxic and are used as nerve agents in military purposes or as insecticides.

Mechanism of action of reactivators of acetylcholinesterase. These drugs can reactivate inhibited AchE and use as antidotes for irreversible anticholinesterases.

Pharmacologic characteristic of Cholinergic agonists

Indications for M-cholinomimetics use:

Pilocarpine:

Glaucoma

Trombosis of central vien of retina, acute retinal artery occlusion, optic atrophy to improve the eye trophic

Xerostomia (dry oral mucosa)

Systemic effect of the drug is not used because of its high toxycity. The most dangerous manifestation of pilocarpine poisoning is pulmonary edema.

Aceclidine:

Glaucoma

Atonia of intestine, gall bladder, urinary bladder, uterus

Uterus blood bleeding after delivery

To accelerate the peristalsis in the digestive tract in case of X-ray examination

Cisapride:

Reflux-ezophagit

Atony of GIT, gall bladder, urinary bladder, uterus

To accelerate the peristalsis in the digestive tract in case of X-ray examination

Adverse effects of M-cholinomimetics:

Miosis

Spasm of accommodation

Bradycardia, blockage of heart, arterial hypotension

Bronchospasm

- Intestine spasm abdominal pain, diarrhea/fecal incontinence/encopresis

Hypersalivation, sweating

Frequent uresis/ urinary incontinence

Convulsion (cramps)

Contraindications for M-cholinomimetics use:

- Bronchial asthma, obstructive bronchinis

Angina pectoris (IHD)
Atherosclerosis
Organic heart lesions, conduction disturbances in the myocardium
Malfunction of liver and kidney
Epilepsy
Hyperkinesias, Parkinson disease
Pregnancy
Inflammatory process in abdominal cavity

Acute poisoning with drugs with M-cholinomimetic effect may occur when they overdose or when using fungi of the genus *Inocybe*, fly agaric *(Amanita)* – they contain a toxic substance muscarine. Diarrhea, abdominal pain, constriction of the pupils, salivation, bronchospasm, confusion, convulsions, and coma are developed in the patient. Medical care in such poisoning is gastric lavage and administration of physiological antagonists: drugs with M-cholinolytic action – atropine sulfate, and – symptomatic treatment.

Indications for N-cholinomimetics use:

In current clinical practice, they are used very rarely, more often – in experimental pharmacology.

Depress of respiratory center – respiratory arrest of reflex origin, namely due to the inhalation of irritating substances in injuries, electric shock, surgical operation, morphine poisoning, carbon monoxide poisoning (cytitone – 0.15% solution of cytisine, or 1% solution of lobeline)

Shock, collapse, impairment of blood circulation and respiration in patients with infection diseases (cytitone as a drug that can increase BP through reflex excitation of vasomotor center, stimulation of sympathetic ganglia and adrenal medulla

Smoking (tablets “Tabex” and “Lobesilum”): in recent years, N-cholinomimetics are used as aids to relieve withdrawal symptoms in case of failure of tobacco

Adverse effects of N-cholinomimetics:

in case of quick injection:
Respiratory standstill
Disturbances in heart muscle conductivity
Arterial hypotension

in case of orally administration:
Weakness
Dizziness
Nausea
Headache

Contraindications for N-cholinomimetics use:

in case of orally administration:
Blood circulation insufficiency
Arterial hypertension

Bleeding, intensification of ulcerative disease

in case of intravenous administration:

Bleeding
Pulmonary edema
Pneumothorax
Rib's ruptures
Fibrocavernous tuberculosis
Lesions of cardiovascular system
Foreign bodies in trachea and bronchi
Full depression of respiratory center

Indications for Anticholinesterases use:

Glaucoma (except for Galanthamine that can cause edema of conjunctiva
Intestine and urine bladder atony after surgical operation (appropriate to appoint quaternary amines*:* Neostigmine methylsulfate, Pyridostigmine bromide, Ambenonium chloride, Distigmine bromide; they can not overcome BBB)
Myasthenia
Paresis, paralysis, polyneuritis
Muscle paralysis associated with dysfunction of the brain and spinal cord (appropriate to appoint tertiary amines: Physostigmine, Galanthamine; they overcome BBB)
For the activation of mental (cognitive) function in Alzheimer's disease (tertiary amines: Physostigmine, Galanthamine)
Antidotes in case of overdoses by Nondepolarizing Myorelaxants and M-cholinoblockers (the most frequently Neostigmine methylsulfate is used as a drug of peripheral and short action)
Xerostomia (in dental practice)

Adverse effects of Anticholinesterases:

Miosis
Spasm of accommodation

in case of system action:

Bradycardia, heart blockages, arterial hypotension
Bronchospasm
Spasm of intestine, abdominal pain, diarrhea/ fecal incontinence/encopresis
Hypersalivation, sweating
Frequent uresis/ urinary incontinence
Convulsion (cramps)

Contraindications for Anticholinesterases use:

Epilepsy
Hyperkinesias
Bronchial asthma, obstructive bronchinis
Angina pectoris (IHD)
Bradycardia

Reactivators of cholinesterase are used in case of poisoning by irreversible anticholinesterases.

Table 17. Medicinal forms of Cholinergic agonists, Anticholinesterases, Reactivators of cholinesterase

INN	Trade names	Medicinal forms	
Acetylcholine	Acetylcholine chloride	Powder in ampoules	0.1; 0.2
Carbachol	Carbacholine, Isopto carbachol, Oftan carbachol, Secretin, Carbachol, Carbaminoylcholine Carbamiotin, Carcholin, Doryl, Duracholine, Enterotonin, Glaucomil, Jestril, Lentin, Moryl, Tonocholin, etc.	Eye drops; Eye drops (Carbacel, Isopto carbachol); Powder/tablets Parenteral solution (i/v, i/m, sub skin) in ampoules	0.5%; 1%; - 5 ml 0.75 %; 1.5 %; 2.25 %, 3 % - 5 ml 0,001 0.01%; 0.025% - 1 ml
Pilocarpine	Isopto-carpine, Pilocarpinum hydrochloridum, Oftan Pilocarpine, Pilocar, Pilogel, Pilocarpine optifilm, Pilocarpine-long, Humacaprine, Salagen	Eye drops: in containers, flacons, in tube-droppers, in flacons; Eye ointment in tubes Eye ointment in containers; Water solution in flacons; Eye films; Eye gel (Pilogel) in tubes; Tablets (Salagen)	1%; 2%; 4% - 0.5 ml; 10 ml 1% - 1.5 ml 1%; 6% - 5 ml 1%; 2%; 4% - 5.0 1%; 2%; 4% - 5 ml 1% - 5 ml 0.0027 4% - 5.0 0,005
Aceclidine	Aceclidine, Glaudin, Glaunorm, Glaucostat	Parenteral solution (subskin) in ampoules Eye ointment; Powder for eye drops: Eye drops (extemporal solutions)	0.2% 1ml 3%; 5% - 20.0 2%; 3%; 5%
Cisapride	Coordinax, Peristil, Cisapro, Cisap, Cisapid, Prepulsid	Tablets; Suspension per oral in flacons; Parenteral solution in ampoules	0.005; 0.01 0.1% - 60ml; 100ml 0.2%; 0.5% - 2 ml
Lobeline	Lobeline hydrochloride, **Lobesil**, Antisol, Atmulatin, Bantron, Lobatox, Lobeton, Lobidan, etc.	Parenteral solution (i/v, i/m) in tube-syringes, in ampoules Tablets	1% -1 ml 0.002

Cytisin	Cytitone **Tabex**, Cypercuten TTS, Cytisin films	Water solution in ampoules (i/v, i/m); Tablets; Transdermal therapeutic systems (TTS); Films bonded to the gum	0.15% - 1ml 0.0015 125 mg/30 sq. cm 0.0015
Physostigmine	Physostigmine salicylate, Eserine salicylas, Physostigminum salicylicum	Powder	
Galanthamine	Galanthamine hydrobromide, Nivalin, Reminyl	Powder Parenteral solution (sub skin) Peroral solution Tablets	 0.1%, 0.25%, 0.5%, 1% - 1 ml 0.4% - 100 ml 0.004; 0.008; 0.012
Neostigmine methylsulfate	Proserinum	Powder Parenteral solution in ampoules (s/c, i/v, i/m) Proserin granules for children Tablets	 0.05% - 1ml 60.0 0.015
Pyridostigmine bromide	Kalymin 60 N, Kalimin forte, Mestinon	Tablets Parenteral solution in ampoules (s/c, i/v, i/m) Tablets Dragee	0.06 0.5% - 1ml 0.01; 0.06
Ambenonlum chloride	Oxazylum	Powder Tablets	 0.001; 0.005; 0.01
Distigmine bromide	Hexamarium bromide, Ubretid, Ubritil	Tablets; Parenteral solution in ampoules (i/m)	0.005; 0.1% - 1 ml
Arminum	Arminum	Eye drops	0.005%; 0,01% - 10 ml
Trimedoxine bromide	Dipyroximum	Powder Parenteral solution in ampoules (i/v)	 15% - 1 ml
Alloximum	Alloximum	Powder for injections in ampoules (i/m)	0.075
Izonitrozinum	Izonitrozinum	Parenteral solution in ampoules (i/v, i/m)	40% - 3 ml
Diaethyximum	Diaethyximum	Parenteral solution in ampoules (i/m)	10% - 5 ml

Chapter 5. Cholinergic antagonists

Cholinergic antagonists (also called **cholinergic blockers, anticholinergic drugs, parasympatholytics)** bind to cholinergic receptors and block transmission of nerve impulse in parasympathetic autonomic nervous system**.** One group of these drugs blocks M-cholinoreceptors. A second group of these drugs blocks N-cholinoreceptors. There are Ganglioblockers and Myorelaxants (neuromuscular blocking drugs).

Mechanism of action of Ganglionic blockers. Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia.

Mechanism of action of Myorelaxants *(Depolarizing drugs, Nondepolarizing drugs* and *drugs of mixed action)*. *Depolarizing (leptocurare) drugs* connect with N-cholinoreceptors and act similar as Ach, but unlike Ach *Depolarizing drugs* cause stable depolarization of N-cholinoreceptors because of they aren't instantly destroyed by AchE like Ach. As a result, Depolarizing drugs persist at high concentrations in the synaptic gap, remain bound with N-cholinoreceptors for a relatively longer time and provide a constant stimulation of N-cholinoreceptors. This renders the receptor incapable to transmit further nerves impulse. Thus the nerves impulse transmission in skeleton muscles is stopped. The duration of action of Depolarizing agent depend on diffusion to plasma and hydrolysis by plasma cholinesterase. Clearly that Depolarizing drugs haven't antidotes.

Nondepolarizing (pahycurare) drugs interact with N-cholinoreceptors to prevent the binding of acetylcholine, in this way decrease the sensitivity of N-cholinoreceptors to Ach that lead to prevent depolarization of muscle cell membranes and inhibit muscular contraction. As *Nondepolarizing drugs* compete with Ach at the receptors and don't activate them, they are named competitive blockers. Their effects can be overcome by increasing concentration of Ach in the synaptic gap. It follows that, antidotes of Nondepolarizing drugs are reversible anticholinesterases - inhibitors of cholinesterase in the synaptic gap.

Myorelaxants of mixed action in the first phase cause depolarization of N-cholinoreceptors and in the second phase act as Nondepolarizing drugs. In case of overdose can use reversible anticholinesterases.

Muscle relaxation under the influence of ***Myorelaxants*** is as follows: fingers, toes, eyes, extremities, head, neck, trunk, intercostal muscles, diaphragm, and as a result – respiratory arrest. Restoration of muscle tone is in reverse.

Table 18. Places of location and effects* of blockage of M-cholinoceptors

Places of location	Effects of blockage
CNS	depression
Vegetative ganglions	deceleration of nervous impulses transmission
Eye	-mydriasis, -increasing of intraocular pressure, -paralysis of accommodation (the vision is established on distal visibility)
Bronchi	reducing of bronchial muscle tonus and bronchial glands secretion that lead to bronchodilatation
Heart	Cardiopositive effects: increase of heart contractility (positive inotropic efferct); increase of heart conductivity (positive dromotropic efferct); tachycardia (positive chronotropic effect); increase of heart excitability (positive batmotropic efferct)
GIT	reducing of smooth muscle tonus of walls and increase of sphincter tonus that lead to atonia of GIT and constipation
Gall bladder	reducing of smooth muscle tonus of walls and increase of sphincter tonus that lead to retention of gall
Urinary bladder	reducing of smooth muscle tonus of walls and increase of sphincter tonus that lead to urine retention/ischuria
Uterus	reducing of smooth muscle tonus
Exocrine glands: bronchial, salivary, gastric, intestinal, lachrymal, sweat	oppression of glands secretion that lead to dryness of mucous (xerosis)

* - effects of blockage of M-cholinoceptors are the pharmacologic effects of M-cholinergic antagonists.

Table 19. Places of location and effects* of blockage of N-cholinoreceptors

Places of location	Effects of blockage
Posterior lobe of pituitary	reducing of secretion of antidiuretic hormone (ADH)
Vegetative ganglions	deceleration of nervous impulses transmission in parasympathetic and sympathetic ganglions
Carotid sinus	reducing of activity of respiratory center and vasomotor center that lead to respiratory center paralysis (stop of breath), dilatation of the vessels and hypotension
Cerebral layer of adrenal gland	reducing of secretion of epinephrine reducing of the blood pressure (hypotension) and deceleration of the heart rate (bradycardia)
Skeletal muscles	deceleration of neuromuscular transmission

- effects of blockage of N-cholinoceptors there are the pharmacologic effects of N-cholinergic antagonists.

Classification of antagonists of cholinergic receptors

M-, N- cholinoblockers (central blocking agents)

Trihexyphenidyl
Benactyzine
tertiary amines: Adiphenine
Aprophene
Arpenalum

M-cholinoblockers

plant origin:

Atropine
Platyphylline
Scopolamine
Homatropine hydrobromide
Atropa Belladonna medications: Extract/Tincture Belladonnae; Besalolum; Bepasalum; Bethiolum; Anusolum; Bellaspon; Bellastesin; Belalginum

synthetics:

- *quarterly amines (peripheral action):* Metocinium iodide
Hyoscine butylbromide
Ipratropium bromide
Pirenzepine
Tropicamide
Tiotropium bromide
Troventolum

- ***N-cholinoblockers:***

Ganglioblockers:

tertiary amines (central action): Pempidine
Pachycarpine hydroiodide
quarterly amines (peripheral action): Hexamethonii benzosulfonas
Azamethonium bromide
Trepirium iodide
Dimecolinum

- ***N- cholinoblockers:***

Myorelaxants (neuromuscular blocking drugs):

1) Depolarizing (leptocurare)

Suxametonium chloride, Succinylcholine

2) Nondepolarizing (pahycurare)

Tubocurarine chloride
Pancuronium bromide
Pipecuronium bromide
Mellictinum
Atracurium besilate
Vecuronium bromide

3) Mixed

Dioxonium

Myorelaxants (neuromuscular blocking drugs):

Shot action (duration is 5-7 minutes): Suxametonium chloride

Middle action (duration is up to 40 minutes): Atracurium besilate
Vecuronium bromide

• *Long action (duration is more than 40 minutes):* Tubocurarine chloride
Pancuronium bromide
Pipecuronium bromide

Pharmacologic characteristic of Cholinergic antagonists

Indications for M-,N-cholinoblockers use:

Parkinson disease/syndrome
Biliary colic, intestinal colic, stomach/duodenum ulcer disease, renal colic, liver colic (abdominal pain)
Endarteritis
Neuritis
Premedication in patients with spasm of the smooth muscles
Examination of eyeground (eye bottom/ocular fundus)
Dry cough (oppresses the cough reflex)

Adverse effects of M-,N-cholinoblockers:

Depression of CNS
Mydriasis
Increasing of intra-ocular pressure
Paralysis of accommodation (the vision is established on distal visibility) – cycloplegia
Tachycardia, extrasystoles
Constipation
Dysfunction of the gall bladder
Urinary retention

Contraindications for M-, N-cholinoblockers use:

Glaucoma
Organic heart diseases with tachycardia, extrasystoles
Atherosclerosis
Acute kidney and liver insufficiency
Hypertrophy of prostate

Indications for M-cholinoblockers use:

Eye bottom (fundus of the eye, eyeground) examination
Glasses selection
Acute infections in iris of the eye, cornea and tissues in the eye for medicinal immobilization

Trauma of the eye (for medicinal immobilization of the eye)
Spasm of smooth muscles of the internal organs (biliary colic, intestinal colic, stomach/duodenum ulcer disease, renal colic, liver colic – abdominal pain)
Hemorrhoids
Anal fissures
Cystitis
Nocturnal enuresis (incontinence of urine, nocturia, nocturnal urinary incontinence)
Bronchospasm
Spasm of the vessels in patients with arterial hypertension or IHD *(platyphylline)*
Spasm of the brain vessels
Migraine
Atrioventricular block in the heart
Premedication
Vestibular disorders

Adverse effects of M-cholinoblockers:

Mydriasis
Cycloplegia – paralysis of accommodation (the vision is established on distal visibility)
Depression of exocrine gland secretion (xerosis) – xerophtalmus, xeroderma, xeromycteria, xerostomia, decreasing of viscosity of sputum, hoarseness (of voice), fever
Ischuria (retention of urine)
Peripheral vessels dilatation
Arterial hypotension
Oppression/Excitement of CNS
Paralysis of breath
Increasing of intra-ocular pressure
Constipation

Contraindications for M-cholinoblockers use:

Glaucoma
Organic heart diseases with tachycardia, extrasystoles
Atherosclerosis
Acute kidney and liver insufficiency
Hypertrophy of prostate
Intestine atony

Indications for Ganglioblockers use:

Control of arterial hypotension during surgical operation
Enforcement of contractile ability of myometrium *(pachycarpine hydroiodide)*
Spasm of peripheral vessels

Hypertensive crisis
Pulmonary edema
Brain edema
Ganglionitis
Ulcerative diseases of stomach and/or duodenum

Adverse effects of Ganglioblokcers:

Orthostatic (postural) hypotension
Tachycardia
Constipation
Meteorism (distension)
Xerophthalmus
Cycloplegia (paralysis of eye accommodation)
Mental disorders
Tremor
Increase of intra-ocular pressure

Contraindications for Ganglioblockers use:

Glaucoma
Arterial hypotension
Atherosclerosis
Myocardial infarction/IHD
Cerebral insult
Pheochromocytoma
Renal and liver insufficiency

In the 50 - 60 years of the last century ganglionic blockers were the first effective drugs for the treatment of hypertension. But according to the role of ganglionic parasympathetic and sympathetic nervous transmission and support regarding the hypotensive effect of ganglionic numerous negative side effects in clinical practice greatly limited their use.

Indications for Myorelaxants use:

For relax of skeleton muscles during different surgical operations
Reposition of broke bones
Set a bone
Tetanus

In anesthesiological practice *Nondepolarizing (pahycurare) muscle relaxants* are used for prolonged muscular relaxation, while *Depolarizing (leptocurare) muscle relaxants* – are used for short-term muscular relaxation.

Adverse effects of Myorelaxants:

Weakening of a diaphragm
Arterial hypotension, collapse
Micro trauma and pain in muscles after surgical operation
Hypertermia (inherent in patients with congenital structural myopathy – a disease of the central rod)
Long apnea

Hyperkalemia
Anaphylaxis (rarely)

The peculiarity of the pharmacological effects of muscle relaxants is their ability to increase histamine release, which causes side effects such as prolonged apnea, anaphylaxis, cardio-vascular collapse. In addition, there are conditions that contribute to the emergence of side effects of muscle relaxants: a change in body temperature; electrolyte imbalance, particularly with respect to potassium content, as well as muscle relaxants may displace potassium from the cells (succinylcholine-induced hyperkalemia can be life-threatening); low level of butyrylcholinesterase (genetic defect, prior appointment anticholinesterase drugs, delivery with food organophosphorus compounds, pregnancy, liver disease), leading to a decrease in the rate of biotransformation of succinylcholine (lengthens the duration of its action and, consequently, the intercostal muscle relaxation and apnea duration), presence of patients with latent myasthenia gravis or malignant disease, such as small cell lung carcinoma with myasthenic syndrome of Eaton-Lambert; decrease in blood flow to skeletal muscles, which results in slower elimination of muscle relaxants, besides a violation of hepatic function (for vecuronium), renal function (for pancuronium) leads to slower elimination of muscle relaxants also.

Contraindications for Myorelaxants use:

Allergy
Myasthenia
Respiratory failure
Heart failure
Renal and/or liver failure
Disturbances of electrolyte balance (especially hyperkalemia)

Table 20. Medicinal forms of Cholinergic antagonists: M-N-cholinoblockers, M-cholinoblockers, Ganglioblockers and Myorelaxants

INN	Trade names	Medicinal forms	
Trihexyphenidyl	Cyclodolum, anti-Spas, Antitrem, Aparkan, Atrane, Apo-Trihex, Parkopan, Peragit, Pipanol, Tremin, Trixyl, Trifen, etc.	Tablets	0.001; 0.002; 0.005
Benactyzine	Actozine, Amitakon, Amizylum, Benactina, Benactyzinum, Cafron, Cevanol, Lucidil, Nervatil, Neurobenzile, Parasan, Phobex, Procalm, Suavitil, Tranquilline, etc.	Powder for eye drops (extemporal solution); Tablets	1%; 2% 0.001; 0.002

Adiphenine	Spasmolytin, Trasentin, Vagospasmyl, Vegavthin	Powder	
Aprofene	Aprofene, Aprophenum	Tablets; Parenteral solution in ampoules (s/c, i/m)	0.025 1% - 1ml
Arpenalum	Arpenalum	Tablets	0.05
Atropine	Atropinum, Atropine sulfate, Atromed	Powder; Parenteral solution in ampoules (s/c, i/v, i/m); Parenteral solution in tube-syringes; Peroral solution in flacons; Tablets; Eye drops in flacon-droppers; Eye ointment; Eye films	 0.05%; 0.1% - 1 ml 0.1% - 1 ml 0.1% - 10 ml 0.0005 1% - 5 ml; 10 ml; 15 ml; 20 ml; 30 ml 1% 0.0016
Tropicamide	Mydriacyl, Mydrum, Midriatikum-Stulln PU	Eye drops in flacon-droppers; Eye drops in flacon	0.5% - 10 ml; 0.5%, 1% - 10 ml
Platyphylline	Platyphylline-Ferein, Platyphylline-Darnitsa, Platyphylline hydrotartrate, Platyphylline hydrotartrate 0.2% Leciva-Geo, Platyphylline hydrotartrate solution for injections 0.2%, Platyphylline hydrotartrate tablets 0.005 g Thepaphyllinum, Platyphyllinum Palufinum	Powder; Tablets; Parenteral solution in ampoules; Peroral solution (extemporal); Solutio for microclysters (extemporal); Rectal suppositories; Tablets (Platyphylline hydrotartrate 0.003; Phenabarbital 0.03; Papaverine hydrochloride 0.03) Tablets (Platyphylline hydrotartrate 0.005; Phenabarbital 0.02, Papaverine hydrochloride 0.02)	 0.005 0.2% - 1 ml 0.5% 0.5%; 1% 0.01
Scopolamine	Hyoscini hydrobromidum, Scopolaminum hydrobromicum	Powder; Parenteral solution in ampoules (s/c);	 0.05% - 1 ml

	Scopolaminum hydrobromicum cum methylcelluloso Aeronum	Eye drops; Eye ointment; Transdermal therapeutic systems (TTS); Solution in flacons; Tablets	0.25% 0.25% 0.25% -5 ml; 10 ml scopolamine camphoric acid 0.0001 cum hyoscyamine camphoric acid 0.0004
Homatropine hydrobromide	Homatropinum hydrobromidum	Powder; Eye drops in flacons	 0.25% - 5 ml
Extract of Belladonnae siccum	Extractum Belladonnae siccum	Extract	0.015
Tincture of Belladonnae	Tinctura Belladonnae	Tincture	10 ml
Extract of Belladonnae + Phenyl salicylate	Besalolum	Tablets	Extractum Belladonnae 0.01 + Phenyl salicylate 0.3
Phenyl salicylate + Papaverinum h/cl. + Extractum Belladonnae	Bepasalum	Tablets	Phenyl salicylate (salol) 0.3 + Papaverinum h/cl. 0.03 + Extractum Belladonnae 0.012
Extract of Belladonnae + Ichthyol	Bethiolum	Rectal suppositories	Extractum Belladonnae 0.015 + Ichthyol 0.2
Extract of Belladonnae + Xeroformium + Zinc sulfate + Glycerol	Anusolum	Rectal suppositories	Extractum Belladonnae 0.02 + Xeroformium 0.1 + Zinc sulfate 0.05 + Glycerol 0.12
Phenobarbital + Ergotamine tartrate + Belladonnae alkaloids	Bellaspon	Tablets	Phenobarbital 0.02 + Ergotamine tartrate 0.0003 + Belladonnae alkaloids 0.0001
Belladonnae extract + Benzocaine	Bellastesinum	Tablets	Belladonnae extract 0.015 + Benzocaine 0.3
Metamizole sodium + Benzocaine + Belladonna extract + Sodium hydrocarbonate	Bellalginum	Tablets	Metamizole sodium 0.25 + Benzocaine 0.25 + Belladonna extract 0.015+Sodium hydrocarbonate 0.1

iodide	Methacinum	Tablets; Parenteral solution (s/c, i/m, i/v)	0.002 0.1% - 1 ml
Hyoscine butylbromide, Butylscopolamine	Butylscopolamini bromidum, Buscolysin, Buscopin, Buscopan, Buscoridin, Hyoscine-N-butylbromide, Spanil, Spasmalexin, Tirantil, Toscopan	Dragee; Rectal suppositories; Parenteral solution (s/c, i/m, i/v)	0.01 0.01 2% 1 ml
Ipratropium bromide	Atrovent, Arutropid, Itrop, Normosecretol, Vagos	Aerosol in balloon; Solution for inhalation in flacons; Powder for inhalation in capsules; Parenteral solution in ampoules (i/v)	15 ml 0.025% - 20 ml 0.005 0.0005 mg/1 ml
Tiotropium bromide	Spiriva, Tiova	Capsules with specific HandiHaler inhaler	18 mg
Pirenzepine	Abrinac, Bisvanil, Duogestral, Gastril, Gastrol, Gastrozepin, Gastromen, Gastropin, Gastropiren, Gastrozem, Leblon, Pirehexal, Piren, Pirigast, Ulcepin, Ulcin, etc	Tablets; Parenteral solution (i/m, i/v) in ampoules	0.025; 0.05 0.5% - 2 ml
Pempidine	Pirilenum	Powder; Tablets	 0.005
Pachycarpine hydroiodide	Pachycarpine hydroiodide	Powder; Tablets; Parenteral solution in ampoules (s/c, i/m)	 0,1 3% - 2 ml
Hexamethonii benzosulfonas	Benzohexonium, Hexonium, Bistrium, Gangliostat, Hexameton, Hexanium, Hexathide, Hiohex, Methobromin, Methonium, Vegolysen, etc.	Tablets; Parenteral solution in ampoules (s/c, i/v, i/m)	0,1 2,5% - 1ml
Azamethonium bromide	Pendiomid, Pentamethazene, Pentaminum	Parenteral solution in ampoules (i/v, i/m)	5% - 1 ml; 2 ml
Dimecolinum	Dimecolonium iodide	Tablets	0.025; 0.05
Trepirium iodide	Hygronium	Powder for injection in flacons (i/v)	0,1

Suxametonium chloride, Succinylcholine	Dithyllinum, Anectine, Quelicin	Parenteral solution in ampoules (i/v, i/m)	2% - 5 ml; 10 ml
Tubocurarine chloride	Amelizol, Tubadil,Curadetensin, Curarin, Delacurarine, Myostatine, Myricin, Tubaril, Tubarine, Tubocuran, etc.	Parenteral solution in ampoules (i/v)	1% - 1ml
Pancuronium bromide	Pavulon	Parenteral solution in ampoules (i/v)	0.2% - 2 ml
Pipecuronium bromide	Arduan, Pipecurium bromide	Powder for injection in ampoules (i/v)	0.004
Mellictinum		Tablets	0.02
Atracurium besilate	Tracrium	Parenteral solution in ampoules (i/v)	1% - 2.5; 5 ml
Atracurium chloride	Alloferin	Parenteral solution in ampoules (i/v)	0.5% - 2 ml
Vecuronium bromide	Muscuron, Norcuron	Powder for injection in flacons (i/v)	0.004
Dioxonium	Dioxonium	Parenteral solution in ampoules (i/v)	0.1% - 5 ml

Chapter 6. Adrenergic agonists

Drugs that act on the adrenergic receptors are named **adrenergic drugs**. The main mediator (neurotransmitter) of adrenergic nerves system is ***Norepinephrine (NE)***.

The ***process of neurotransmission in adrenergic neurons*** includes five steps. The *first step* is synthesis of NE. Tyrosine is transported to adrenergic neurons, where is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limited step in catecholamine transmitter synthesis. DOPA is decarboxylated by dopa-decarboxylase to dopamine (D) in cytoplasm of presynaptic neurons. *Dopamine* is hydroxylated by dopamine-β-hydroxylase to NE. The *second step* is storage of NE in vesicles. Dopamine, norepinephrine, ATPh, β-hydroxylase are in synaptic vesicles. In adrenal medulla and certain areas of the brain NE is transformed into *epinephrine* (Ep) by methylation. The adrenal gland releases 80% of Ep and 20% of NE directly into bloodstream. The *third step* is release of NE from synaptic vesicles, and NE diffuses to synaptic gap. After release from synaptic vesicles NE may be metabolized by monoamine oxidase (MAO) in presynaptic structure, may be metabolized by catecol-orto-methyltransferase (COMT) in synaptic gap, may be recaptured by an uptake system that returns NE into the neuron (this is the primary mechanism for termination of NE's effects and are called neuronal recapture), NE may diffuse out of synaptic space and enter the general circulation. After neuronal recapture NE may be taken up into adrenergic vesicles or may persist in a protected pool or can

be oxidized by MAO. The *fourth step* is receptor binding of NE: as presynaptic receptors on the nerve endings and postsynaptic receptors on the effector organs. The *fifth step* is removal of NE from the synaptic gap. There are inactive products of NE metabolism: vanillylmandelic acid, metanephrine, normetanephrine.

There are several classes of ***adrenergic receptors (adrenoceptors)***: α, β and dopaminergic receptors (D). There are the several subtypes of them: α1, α2, β1, β2, β3, and there are ***dophaminergic receptors***: D1, D2, etc.

Adrenergic agonists (also called **adrenomimetics**) increase activity of adrenergic nerve system. In accordance with the ***mechanism of action*** some adrenergic drugs act directly on the adrenergic receptors, stimulate them and are named *direct-action adrenergic agonists (mimetics)*; other adrenergic agonists act on neurotransmitters of adrenergic nerves system (norepinephrine and/or its predecessor – dopamine), increase the amount of neurotransmitters in adrenergic synapses and are named *indirect-action adrenergic agonists or sympathomimetics*. They not only release stored NE from nerve endings but also inhibit neuronal uptake of NE by presynaptic structure in the adrenergic synapse and directly stimulate both α and β receptors. Adrenergic neurons are located in CNS, as well sympathetic (adrenergic) nervous system and release neurotransmitter norepinephrine that is the final product of catecholamine synthesis in most sympathetic postganglionic neurons. Catecholamine transmitters are stored in membrane-bound vesicles. Adrenergic neurons are a bridge between the ganglia and effector organs. There are presynaptic and postsynaptic adrenergic neurons and receptors on the effector organs. Long-term use of β-agonists leads to internalization, or sequestration, or down-regulation of the β -adrenergic receptors. This means that β -adrenergic receptors go into a state of low affinity and disappear from the surface of the membrane. This phenomenon explains tolerance to β-agonists.

Table 21. Places of location and effects* of activation of adrenergic receptors

Receptors	Places of location	Effects of activation
α1	Vessels of skin, mucous, mesentery, abdominal cavity, heart, lung, kidney	constriction of the vessels, increase of BP
	Eye	mydriasis, reducing of intraocular pressure
	Sphincters of GIT	increase of tonus
	Sphincters of Urinary bladder	increase of tonus
	Uterus	increase of tonus
	Exocrine glands: bronchial, salivary, gastric, intestinal, lachrymal, sweat	increase of gland secretion
	CNS	excitement
α2	CNS (vasomotor center)	depression, reducing of BP
	Vessels	dilatation

	GIT	reducing of tonus
	Thrombocytes	increase of aggregation
β1	Heart	cardiopositive effects: positive inotropic effect; positive dromotropic effect; tachycardia (positive chromotropic effect); positive batmotropic effect
	Vessels of skeleton muscles	reducing of tonus (relaxation)
	Kidney	increase of renin secretion
	Lipid tissues	lipolysis
β2	Bronchi	reducing of tonus (bronchodilatation)
	Peripheral vessels	reducing of tonus (dilatation)
	GIT	reducing of tonus (atony)
	Uterus	reducing of tonus (tocolytic effect)
	Thrombocytes	reducing of aggregation
	Urinary bladder	reducing of smooth muscle tonus (urinary retention)
	Hepar	glycogenolysis, glycogenoneogenesis
	Pancreas	insulin and glucagon secretion
	Skeletal muscles	increase of contractility, glycogenolysis, capture of K^+
β3	Lipid tissues	increase of lipolysis, increase of FFA level in the blood
		increase of glycogenolysis, increase of glucose level in the blood
D1	Heart	cardiopositive effects: positive inotropic effect; weak positive chronotropic effect
	Peripheral vessels	reducing of tonus, improvement of peripheral blood circulation
	Sphincters of GIT	reducing of tonus

	Sphincters of Urinary bladder	reducing of tonus
	CNS	stimulation of motor activity
D2	CNS	reducing of synthesis and secretion of NE, Ach, D, Ep
	Peripheral n.s.	deceleration of nervous impulse transmission
	Kidney	reducing of rennin secretion

* - effects of activation of adrenergic receptors/dopamine receptors there are pharmacologic effects of adrenergic/dopaminergic agonists.

Classification of Adrenergic agonists

Adrenomimetics of direct action:

Nonselective α-, β- adrenomimetics (Drugs that stimulate α- and β-ARs):

α1, α2, β1: Norepinephrine h/tr.

β1 β2 α1, α2: Epinephrine h/chl., h/tr., Dipivefrine

Drugs that stimulate α-ARs:

α1: Phenylephrine
Oxymetazoline
Tetryzoline

α1, peripheral α2: Xylometazoline
Naphazoline

central α2: Clonidine
Guanfacine
Methyldopha

c) Drugs that stimulate β-ARs:

β1 β2: Isoprenaline
Orciprenaline sulfas

β1: Dobutamine

β2: shot action (3-8h.) Fenoterol
Salbutamol
Terbutalin
Hexoprenaline

long action (10-12h.)
Salmeterol
Formaterol

Adrenomimetics of indirect action (Sympathomimetics):

Ephedrine, Pseudoephedrine

Dopaminomimetics:

D, α1, α2, β1: Dopamine (Dophamine), Ibopamine

D2: Bromocriptine, Cabergolin, Quinagolide

Pharmacologic characteristic of Adrenergic agonists

Peculiarities of the several Adrenomimetics

Epinephrine h/chl, h/tr. (β1 β2 α1, α2,)

The main feature of epinephrine is the fact that its impact on the corresponding receptors depends on the dose. Thus, in small doses it stimulates β-adrenergic receptors alone and in medium and large doses – as β-, and α-adrenergic receptors. Under the influence of epinephrine on the heart there are two opposing mechanisms of action: direct β1-adrenoreceptor stimulating and inhibitory reflex via the vagus nerve.

Pharmacological effects of epinephrine

- Cardiopositive (cardiostimulator) – by stimulation of β1-adrenergic receptors, but increasing stroke volume leads to a reflex bradycardia due to the exposure of the vagus nerve
- Bronchodilatation (bronchodilatator) – by stimulation of β2-adrenergic receptors (subcutaneous injection of drug is sufficient)
- Functional antagonist of insulin (epinephrine increases the glucose level in the blood due to stimulation of glycogenolysis in the liver – stimulatory effect of epinephrine on β2-adrenergic receptors)
- Increase of the functional ability of skeleton muscles, increase of blood flow to the skeletal muscles
- Stimulation of the glycogen degradation to lactic acid, increase of lactate level in blood (β-stimulating effect on the skeleton muscles)
- Constriction of arterioles in the skin, mucous membranes, and viscera (α-stimulating effects), and dilatation of vessels going to the liver and skeletal muscles (β2-stimulating effects). Renal blood flow is decreased
- Inibition of the release of biology active remedies (BAR) from mast cells
- Reduction of the intraocular pressure through vasoconstriction, and decrease in production of intraocular fluid
- Mydriasis by means of stimulation of α1 adrenergic receptors of musculus dilatator pupilla
- After introduction of epinephrine first the blood pressure increases, but in the future – decreases. The cumulative effect of epinephrine is an increase in systolic BP, coupled with a slight decrease in diastolic BP
- Increase of BP in case of i/v bolus administration of epinephrine due to stimulation of α-adrenergic receptors of skin, mucous membrane, mesentery, abdominal organs (α1-adrenergic receptors) and increased cardiac activity (β1-adrenergic receptors)

Indications for epinephrine use:

- Cardiac arrest (i/v, intratracheal administration of epinephrine)
- Anaphylactic shock

Angioneurotic edema of larynx
Bronchospasm
Hypoglycemic coma (in case of insulin overdoses) – useful in this case where is a stimulation by epinephrine of α2-adrenoceptor of pancreas, which leads to inhibition of insulin secretion
Insufficiency of peripheral blood circulation (during the operation, local anesthesia)
Open-angle glaucoma
Examination of eye bottom
Local anesthesia (together with local anesthetics for it prolonged action)

Advers effects of epinephrine:

Cardiac arrhythmia, especially in condition of hypoxia: Epinephrine increases the requirement in oxygen of heart muscle
Hypotonia after short hypertension
Atonia of GIT
Mydriasis and light disturbance of accommodation
Bronchospasm that connect with a loss of sensitivity of β2-adrenergic receptors epinephrine and a saving of sensitivity of α-adrenergic receptors to epinephrine (with repeated administration of epinephrine as manifestations of tachyphylaxis)
Hypokalemia
Tremor
Constriction of the vessels of the mucous, of the skin, of the abdominal cavity
In high doses Epinephrine penetrates BBB and causes excitement of CNS: headache, nervousness, sleeplessness (insomnia), vomiting

Contraindications for epinephrine use:

Together with other adrenomimetics (threat of heart arrhythmia)
Together with general anesthetics: Cyclopropane, Phthorothanum, Isoflurane (threat of heart arrhythmia)
Together with diuretics and cardiac glycosides (threat of heart arrhythmia)
In patient with bronchial asthma and IHD, hypertension, atherosclerosis and other organic diseases of myocardium
In patient with diabetes mellitus

Dipivefrine (eye drops – antiglaucoma drug) – prodrug, it easily penetrates into the anterior chamber, where exposed to enzymatic hydrolysis with the formation of e*pinephrine*. *Epinephrine* is distributed in the ciliary muscle and trabecular tissue of the eye; it reduces the production of intraocular fluid and increases its outflow.

Norepinephrine h/tr.(α1, α2,β1)

The peculiarity of the mechanism of norepinephrine action is the fact of preferred and overriding stimulation of α-adrenergic receptors, to a lesser extent – β1-adrenergic receptors.

Pharmacological effects of norepinephrine:

Constriction of the vessels
Cardiopositive (cardiostimulating)
Hypertensive

Indications for norepinephrine use:

Acute arterial hypotonia (during the surgical operation, shock, collapse, poisoning, after removing of pheochromocytoma)
Local anesthesia (together with local anesthetics for it prolonged action), *e.g.*, *Xylestesin-F (forte) (lidocaine+norepinephrine), Trimecaine with norepinephrine for injections (trimecaine+norepinephrine)*

Adverse effects of norepinephrine:

Deterioration of the peripheral blood circulation
In cardiogenic and hemorrhagic shock with severe arterial hypotension norepinephrine may impair blood flow to internal organs
Bradycardia as a reflex response to an increase in stroke volume that leads to immutability of minute volume or even to reduce of minute volume
Cardiac arrhythmia
Vasoconstriction and as a result of gangrene (necrosis of the tissues) in case of introduction to tissues
ONLY INTRAVENOUS INTRODUCTION!!!
Tremor
In high doses norepinephrine penetrates BBB and causes excitement of CNS: headache, nervousness, sleeplessness (insomnia), vomiting

Contraindications for norepinephrine use:

Together with other adrenomimetics (threat of heart arrhythmia)
Together with general anesthetics: Cyclopropane, Phthorothanum, Isoflurane (threat of heart arrhythmia)
Heamorrhagic and cardiogenic shocks
Atherosclerosis
Pregnancy
AV-blocks

Introduction of norepinephrine to the tissues of the body (at accidental norepinephrine delivery under the skin, in the muscles should be immediately drugged around the site of solution norepinephrine injection by α-adrenoblockers such as phentolamine).

Phenilephrine (α1)

It is a synthetic α1-adrenomimetic.

Pharmacological effects of phenilephrine:

Vasoconstrictive
Mydriasis
Decongestive

Indications for phenilephrine use:

Collaps, arterial hypotonia
Prophylaxis of BP reduction in case of infection diseases and poisoning

Rhinitis
Conjunctivitis, iridocyclitis
Examination of eye bottom
Local anesthesia (together with local anesthetics for it prolonged and safe action)
It may be used in case of arterial hypotonia during halothane and isoflurane general anesthesia

Adverse effects of phenilephrine:

Bradycardia
Deterioration of the peripheral blood circulation
Xerosis (dryness of mucous)

Contraindications for phenilephrine use:

Heart blockages
Atherosclerosis
Tendency to angiospasm
Heart insufficiency

Oxymetazoline (α1), Tetryzoline (α1), Xylometazoline (α1, peripheral α2), Naphazoline (α1, peripheral α2)

Pharmacological effects of them:

Vasoconstriction

Indications for their use:

Acute and allergic rhinitis, conjunctivitis, iridocyclitis, sinusitis, eustachitis, hay fever

Adverse effects of them:

Xeromycteria, mucous atrophy
Arterial hypertension
Excitement of CNS: headache, nervousness, sleeplessness (insomnia), nausea, vomiting
Tachycardia
Mydriasis
Tahyphylaxia

Contraindications for their use:

Arterial hypertension
Cardiac arrhythmia

Clonidine (central α2), Guanfacine (central α2), Methyldopha (central α2)

Pharmacological effects of them:

Arterial hypotension
Reduction of the intraocular pressure

Indications for their use:

Arterial hypertension
Glaucoma (*for clonidine*)

Alcohol abstinence

Adverse effects of them:

clonidine, guanfacine:

Sedative
Analgesive
Withdraval (abolition) syndrome
Ortostatic hypotension

methyldopha:

Bradicardia
Addiction

Contraindications for their use:

Atherosclerosis
IHD
Together with other drugs that depress CNS
Heart arrhythmia, heart blockages

Isoprenaline (β1 β2), Orciprenaline sulfas (β1 β2)

Pharmacological effects of them:

Cardiopositive
Bronchodilatative
Vasodilatative due to reduction of peripheral vascular resistance of kidney, mesentery, sckeleton muscles that leads to decline of diastolic and systemic BP
improvement of blood circulation to the internal organs
They hamper the release of BAR (biology active remedies) from mast cells

Indications for their use:

Bronchospasm
Bronchial asthma
Heart blockages
Prophylaxis of Gerbezius-Morgagni-Adams-Stokes syndrome

Adverse (side) effects of them:

Tachycardia
Cardiac arrhythmia
Tremor
Excitement of CNS
Hyperglycemia
Arterial hypotonia
Headache
Tocolitic tffect

Contraindications for their use:

Atherosclerosis
Heart arrhythmia
Arterial hypotonia
Diabetes mellitus
Organic diseases of CNS

Dobutamine (β1)

Pharmacological effects of dobutamine:

Strong positive inotropic
Improvement of the kidney blood circulation

Indications for dobutamine use:

Cardiogenic shock
Acute heart insufficiency
Chronic heart insufficiency (sometimes)

Adverse (side) effects of dobutamine:

Tachycardia
Cardiac arrhythmia
Heart pain
Bronchospasm
Excitement of CNS
Tolerance in case of uninterrupted introduction within 3-4 days

Contraindications for dobutamine use:

Organic heart diseases with disorder of heart rhythm
Organic diseases of CNS
Atherosclerosis
Arterial hypertension

Fenoterol, Salbutamol, Terbutalin, Salmeterol, Hexoprenaline, Formoterol (β2)

Pharmacological effects of them:

Bronchodilatation
Tokolitic effect

Indications for their use:

Bronchospasm
Bronchial asthma
Premature (untimely) delivery
Hypertonus of uterus
Swift delivery

Adverse (side) effects of them:

Tachycardia (mainly occurs in patients with concomitant cardiovascular disease and rarely without it, as well as the combined use of MAO-inhibitors or other sympathomimetics)
Cardiac arrhythmia (mainly occurs in patients with concomitant cardiovascular disease and rarely without it, as well as the combined use of MAO-inhibitors or other sympathomimetics)
Arterial hypotonia
Excitement of CNS: anxiety, trouble
Tachyphylaxis
Allergic reaction
Urinary retention, especially in old people

Tremor that can be avoided or reduced by the use of β2 adrenergic agonists beginning with small doses with a gradual increase of them. In case of parenteral use these drugs can increase concentration of glucose, lactate, free fatty acids (FFAs) in blood plasma and reduce concentration of K^+ ions

Hyperglycemia in the patients with diabetes mellitus that requires correction of hypoglycemic drug doses

All adverse effects of β2 adrenergic agonists are diminished in inhalation therapy in comparison with peroral or parenteral administration.

Contraindications for their use:

Organic heart diseases with disorder of heart rhythm

Organic diseases of CNS

Old age

Uterine inertia

Ephedrine, Pseudoephedrine

According to the mechanism of action they are similar to *epinephrine*, but less powerful. Besides, they aren't catecols and are poor substrates for COMT and MAO, as a result these drugs have long action, good oral absorption and penetration into the CNS. *Ephedrine, Pseudoephedrine* are α-, β-adrenergic agonists, they stimulate release of norepinephrene from sympathetic neurons, thereby, they activate adrenergic receptors. These drugs are the drugs of mixed sympatomimetic action.

Ephedrine increases the heart rate, cardiac output, peripheral vascular resistance, BP, stimulates CNS, causes addiction, euphoria and tahyphylaxia. Stimulation of α-adrenergic receptors of smooth muscles of sphincters of urinary bladder elicits urinary retention. Activation of β-adrenergic receptors of smooth muscles of bronchi leads to bronchodilatation.

Ephedrine, Pseudoephedrine have limited clinical applications in nowadays through their adverse effects.

Dopamine (Dophamine), Ibopamine (D1, α1, β1)

Dopamine is the immediate metabolic precursor of NE and it is the neurotransmitter in the CNS in the basal ganglia. *Dopamine* activates α and β adrenergic receptors. *Dopamine* is a dose-dependent drug: in *low doses dopamine* stimulates D1 receptors that lead to vasodilatation of peripheral mesenteric vessels, renal vessels and vessels of the heart and the brain, increasing blood flow to renal, mesenteric, coronary arteries, and brain arteries, increasing overall renal perfusion, induces natriuresis (sodium loss) in the kidneys, and has a diuretic effect; in *moderate doses dopamine* stimulates β1 adrenoceptors and causes an increase in cardiac output and stroke volume, it has a positive inotropic and chronotropic effect; in *high doses dopamine* activates α1 adrenoceptors and causes vasoconstriction of the kidney vessels to the point that urine output is reduced, increases systemic vascular resistance, blood pressure, causes heart arrhythmia, nausea, vomiting. Thereby, the *low doses of dopamine* are considered the *"renal*

doses", the *moderate doses of dopamine* are known as the *"cardiac doses"*, the *high doses of dopamine* are the *"pressor doses"* . *Ibopamine* on structure and pharmacological properties similar to dopamine, but it is effective after oral administration.

Pharmacological effects of dopamine, ibopamine:

Positive inotropic
Positive chronotropic
Vasodilatative
Increase of cardiac output
Increase of BP

Indications for dopamine use:

Heamorrhagic and cardiogenic shocks
The emergency clinical treatment of severe hypotension
Bradycardia
Cardiac arrest for the purpose of cardiopulmonary resuscitation

Adverse (side) effects of dopamine:

May be a tissue necrosis (ONLY INTRAVENOUS INTRODUCTION!!!)
Cardiac arrhythmia, tachycardia

Indications for ibopamine use:

Chronic heart insufficiency

Adverse (side) effects of ibopamine:

Cardiac arrhythmia, tachycardia
Dyspepsy
Hyperglycemia (in high doses)

Bromocriptine

(powerful agonist of D2 receptors and lesser extent of D1 receptors)

Pharmacological effects of bromocriptine:

Stimulates dopamine receptors of hypothalamus that lead to decreasing of secretion (not synthesis) of hormones of anterior lobe of hypothalamus, especially of *prolactin* and in a less degree – of *somatotropin* (growth hormone)
Emetic
Hypothermic
Hypotensive
Reduces the smooth muscle tonus in the vessels
Inhibits the uterus contractions that were caused by methylergometrine
Reduces the blood level of catecolamines
Strong sedative effect

Indications for bromocriptine use:

For suppression of postpartum lactation
For normalization of the menstrual cycle in women with hyperprolactin amenorrhea

Sterility
Acromegaly
Icenko-Cushing disease/syndrome
Benign tumors of the mammary glands
Prolactinoma
Parkinson disease/syndrome (in high therapeutic doses)

Adverse (side) effects of bromocriptine

Nausea, sometimes vomiting
Constipations
Headache
Dizziness
Sleepiness
Postural hypotension
Disorder of peripheral blood circulation

Contraindications for bromocriptine use:

Toxemia of pregnancy
Lactation
Arterial hypotension
Recent myocardial infarction
Cardiac arrhythmia
Disorder of peripheral blood circulation
GIT diseases
Psychical diseases

Pergolide
(partial agonist of D1 receptors and powerful agonist of D2 receptors)

Pergolide in modern terms is almost never used because of the high risk of valvular heart disease. In addition, there can be hypotension (especially in the first days of therapy), arrhythmia, dizziness, insomnia, dyskinesia, and peripheral edema.

Cabergolin (agonist of D2 receptors)

Cabergolin has the similar effects as *bromocriptine*, but *cabergolin* is a long-term action drug.

Quinagolide (agonist of D2 receptors)

Quinagolide inhibits the prolactin secretion.

Table 22. Medicinal forms of Adrenomimetics, Sympatomimetics

INN	Trade names	Medicinal forms	
Norepinephrine	Noradrenaline hydrotartrate, Arterenol, Levarterenol, Levophed, Norartrinal, Norexadrine, etc.	Solution for injections in ampoules (i/v)	0.2% - 1ml
Epinephrine	Adrenaline, Adnephrine, Adrenamine, Adrenine,	Solution for injections in	0.18% - 1ml; 0.1% - 1ml;

	Epirenan, Epirinamine, Eppy, Hypernephrine Levorenine, Nephridine, Paranephrine, Renostypticin, Styptirenal, Suprarenalin, Suprarenin, Tonogen, etc.; Dipivalat, Diopine, Oftan Dipivefrine, Propin, Thilodrin, Vistapin, Epifrin, Epiglaucon, Epinal, Glaucon, Glauconin, Glaukosan, etc. Adrenaline auto-injector devices for anaphylaxis: Anapen, Epipen,	ampoules (s/c, i/m, i/v); Solution for external use in flacons; auto-injector;	0.1% - 10ml; 0.18% - 10ml; 150mcg, 300mcg, 500mcg, 0.15 mcg, 300mcg, 150 mcg, 300mcg;
Dipivefrine	Jext	Eye drops in flacons-droppers	0.1% - 5ml
Phenylephrine	Irifrin, Vistosan Mesaton, Adrianol, Almefrin, Derizene, Idrianol, Isophrin, Neophryn, Neo-Synephrine, m-Sympatol, Visadron, etc.	Eye drops in flacons; Parenteral solution for injections in ampoules (s/c, i/m, i/v)	2.5% - 5ml; 10% - 5 ml; 1% - 1 ml
Oxymetazoline	Fazin, Fervex, Nasivin, Nazol, 4-Way, Alka-Seltzer plus nosespray Afrin, Bartell Drugs 12 Hour Decongestant Nasal, Wick Sinex, Lekonyl, Oxymetazoline, Vistoxyn, etc.	Nasal spray in flacons, in flacon-inhalator; Nasal drops in flacon-dropper; Eye drops in flacons	0.05% - 5 ml, 20 ml, 30 ml; 0.05% - 10 ml; 0.01% - 5 ml; 0.025% -10ml; 0.05% -10 ml; 0.025% -10ml, 20ml
Tetryzoline	Berberill N, Visine, Octilia, Tyzine, Burnil, Visine, etc.	Eye drops in flacons; Nasal drops in flacons; Nasal solution; Ophthalmic solution	0.05% - 10 ml; 0.05% - 0.5ml; 0.05% - 15 ml; 0.05% - 8 ml; 0.1% - 10 ml; 0.05% - 10 ml; 0.05%, 0.1% 0.05% - 15 ml
Xylometazoline	Brizoline, Galazolin Grippostad Rhino, Dlianos, Xilen, Xylobene,	Nasal drops in flacons Nasal gel in tubes Nasal drops and Nasal	0.05%, 0.1% - 10ml; 0.05%, 0.1% - 5.0 ml; 0.1%, 0.05% - 10ml;

	Xylometazoline-Rusphar, Xylometazoline, Xylometazoline hydrochloride, Xymelin, Doctor Theiss, Olynth, Otrivin, Rhinostop, NasenSpray ratiopharm, Pharmazolin, Galazolin, etc.	spray in flacons Nasal drops Nasal spray in flacons Nasal drops in flacons Nasal drops in flacons Nasal spray in flacons Nasal spray in flacons Nasal spray in flacons Nasal drops in flacons Nasal drops in flacons Nasal spray in flacons Nasal drops in flacons Aerosol and Nasal drops in flacons	0.1%, 0.05% - 10ml; 5mg, 10mg - 10ml; 0.05%, 0.1% - 10ml; 0.05%, 0.1% - 15ml, 20ml, 25ml, 30ml; 0.5, 1.0 mg/ml - 10ml, 15ml 0.1% - 10ml; 0.05%, 0.1% - 10ml; 0.05%, 0.1% - 10ml; 0.05%, 0.1% - 10ml, 15ml, 20ml, 5mg - 10ml; 0.05%, 0.1% - 10ml 0.05%, 0.1% - 10ml
Naphazoline	Nafazol-Hemofarm, Naphazoline-Ferein, Naphazoline, Naphthyzin-Rusfur, Naphthyzin-UBF, Naphthyzin, Sanorin, etc.	Nasal drops in flacons Solution in flacons Solution in flacons and Nasal drops in flacons Nasal drops in flacons Nasal drops in flacons and Nasal spray in flacons and Nasal emulsion	0.05%, 0.1% - 10ml; 0.05%, 0.1% - 5ml, 10ml; 0.05%, 0.1% - 10ml, 20ml; 0.05%, 0.1% - 10ml; 0.1% - 5ml, 10ml, 15ml, 20ml; 0.05%, 0.1% - 10ml; 0.1% - 10ml; 0.05%, 0.1% - 10ml

Clonidine	Hemiton, Clophelin-Darnitsa, Clophelin, Clonidine hydrochloride, Clophelin-M, Clophelin Chlophasolin, Hyposyn, Normopresan, Prescatan, etc.	Tablets Parenteral solution for injections in ampoules (s/c, i/m, i/v) Eye drops: solution in tube-droppers -	0.075mg, 0.3mg, 0.15mg 0.01% - 1ml 0.125%, 0.25%, 0.5% - 1.5ml
Guanfacine	Estulic, Hipertensal, Tenex	Tablets	1mg
Methyldopha	Dopegyt, Aldomet, Alfadopha, Dopanol, Equibar, Hypotonal, Levomet, Modepres, Normopres, Presinol, Presolisin, etc.	Tablets	0.25, 0.5
Isoprenaline	Isadrin, Novodrin, Euspiran Novodrin, Euspiran, Aleudrin, Aludrin, Antasthmin, Bronchodilatin, Iludrin, Isodrenal, Isonorin, Isoprenalini hydrochloridum, Isoprenaline hydrochloride, Isopropylarterenol, Isoproterenol, Isorenin, Isuprel, Neodrenal, Neoepinephrine, Norisodrin, etc.	Tablets Solution for inhalations in flacons Aerosol	0.005 0.5%, 1% - 25ml, 100ml 25ml (350 single doses - 0.075mg/dose)
Orciprenaline	Astmopent, Alupent, Alotec, Astor, Dosalupent, Metaproterenolsulfat, Novasmasol	Aerosol; Tablets; Parenteral solution for injections in ampoules (s/c, i/m, i/v)	20ml-400doses - 0.75mg/dose 0.02; 0.05% - 1ml;
Dobutamine	Dobutamine-Grindeks, Dobutamine Hexal, Dobutamine Lachema, Dobutamin Solvay, Dobutrex, Dobuject, Dobutamin Giulini, Dobutamin Nycomed, Inotrex	Parenteral solution for injections in ampoules (i/v) Powder for injections in flacons	0.5% -50ml; 1.25% - 20ml 0.25, 0.53

Fenoterol	Berotec,	Solution for inhalations in flacons;	1.25mg - 2ml; 0.1% - 20ml, 40ml, 100ml;
	Aruterol,	Aerosol for inhalations;	10ml, 15ml, 20 ml (100, 200 single doses - 0.1, 0.2 mg/dose)
	Partusisten,	Tablets;	0.005;
		Parenteral solution for i/v injections in ampoules;	0.5mg - 10ml;
	Fenoterol, Ftagirol, Airum, Dosberotec, Segamol, etc.	Tablets; Aerosol for inhalations;	0.005; 300 single doses - 0.2 mg/dose),
Ipratropium bromide+Fenoterol	Berodual, Berodual N,		15 ml (300 single doses - 0.02, 0.5 mg/dose);
		Solution for inhalations in flacons;	10ml 10ml (200 single doses);
Fenoterol+Cromoglicic acid	Ditec	Aerosol for inhalations	10ml (200 single doses)
Salbutamol	Saltos, Asthalin, Ventolin, Salamol, Ventolin, Nebules, Salben, Salgim, Sterineb Salamol, Cybutol cyclocaps, Airomir, Asthalin, Bronchovaleas Gen-Salbutamol, Salamol easi-breathe, Salmo, Aloprol, Albuterol, Asmadil, Salbuvent, Ventodisk, Volmax, Salbuvent, Salbupart, Spreor, Ecovent,	Tablets; Tablets-retard; Syrup; Aerosol for inhalations; Solution for inhalations in ampoules, in flacons; Powder for inhalations; Solution for injections (s/c, i/m, i/v); Capsules for inhalations;	0.002, 0.004; 0.006, 0.007; 0.004, 0.008; 0.04% - 100ml 0.025 i 0,1mg /dose; 120, 200, 400 doses 0.1% - 2.5ml; 2.5; 5; 10, 50ml; 0.1; 0.2 i 0.4 mg/dose; 0.1% - 5 ml; 0.002, 0.004;
Budesonide+Salbutamol Ipratropium bromide+Salbutamol	Biasten, Combivent, etc.	Aerosol for inhalations; Powder for inhalations in capsules;	0.1; 0.2, 0.4 mg/dose - 100, 200 dose; 0,02 mg/0,12 mg – 1dose /200 doses/ - 10 ml;

		Solution for inhalations in flacons	2,5 ml
Terbutaline	Aironyl Sedico, Bricanyl, Arubendol, Bricanyl inchaler Bricanyl, Bricanyl turbuhaler Asthmasian, Betasmac, Bricalin, Dracanyl, Spiranyl, Terbasmin, Terbutol, Tergil, etc.	Tablets; Aerosol for inhalations; Solution for injections in ampoules (s/c, i/v); Powder for inhalations	2.5mg 400 single doses - 0.25mg/dose; 0.05% - 1ml; 200 single doses - 0.5mg/dose
Salmeterol	Salmeter, Serevent	Aerosol for inhalations; Powder for inhalations	60, 120 single doses - 25 microgram/ dose 4 single doses -50microgram/ dose
Hexoprenaline	Gynipral, Ipradol	Tablets; Solution for injections in ampoules (i/v); Powder for for injections in ampoules	0.5mg 0.00025% - 2ml, 0.0005% - 2ml, 5ml 25 microgram
Formoterol Budesonide+Formoterol	Oxis Turbuhaler, Foradil, Simbicort Turbuhaler	Powder for inhalations; Powder for inhalations in capsules; Aerosol for inhalations; Powder for inhalations	60 doses - 4.5 mcg/dose 9 microgram/ dose 12 microgram /dose 120, 60 doses - 160 microgram - 4.5 microgram /dose, 80 microgram - 4.5 microgram/ dose
Ephedrine	Ephedrine hydrochloride	Nasal drops in flacons; Solution for injections in tube-syringes, in ampoules	2%, 3% - 10ml; 5% - 1ml;

		(s/c, i/m, i/v); Tablets	0.002, 0.003, 0.01, 0.025
Pseudoephedrine: Pseudoephedrine+ Ibuprofen, Pseudoephedrine+ Guaifenesin, Pseudoephedrine+ Bromhexine, Pseudoephedrine+ Lorataidine, Pseudoephedrine+ Paracetamol, Pseudoephedrine+Paraceta-mol+Chlorphenamine, Pseudoephedrine + Paracetamol + Dextromethorphan + Chlorphenamine, Pseudoephedrine +Triprolidine, Pseudoephedrine+Dextromet horphan + Chlorphenamine	Nurofen Stopcold Sudafed Solvin plus, Solvin expectorant Clarinase Dynafed plus TeraFlu, AntiFlu, Our choice - drug against grippus and cold, Fervex rhinitis Children's Tylenol cold, Mulsynex Pyranol plus Rinasek Benicol	Tablets; Syrup in flacons; Tablets; Peroral solution Tablets Tablets Tablets, Metered-dose powders Syrup in flacons Tablets Powder for peroral solution Tablets, Syrup in flacons	100ml; 0.008/0.06; 60ml, 100ml 120ml; 0.005/0.12; 60ml, 120ml; 60mg/2.5mg; 100ml
Dopamine	Aprical, Cardiosteril, Dopamex, Dopastat, Dophan, Dopmin, Dynatra, Giludop, Hydroxytyra-Min, Inovan, Intropan, Intropin, Revivan, Rivimine, Dynatra	Parenteral solution in ampoules (i/v)	0.5%, 1%-2ml; 2% - 10ml; 4% - 5ml
Ibopamine	Escandin	Tablets	0.05, 0.1
Bromocriptine	Aberginum, Bromergon, Bromocriptinum mesilat, Lactodel, Parlodel, Pravidel, Serocriptine	Tablets; Capsules	0.0025, 0.004, 0.01; 0.005, 0.01
Pergolide	Permax	Tablets	0.05 mg, 0.25 mg, 1 mg
Cabergolin	Dostinex	Tablets	0.0005
Quinagolide	Norprolac	Tablets	0.025mg, 0.05mg, 0.075mg, 0.15mg

Chapter 7. Adrenergic antagonists

Adrenergic antagonists (also called **adrenoblockers, direct adrenergic antagonists**) bind to adrenergic receptors and prevent its action by endogenous catecholamines. Adrenergic antagonists are classified according to their relative affinities for α or β receptors.

Sympatholytics (also called **indirect adrenergic antagonists**) don't bind to adrenergic receptors directly. Instead, they regulate the quantity of neurotransmitter in adrenergic neurons. There are the two types (two subgroups) of sympatholytics according to the mechanism of their actions: the first subgroup *(reserpine, Rauwolfia alkaloids)* block the Mg^{+2}/ATP-dependent transport of biogenic amines, norepinephrine, dopamine, serotonin from cytoplasm into storage vesicles in adrenergic nerves that induces the ultimate depletion of biogenic amines. The result of this process is the reducing of the norepinephrine release and an impairment of sympathetic function. The drugs have a slow onset, a long duration of action and cause Parkinson syndrome. The second subgroup *(guanethidine, bretylium tosilate)* displace norepinephrine from storage vesicles that cause a transient increase in BP. Thereafter the part of norepinephrine quantity is destroyed by MAO, and thus it leads to gradual depletion of norepinephrine in nerve endings except for those in the CNS. In this way, the drugs commonly cause orthostatic (postural) hypotension and interfere with male sexual function. In the patient with pheochromocytoma they induce hypertensive crisis due to supersensitivity to norepinephrine.

Classification of adrenoblockers

■ **α-adrenoblockers**

- ***Nonselective α1-, α2- adrenoblockers:***

Ergot alkaloids: Dihydroergotamine (dehydrated derivative of ergot alkaloid ergotamine)
Dihydroergotoxine (dehydrated derivative of total alkaloids of ergotoxinum that is similar in structure and pharmacological properties of Dihydroergotamine).

Analogs of Ergot alkaloids: Nicergoline

Synthetic drugs: Phentolamine
Tropodifene
Proroxan
Phenoxybenzamine
Ketanserin
Urapidil
Indoramin

- ***Selective α1-adrenoblockers:***

Prazosin

Doxazosin
Tamsulosin
Terazosin

- ***Selective α2- adrenoblockers:***

alkaloid from the bark of a tree Corynanthe Yohimbe: Yohimbine

■ **β-adrenoblockers:**

- ***Nonselective (β1, β2):***

Propranolol
Sotalol
Timolol
Nadolol
with internal sympathomimetic activity: Pindolol
Oxprenolol
with additional vasodilating properties: Dilevalol
Bucindolol
Carteolol

- ***Selective (β1):***

Atenolol
Metoprolol
Betaxolol
Bisoprolol
Talinolol
with internal sympathomimetic activity:
Acebutolol *with additional vasodilating properties:* Celiprolol Nebivolol

Nonselective (β1, β2, α1):
Labetalol
Carvedilol

■ **Sympatholitics:**

- ***Drugs that are the pharmacologic competitor of NE in adrenergic synapses:***

Guanethidine
Bretylium tosilate

- ***Drugs that decrease the store (supply) of NE in adrenergic synapses:***

Reserpine
Rauwolfia alkaloids

Pharmacologic characteristic of α-adrenergic antagonists

In general, α-adrenoblockers affect BP due to reducing of sympathetic tone of the vessels, decreasing of peripheral vascular resistance, diminishment of

vessel's smooth muscle tone, that lead to vasodilation. Lowering of BP induces a reflex tachycardia.

Pharmacodynamics of α-adrenoblockers:

Vessels: relaxation, as a result – hypotension, improving of peripheral blood circulation; *Heart:* reflex tachycardia; *GIT:* increase of motor activity, relaxation of sphincters, increase of secretion of exocrine glands; *Eye:* miosis; *Exocrine glands:* sweating, nasal congestion; Urogenital *system:* sphincter relaxation, improving erection.

All α-adrenoblockers have opposite α-agonist (epinephrine) activity. So, vasoconstrictive effect of *epinephrine* caused by stimulation of α-adrenergic receptors under the influence of α-blockers is interrupted, while vasodilatation mediated by β2-adrenoreceptor stimulation is not blocked. It becomes apparent that the α-adrenoblockers prevent the peripheral vasoconstrictive effects of epinephrine, leaving the vasodilating (β2-stimulation) unopposed. These results in a marked decrease in diastolic pressure coupled with a slight increase in systolic pressure due to increased cardiac output. This phenomenon is named *"epinephrine reversal",* and it is characteristic of the effect of α-adrenoblockers on the cardiovascular effects of epinephrine. The action of *norepinephrine* aren't reversed, but are decreased because of *norepinephrine* lacks significant β-agonist action on the vessels.

Peculiarities of the several α-adrenoblockers

Nonselective α1-, α2- adrenoblockers

Ergot alkaloids: Dihydroergotamine, Dihydroergotoxine

Dihydroergotamine blocks α1, α2- adrenergic receptors and stimulates 5-HT2A и 5-HT1D serotonine receptors that are located on intracranial blood vessels of the brain and the dura mater.

Pharmacological effects of dihydroergotamine:

Reduction of arterial tonus
Increase of vein tonus
Selective narrowing (vasoconstriction) of the external and internal carotid arteries
Reduction of phonophobia and photophobia (in case of migraine)

Indications for dihydroergotamine use:

For relief of migraine attacks
Disorder of peripheral blood circulation
Varicose veins of lower extremities
Intestinal atony
Autonomic regulation disorders with a predominance of adrenergic system tonus

Adverse effects of dihydroergotamine:

- Arterial hypotension

Vomit, nausea
Sickness
Sleepiness
Diarrhea (seldom)
Paresthesia
Nasal congestion
Collapse
Allergic reactions

Contraindications for dihydroergotamine use:

Arterial hypotension
Atherosclerosis
Organic heart diseases
Renal and hepatic insufficiency
Pregnancy
Lactation

Overdose symptoms or poisoning is named ergotism: chest pain, dyspnea, depression of the respiratory center until his paralysis, dilated pupils, drowsiness, confusion, delirium, dizziness, disorientation, delusions, disorders of speech and movement, cooling and paresthesia of fingers and toes, prolonged vasospasm, which can lead to gangrene of the extremities, pallor, hypothermia, cruel blood pressure reduction is possible orthostatic collapse, tachycardia, abdominal pain, difficulty in urinating, abortion in pregnant, uterine bleeding, nausea, vomiting, not related to migraines, myasthenia gravis, twitching of individual muscle groups, convulsions, coma.

In case of overdose or poisoning: Gastric lavage, activated charcoal, saline laxatives, forced diuresis. In the case of vascular spasm – i/v *sodium nitroprusside*, *phentolamine* or *dihydralazine*, local application of heat. In the case of coronary spasm – *nitroglycerine*. In the case of convulsions – *diazepam*. Further – symptomatic therapy.

There may be persistent neurological disorders, trophic ulcers of limbs, endarteritis *after recovery*.

Interactions with other drugs: dihydroergotamine increases the toxicity of reserpine. Macrolide antibiotics (*oleandomitsin, erythromycin, josamycin*), *doxycycline, tetracycline, dopamine, nitroglycerin*, vasodilators, α-blockers, β-agonists enhance the effects of *dihydroergotamine*. The α-agonists, *clonidine*, *vasopressin* impair the effects of *dihydroergotamine*. Vasoconstrictor drugs (*ergotamine, sumatriptan, nicotine*) increase the likelihood of vasospasm.

Dihydroergotoxine blocks α1, α2-adrenergic receptors and D receptors

Pharmacological effects of dihydroergotoxine:

Vasodilation
Bradycardia
Improves NE synthesis and its release
Positive inotropic

Overcomes the histohematogenous barriers
Reduces the intensity of anaerobic metabolism and stimulates oxygen consumption by the brain cells
Activates the intracellular metabolism of functionally damaged neurons
Acts on the neurochemical processes in aging brain tissue

Indications for dihydroergotoxine use:

Migraine
Disorder of peripheral blood circulation
Disorder of brain blood circulation
Diabetic angiopathy
Thrombophlebitis
Consequences of traumatic brain injury
Transient arterial hypertension
Meniere's syndrome
Poor blood circulation in the retina

Adverse effects of dihydroergotoxine:

Anorexia
Dispepsy
Vision disorders
Nasal congestion
Orthostatic collapse
Skin rash

Contraindications for dihydroergotoxine use:

Kidney insufficiency
IHD
Senile age
Organic heart disease
Arterial hypotonia
Idiosyncrasy

Nicergoline

Nicergoline is analog of Ergot alkaloids, blocks α1, α2-adrenergic receptors. *Nicergoline* contains in its structure ergoline nucleus and bromosubstituted nicotinic acid remainder.

Pharmacological effects of nicergoline:

Vasodilation (brain and peripheral vessels)
Improves microcirculation
Increases vascular permeability to glucose
Increases cerebral, pulmonary and renal blood flow
Lowers the tone of the central vessels
Increases arterial blood circulation
Increases oxygen and glucose delivery to the tissues

Indications for nicergoline use:

Cerebral blood circulation disorders

Vascular dementia
Migraine
Peripheral blood circulation disorders
Diabetic retinopathy
Combination therapy of hypertensive crisis
Ischemia of visual nervous
Dystrophy of cornea

Adverse effects of nicergoline:

Arterial hypotension
Dizziness
Dyspepsia
Insomnia
Redness of skin and upper half of the body
Allergic reactions
Hyperuricemia

Contraindications for nicergoline use:

Arterial hypotension
IHD, stenocardia
Atherosclerosis
Hypersensitivity
Bradycardia

Caution: hyperuricemia, gout, pregnancy, lactation.

During the period of the treatment one must be careful when driving and during occupation of other potentially hazardous activities that require high concentration and quickness of psychomotor reactions.

Phentolamine

Phentolamine is imidazoline derivator, blocks α1, α2- adrenergic receptors.

Pharmacological effects of phentolamine:

Vasodilation of arteries and vein, especially the arterioles and precapillaries
Improving blood supply to the muscles, skin, mucous membranes
Reduces the total peripheral vascular resistance and pulmonary vascular tone
Reduces left ventricular filling pressure
Positive inotropic
Positive chronotropic – tachycardia is mediated by the baroreceptor reflex and by blockade of the α2-adrenoreceptors of the cardiac sympathetic nerves
Increases NE release, as a response to blockade of presynaptic α-adrenoceptors
Stimulates the insulin hyposecretion in patient with chronic heart insufficiency and thus has beneficial effects on myocardial metabolism
In patients with pheochromocytoma distorts the effect of epinephrine (also endogenous), which reinforces its hypotensive effect in this pathology

Indications for phentolamine use:

- Arterial hypertension in patients with pheochromocytoma

Disorders of peripheral blood circulation
Trophic ulcers of limbs, frostbites, bedsores
Acute heart insufficiency
Phentolamine can be combined with *propranolo*l in the treatment of patients with the withdrawal syndrome of *clonidine*
For short-term BP management in the patients with pheochromocytoma
Rarely phentolamine is used for treatment of impotence (intracavernosally injections to produce vasodilation of penile arteries)
Locally phentolamine is used for prevention of tissue necrosis in case of accidental administration of α-adrenergic agonists under the skin or into muscles
For stopping or reducing of actions of combined forms (together with adrenomimetics) of local anestetics

Adverse effects of phentolamine:

Arterial hypotension, ortostatic collapse
Organic heart diseases
Arrhythmia, tachycardia
IHD, angina pectoris (stenocardia), anginal pain
Sickness
Hypoglycemia (due to increasing of insulin secretion)
Edema of mucous membranes
Diarrhea
Increase the stomach acidity

Contraindications for phentolamine use:

Arterial hypotension
IHD, stenocardia
Stomach ulcer with high acidity
Organic heart diseases
Diabetes mellitus (use with caution)
Hypersensitivity
Heart insufficiency
Kidney insufficiency

Interaction with other drugs: antipsychotic drugs and anxiolytics enhance the hypotensive effect of *phentolamine*.

During the period of the treatment one must be careful when driving and during the occupation of other potentially hazardous activities that require high concentration and quickness of psychomotor reactions. During treatment you should avoid drinking alcohol.

Caution: the presence of sulfite in ampoules with phentolamine, especially in patients suffering from bronchial asthma, may cause in some cases, allergic reactions, which are manifested in the form of asthma attacks, shock and loss of consciousness.

Tropodifene

Tropodifene blocks α1, α2 adrenergic receptors and has weak cholinoblocking activity.

Pharmacological effects of tropodifene:

Vasodilative
Hypotensive
Improves blood supply, relieves pain, improves the functional state of the limbs

Indications for tropodifene use:

Peripheral blood circulation disorders
Trophic ulcers of limbs
Slowly healing wounds
Hypertensive crisis
Arterial hypertension that is associated with increased levels of catecholamines in the blood during general anesthesia and surgical operations
For diagnosis of pheochromocytoma, pheochromoblastoma

Adverse effects of tropodifene:

Orthostatic collapse
Tachycardia

Contraindications for tropodifene use:

Organic heart and vessel diseases
Hypersensitivity
Cerebral atherosclerosis
Heart insufficiency

Proroxan

Proroxan blocks α1, α2- adrenoceptors.

Pharmacological effects of proroxan:

Central and peripheral α-adrenoblocking effects
Vasodilation, especially the arterioles and precapillaries
Inhibits the excitability of diencephalic structures of the brain and regulates the tone of the sympathoadrenal system
Reduces mental stress, anxiety in case of sympathetic hypertone
Antipruritic effect

Indications for proroxan use:

Diseases that are associated with increased sympathetic tone, including diencephalic and hypertonic crises
Overexcitation of the vestibular apparatus (the best use in combination therapy with cholinolytics and antihistamines)
To relieve symptoms of morphine and alcohol abstinence
Anxious-depressive syndrome
Allergic dermatosis

Adverse effects of proroxan:

- Increasing pain in the heart in patients with IHD

Arterial hypotension
Bradycardia

Contraindications for proroxan use:

Expressed atherosclerosis
IHD with stenocardia
Disorders of cerebral circulation
Expressed heart insufficiency

Interaction with other drugs: the effects of *proroxan* are enhanced by neuroleptics.

Phenoxybenzamine

Phenoxybenzamine blocks α1, α2 adrenergic receptors. This blockade is reversible and noncompetitive. New adrenergic receptors for overcoming the blockade are synthesized in the body which requires a day or more. The blockade of α1, α2 adrenergic receptors by phenoxybenzamine is developed during few hours because molecule of phenoxybenzamine must convert to the active form.

Phenoxybenzamine will also affect the postsynaptic α1, α2 adrenergic receptors in the nervous system, and so reduces sympathetic activity. This results in further vasodilation, pupil constriction, an increase in GIT motility and secretions, and also glycogen synthesis.

Besides, phenoxybenzamine has partial agonist/antagonist properties at the serotonin 5-HT2A receptors. Due to 5-HT2A receptor antagonism of phenoxybenzamine, it is useful in the treatment of carcinogenic tumor, a neoplasm that secretes large amounts of serotonin and causes diarrhea, bronchoconstriction, and flushing.

Pharmacological effects of phenoxybenzamine:

Prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines
Decreases the vessel's peripheral resistance
Provokes a reflex tachycardia
Contributes to an increased cardiac output through the stimulation of β-adrenoreceptors of the heart as a result of more NE release mediated by α-adrenoblockade

Indications for phenoxybenzamine use:

Pheochromocytoma
Raynaud's disease/syndrome
Autonomic hyperreflexia, which causes paraplegics as a result of stroke

Adverse effects of phenoxybenzamine

Postural hypotension
Nasal stuffiness (nasal congestion)
Nausea
Vomiting
Inhibition of ejaculation
Reflex tachycardia mediated by baroreceptor reflex

Contraindications for phenoxybenzamine use:

- In patients with decreased coronary reperfusion

Nonselective α1, α2 adrenergic blockers are not represented in today's pharmaceutical market of Ukraine and are not used in clinical practice. However, *phentolamine* and *phenoxybenzamine* play an important role in establishing the importance of α -adrenergic receptors in the regulation of cardiovascular and other body systems. Most researchers attribute these drugs to "classical" α-adrenoblockers as opposed to newer, such as *prazosin*. *Phentolamine* and *phenoxybenzamine* effects on the cardiovascular system are the same: reduction of peripheral vascular tone (resistance), vessel's expansion due to blockade of α-adrenergic receptors of the vessels and cardiac output increase is partly as a result of reflex stimulation of the sympathetic nervous system. Moreover, cardiac stimulation is enhanced by increased release of NE in cardiac sympathetic nerves through the antagonism with presynaptic α2-adrenoceptors of nonselective α1, α2-adrenergic blockers. Postural hypotension is a characteristic feature of these drugs and is accompanied by reflex tachycardia, a possible arrhythmia, which greatly limits the use of nonselective α1, α2-adrenoceptor antagonists for the treatment of essential hypertension.

Ketanserin, Urapidil, Indoramin

They block α1, α2 adrenergic receptors, but not only them and not only block: *ketanserin* besides α adrenergic receptor blockade also blocks 5-HT2A, 5-HT2C, 5-HT6 serotonin receptors and H1 histamine receptors; *urapidil* is a weak β-adrenoblocker, also blocks the 5-HT1A serotonin receptors of vasomotor center (to prevent a reflex increase in sympathetic nervous system); *indoramin* in addition to blockade of α adrenergic receptors also it is a competitive antagonist of 5-HT serotonin and H1 histamine receptors.

Ketanserin

Pharmacologic effects of ketanserin:

Vasodilation
Hypotensive
Bronchodilation
Platelet aggregation inhibitor

Indications for ketanserin use:

Arterial hypertension
Hypertension crisis
Disorder of peripheral blood circulation
Thrombosis, hemorrhoidal thrombosis
Thrombophlebitis

Ketanserin can be used together with β-adrenoblockers and diuretics to enhance the hypotensive effect.

Adverse effects of ketanserin:

- Platelet aggregation inhibitor (microhematuria)

Arterial hypotension
Drowsiness
Reduction in concentration of attention
Headache
Indigestion
Increase in body weight (with prolonged use)

Contraindications for ketanserin use:

Arterial hypotension
Hypersensitivity
Bradycardia
AV-blocks
Ventricular tachycardia
Ventricular fibrillation in the history
Prolongation of QT interval
Hypokalemia
Pregnancy
Lactation

Urapidil

Pharmacologic effects of urapidil:

Vasodilation
Reduction in peripheral vascular resistance
Hypotensive, it reduces both systolic and diastolic blood pressure
Increase of low cardiac output and reduced minute volume of heart
Reduction in preload and afterload on the heart
Blockade of the vasoconstrictive action of catecholamines (endogenous and exogenous)
with prolonged use it lowers triglycerides and total cholesterol
does not cause reflex tachycardia induced vasodilation
it does not lead to arrhythmias
it has no effect on carbohydrate metabolism, metabolism of uric acid, and it does not hold fluid in the human body

Interaction with other drugs: antihypertensive drugs and alcohol increase the antihypertensive effect *urapidil* can be combined with diuretics, β-blockers, calcium antagonists.

Indications for urapidil use:

Hypertension crises that are resistant to other antihypertensive drugs
Arterial hypertension

Adverse effects of urapidil:

Headache
Dizziness
Weakness
Rarely – palpitations, bradicardia, arrhythmia
Gastrointestinal disturbances
Dry mouth

Orthostatic collapse
Sometimes there are allergic skin reactions
Thrombocytopenia
Collapse with the rapid intravenous injection
Priapism (it is a potentially painful medical condition in which the erect penis does not return to its flaccid state, despite the absence of both physical and psychological stimulation, within four hours. Priapism is considered a medical emergency, which should receive proper treatment by a qualified medical practitioner)

Contraindications for urapidil use:

Aortic stenosis
Patent ductus arteriosus
Pregnancy
Lactation
Childhood and adolescence to 18 years
Patients who require rapid mental or physical reactions
It is not recommended to combine with ACE inhibitors
Idiosyncrasy

Indoramin

Pharmacologic effects of indoramin:

- Hypotensive

Indications for indoramin use:

Arterial hypertension
Raynaud's disease/syndrome

Adverse effects of indoramin:

Drowsiness
Nasal congestion
Dry mouth
Ejaculation disorder

Contraindications for indoramin use:

Pregnancy
Lactation

Selective α1-adrenoblockers

Prazosin, Terazosin, Doxazosin, Tamsulosin

They are selective competitive blockers of α1 adrenergic receptors. The use of α1-adrenoblockers in case of arterial hypertension is more preferably in patients with benign prostate hypertrophy, erectile disorders, diabetes mellitus, dyslipoproteinemia, chronic obstructive pulmonary disease and obliterating atherosclerosis of the lower extremities. All selective α1-adrenoblockers decrease peripheral vascular resistance and arterial BP due to relaxation of both, arterial and venous smooth muscles. The first dose of these drugs should be adjusted because it may cause syncope as a result of exaggerated orthostatic hypotension. The first dose of these drugs must be one-third or one-fourth of the therapeutic dose and to be given at bedtime. The risk of development of congestive heart failure is high if selective α1-adrenoblockers use in arterial hypertension as monotherapy. The most

common side effects of selective α1-adrenoblockers are orthostatic hypotension, tachycardia, vertigo and sexual dysfunction.

Prazosin

The peculiarity of *prazosin* is its selective blockage of vessel postsynaptic α1 adrenergic receptors, this leads to interruption of vasospastic action of mediator – NE and vasodilatation. Besides, *prazosin* blocks the α1 adrenergic receptors of urethra and neck of the urinary bladder that leads to dilatation of them and improves uresis. *Prazosin* is short action drug.

Pharmacologic effects of prazosin:

Vasodilative (both, arteries and veins)
Hypotensive
Decreases the peripheral vessel resistance
Diminishes the pre- and afterload on the myocardium
Favorably influences on the lipid composition of blood
Moderate cholinolitic activity
Dilatation of urethra and neck of the urinary bladder

Indications for prazosin use:

Arterial hypertension
Benign prostatic hypertrophy

Adverse effects of prazosin:

Phenomenon of the "first dose" – postural hypotension, collapse
Dizziness
Headache
Weakness
Fatigue
Insomnia
Nausea
Diarrhea
Constipation
Dry mouth
Frequent urination
Peripheral edema
Rarely – tachycardia

Contraindications for prazosin use:

Pregnancy
Lactation
With caution – to patients with kidney diseases

Terazosin

The chemical structure of *terazosin* is closed to *prazosin*, but terazosin is long term action drug. Terazosin blocks postsynaptic α1 adrenergic receptors of the vessels, prostate and the urinary bladder.

Pharmacologic effects of terazosin, indications, side effects, *contraindications for its use are similar to those for prazosin.*

Doxazosin

The chemical structure of *doxazosin* and pharmacological characteristics are closed to *prazosin*, but *doxazosin* is long term action drug.
Pharmacologic effects of doxazosin, Indications, Side effects and Contraindications for doxazosin use are the same as for prazosin. Also, has been described the cases of visual impairment, cholestasis, jaundice, impotence.

Tamsulosin

Tamsulosin is high selective α1A adrenoblocker of the receptors of prostate, neck of urine bladder and prostatic part of urethra and doesn't influences on α1 receptors of the vasculature. *Tamsulosin* is long term action drug. Unlike the first three drugs *tamsulosin* is excreted preferably by the kidneys.

Pharmacologic effects of tamsulosin:

Diminishes the hypertrophy of prostate
Lowers the tone of smooth muscles of the prostate, neck of urine bladder, prostatic part of urethra
Improves uresis
Reduces the symptoms of obstruction and irritation of the urinary tract in benign prostatic hyperplasia

Indications for tamsulosin use:

- Benign prostatic hypertrophy

Side effects and contraindications for tamsulosin use are the same as for prazosin, doxazosin, terazosin.

Selective α2- adrenoblockers

Yohimbine

Yohimbine is an alkaloid of indolealkylamine that is found in bark of a tree Pausinystalia yohimbe and Rauwolfia roots; its structure is similar to the structure of reserpine. Yohimbine is a selective competitive antagonist of α2-adrenergic receptor, easily overcomes the BBB, enters in the CNS, increases the activity of the sympathetic nervous system, potentiates release of norepinephrine from nerve endings, which leads to activation of α1 adrenergic receptors and β1 adrenergic receptors in the heart and peripheral blood vessels, increases BP and heart rate, and locomotor activity and causes tremors.

Pharmacologic effects of yohimbine:

Activates the adrenergic processes in CNS
Enhances the flow of sympathetic impulses from the CNS and release of norepinephrine from nerve endings
Improves the motor activity
Improves the spine reflexes

Relieves vasoconstriction associated with Raynaud's disease

Indications for yohimbine use:

Erectile dysfunction
Incontinence
Atony of urine bladder
Menopause in women
Raynaud's disease

Adverse effects of yohimbine:

Arterial hypertension
Tachycardia
Hand tremor
Headache
Hypererethism
Priapism
Ortostatic hypotension*

- orthostatic hypotension as a side effect of yohimbine may be due to the fact that the drugs affects both the central and the peripheral α2-adrenergic receptors of vessels that can lead to dilatation of peripheral vessels and thus may reduce BP [Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12 edition. Medical. , 2011. - 2084 P.].

Contraindications for yohimbine use:

Arterial hypertension
IHD
High sensitivity to yohimbine
Kidney and/or liver insufficiency

Table 23*. Comparative characteristics of some α-adrenoblockers

Drugs	**Term of action in hours**	**Maximal effect after direction in hours**	**Therapeutic doses in mg/day**	**Multiplicity of drug introduction in day**
Dihydroergotamine	when i/m administ-ration – 3-4	when i/m administration – from 30 minutes to few hours	4-6	2-3 times
Dihydroergotoxinum	its pharmacokinetic parameters correlate poorly with pharmacological effects due to containing in drugs 4 derivatives of Ergot alkaloids, namely dihydroergokornin, dihydroergocrystine, dihydro-		0.3-0.6	1-3 times

	α-ergocryptine, dihydro-β-ergocryptine, each of which has its own pharmacokinetic parameters			
Nicergoline	up to 17	2-4	8-60	2-3 times
Phentolamine	from 10-15 minutes (i/v) up to 4 hours (i/m)	from 2 minutes (i/v) to 20 minutes (i/m)	75-500	3-5 times
Tropodifene		few	20-60	1-3 times
Proroxan	its pharmacokinetic parameters are not defined		180	2-3 times
Phenoxybenzamine	> 48	few	10	1 time
Prazosin	4-6	0,5	1-20	2-3 times
Doxazosin	18-36	5-6	1-20	1 time
Terazosin	> 18	1-1.7	1-20	1-2 times
Tamsulosin	9-22	4-7	0.4	1 time
Indoramin	> 6	2	50-150	2-3 times
Ketanserin	> 12	1-2	20-40	1-2 times
Urapidil	6-8	3-5	15-120	1-2 times

*- adapted from Kaplan N.M. Clinical hypertension 7th edition. Baltimore, 1998 with amendments of authors

Table 24. Medicinal forms of α-adrenoblockers

INN	**Trade names**	**Medicinal forms**	
Dihydroergotamine	Agit, Angionorm, Clavigrenin, Cornhidral; DH-Ergotamin, Diergotan, Dihydergot, Dihydroergotamine mesilate, Dihytamin, Ditamin, Ergomimet, Ergovasan, Ikaran, Migretil, Migrifen, Tonopress, Vasogin, Verteblan, etc.	Peroral solution in flacones; Parenteral solution in ampoules (i/m); Tablets; Aerosol for intranasal introduction	0.2% - 10 ml, 30 ml; 0.1% - 1 ml 0.0025; 1%

Drugs affecting the Autonomic Nervous System

Dihydroergotoxinum	Alkergot, Circanol, Clavor, DH-Ergotoxin, Erginemin, Ergocomb, Ergodibat, Ergohydrin, Ergoloid mesylat, Ergomed, Ergoxyl, Hyderan, Hydergin, Optamine, Redergin, Redergot, Secamin, Secatoxin, Trigot, Vasolax, etc.	Tablets; Peroral solution in flacones; Parenteral solution in ampoules (i/a, i/v, i/m, s/c)	0.0015; 0.1% - 50ml; 0.03% - 1ml
Nicergoline	Sermionum, Dasovas, Dospan, Ergotop, Fisilax, Nargoline, Nicotergoline, Nimergoline, Sinscleron, Varsan, etc.	Tablets; Powder for injections in ampoules (i/v, i/m)	0.005, 0.01; 0.004
Phentolamine	Dibasin, Phentolamine, Regitine, Rogitine	Tablets; Powder for injections in ampoules (i/m, i/v); Parenteral solution in ampoules (i/m, i/v)	0.025; 0.005; 1% - 1ml, 5ml
Tropodifene	Tropaphenum	Powder lyophilized for injections in ampoules to prepare *ex tempore* 1%, 2% solution (i/m, i/v, s/c)	0.02
Proroxan	Pyrroxanum	Parenteral solution in ampoules (i/m, s/c); Tablets	1% - 1ml; 0.015
Phenoxybenzamine	Dibenyline	Tablets	0.01
Ketanserin	Perketal, Serefrex, Sufrexal, Sufroxal, Taseron	Tablets; Parenteral solution in ampoules (i/m, i/v)	20mg, 40mg; 0,5 % - 2ml, 10ml
Urapidil	Ebrantil, Eupressyl	Capsules; Parenteral solution in ampoules (i/v)	30mg, 60mg, 90mg; 0.5% - 5 ml, 10 ml
Indoramin	Baratol, Doralese	Tablets	20 mg, 25mg
Prazosin	Adversuten, Decliten, Deprazolin, Duramipress, Eurex, Furazosin-hydrochloride, Hypovase, Minipress,	Tablets	0.0005, 0.001, 0.002, 0.005

	Orbisan, Patsolin, Peripress, Prastiol, Prazac, Prazopress, Prazosin, Sinetens; Vasoflex, etc.		
Terazosin		Tablets	0.001, 0.002, 0.005, 0.01
Doxazosin	Cardura, Tonocardin	Tablets	0.001, 0.002, 0.004, 0.008
Tamsulosin	Omnic	Capsules	0.4 mg
Yohimbine	Iohimbina, Quebrachin, Yohimvenol	Tablets	0.005

Pharmacologic characteristic of β-adrenergic antagonists

All β-adrenoblockers are competitive antagonists. Non-selective β-adrenoblockers act on β1 and β2 adrenergic receptors, but selective β-adrenoblockers act on β1 adrenergic receptors. β-adrenoblockers also differ in intrinsic sympathomimetic activity (ISA) mediated by stimulation of β2 adrenoceptors of smooth muscles of the vessels and bronchi; in additional vasodilating properties (AVP) due to blockage of α2 adrenoceptors of the vessels; in CNS effects resulting the lipophilic properties and ability to overcome BBB, and in pharmacokinetics. All β-adrenoblockers decrease BP, inhibit renin secretion and reduce renin-angiotensin system activity, but don't induce postural hypotension because α-adrenoceptors remain functional. β-adrenoblockers also are used as drugs for treatment IHD (reduce the need of the heart muscle in oxygen and diminish of heart rate), cardiac arrhythmias (they have negative chronotropic and negative batmotropic effects), congestive heart failure (although β-adrenoblockers themselves can cause heart failure due to negative inotropic effect), hyperthyroidism, glaucoma (lowering intraocular pressure), and they are used for prophylaxis of migraine. β-adrenoblockers belong to antiarrhythmic drugs of the second class. β-adrenoblockers, especially nonselective, deteriorate peripheral blood circulation because result in a narrowing of vessels due to blockade of β-adrenoceptors of the vessels. The names of all β-adrenoblockers end in "-olol" except for *labetalol* and *carvedilol*.

Pharmacodynamics of nonselective β-adrenoblockers:

Vessels: constriction that leads to disoders of peripheral blood circulation; *Heart:* negative inotropic effect, negative chronotropic effect, negative dromotropic effect, negative batmotropic effect; decrease oxygen demand and the influence of β-adrenoblockers on the heart leads to hypotensive, antiarrhithmic, antiischemic effects; *Bronchi:* bronchospasm; *Metabolism:* atherogenic effect, hypoglycemic effect, stimulation of the prostaglandin production, inhibition of platelet aggregation.

Peculiarities of the several β-adrenoblockers

Nonselective β-adrenoblockers:
Propranolol, Sotalol, Timolol, Nadolol

They have all pharmacologic effects which are prescribed in tables 23, 24, 27.

Pharmacologic effects of them:

Negative inotropic, diminish cardiac output, and cardiac work
Negative chronotropic
Negative batmotropic, depress sinoatrial and atrioventricular activity
Decrease the cardiac oxygen consumption
Inhibit the rennin release from the kidney
Decrease the sympathetic stimulation from CNS
Hypotensive
Antarrhythmic
Antiischemic
Decrease the glycogenolysis, decrease the glucagon secretion that may cause expressed hypoglycemia in patient with diabetes mellitus who are receiving insulin or oral hypoglycemic drugs
Debilitate the normal physiological response to hypoglycemia
Diminish the intraocular pressure in glaucoma by decreasing the secretion of aqueous humor by the ciliary body (β-adrenoblockers neither affect the ability of the eye to focus for near vision nor change pupil size, as cholinergic drugs)

Indications for their use:

Prophylactic of IHD and insult
Chronic IHD (β-adrenoblockers not useful for acute IHD)
Increase tolerance to moderate exercises in patients with IHD (but not to strenuous exercises)
Prophylactic of sudden death in patients with cardiovascular disorders
Chronic heart insufficiency
Aortic aneurysm (aortic dilation) – prophylactic of aortic exfoliation
Cardiomiopaty
Organic heart defects
Chronic glaucoma (β-adrenoblockers aren't drugs of choice in an acute attack of glaucoma)
Migraine (β-adrenoblockers reduce migraine episodes and severity of the attacks if are used prophylactically because they block catecholamine-induced vasodilatation in the brain vasculature)
Hyperthyroidism (β-adrenoblockers attenuate the sympathetic stimulation that occurs in hyperthyroidism and prevent serious cardiac arrhythmias)

Adverse effects of them:

Peripheral vasoconstriction, insufficiency of peripheral blood circulation
Bradycardia

Heart blocks
Bronchoconstriction
Decrease the renal perfusion, resulting in an increase in Na^+ retention and plasma volume, and in some cases elevate the BP (the combination with diuretics is needed)
Disturbances of lipid metabolism (atherogenesis)
Disturbances of carbohydrate metabolism (hypoglycemia)
CNS dysfunction, sleep disorders, weakness, hallucinations
Withdrawal syndrome (treatment with β-adrenoblockers must never be stopped quickly because of the risk of cardiac arrhythmias, hypertensive crisis, but this treatment must be stopped gradually for 1 week)
Up-regulation of the β-adrenergic receptors as a result the stoppage of therapy and may lead to worsen angina or arterial hypertension
Sexual impairment in men: the mechanism of this side effect isn't clear, because the sexual function in male occurs through α-adrenergic regulation

Contraindications for their use:

Obstructive pulmonary diseases
Asthma
Impairments of peripheral blood circulation
Diabetes mellitus
Expressed atherosclerosis
Pregnancy (β-adrenoblockers reduce the placental blood circulation)
Lactation
During the period of treatment one should refrain from driving motor vehicles and classes of potentially hazardous activities that require high concentration and quickness of psychomotor reactions

Timolol and *nadolol* are more potent than *propranolol. Timolol* reduces the production of aqueous humor in the eye and is used topically in treatment of chronic open-angle glaucoma. *Nadolol* is a long-term action drug. *Nadolol* reduces the formation of cAMP from ATP which is stimulated by catecholamines, as a result nadolol reduces intracellular calcium ion current. The features of *sotalol* are: ability to block potassium current, increase the action potential and the absolute refractory period in all the areas of cardiac conduction system which gives grounds to consider it as an antiarrhythmic drug of the third and second class (a mixed mechanism of action).

Table 25*. Metabolic adverse effects of nonselective β-adrenoblockers that are connected with blockade of β2-adrenergic receptors

Adverse effects	Mechanism
Impairment of glucose tolerance (diabetogenic effect)	Reduction of insulin secretion and increasing in insulin resistance by 25-30%
Dyslipidemia (hypertriglyceridemia, reduced HDL cholesterol)	Reduced activity of lipoprotein lipase, splitting triglycerides to free fatty acids

Violation of detection of hypoglycemia (in patients with diabetes mellitus receiving glucose-lowering therapy)	Reducing emissions of catecholamines that mediate the symptoms of hypoglycemia (tachycardia, tremor, etc.)
Difficult exit from the hypoglycemic state (risk of hypoglycemic coma)	Braking mechanisms for the release of glucose into the blood (glycogenolysis in liver and muscle and gluconeogenesis in the liver), suppression of glucagon secretion
Worsening of peripheral angiopathy	Arterial vasoconstriction

*- adapted from Shestakova M.V. Beta-blockers in diabetes mellitus: view of endocrinologist. / Diseases of heart and vessels. V 2.- №2. 2006.

Selective β1-adrenoblockers: Atenolol, Metoprolol, Betaxolol, Bisoprolol, Talinolol

Compared with the nonselective β-adrenoblockers selective β-adrenoblockers are less likely cause bronchoconstriction, they are less likely worsen the peripheral blood circulation, they are less likely cause hypoglycemia, they are less manifest atherogenic effect, they rarely cause withdrawal syndrome. A common side effect of therapy by selective β1-adrenoblockers is less frequent compared to that of nonselective β-adrenoblockers. The cardioselectivity is most pronounced at low doses and is lost at high doses. Thereby, the treatment with selective β1-adrenoblackers of the patients with hypertension or/and angina and concomitant diseases such as asthma, obstructive bronchitis, diabetes mellitus must be carefully monitored to make that respiratory activity, level of glucose in the blood, peripheral blood circulation aren't compromised.

Nonselective β1-, β2-adrenoblockers with intrinsic sympathomimetic activity: pindolol, oxprenolol, and Selective β1-adrenoblockers with intrinsic sympathomimetic activity: acebutolol

β-adrenoblockers with ISA (*pindolol, oxprenolol, acebutolol*) stimulate β2-adrenergic receptors and yet they inhibit stimulation by more potent endogenous catecolamines, *epinephrine* and *norepinephrine.* That's why they have less effect on cardiac rate, cardiac output, do not impair the peripheral blood circulation, minimize the bronchoconstriction, disturbances of lipid and carbohydrate methabolism compared to that of β-blockers without ISA. β-adrenoblockers with ISA are effective in patients with angina and hypertensive patients with moderate bradycardia, diabetes mellitus, asthma, obstructive bronchitis, but aren't used as antiarrhythmic drugs.

Nonselective β1-, β2-adrenoblockers with additional vasodilating properties: (dilevalol, bucindolol, carteolol, and Selective β1-adrenoblockers with additional vasodilating properties: celiprolol, nebivolol

β-adrenoblockers with AVP (*dilevalol, bucindolol, carteolol, celiprolol, nebivolol*) block α1-adrenergic receptors of the vessels and don't cause peripheral vasoconstriction. *Nebivolol* also stimulates synthesis of endogenous *NO* (*nitric oxide*) which is an additional factor of vasodilating. *Dilevalol* is the *R,R*-stereoisomer of *labetalol*, it is β2 agonist, and a weak blocker of α1-adrenergic receptors, reduces hypertrophy of the left ventricle, has positive action on plasma lipid profile. The use of *dilevalol* is restricted by its hepatotoxic activity.

Nonselective β1-, β2-, α1-adrenoblockers: Labetalol, Carvedilol

Labetalol and *carvedilol* are simultaneous β1-, β2-, α1-adrenoblockers that induce peripheral vasodilating effect and reduce BP. They are effective in patients with increased peripheral vascular resistance and don't change lipid and glucose blood levels. *Carvedilol* also decreases lipid peroxidation, thickening of the vessel's walls that are very important in the patients with heart insufficiency. *Labetalol* may be used as an alternative to *methyldopa* in the treatment of pregnancy-induced hypertension and as intravenous injections it is also used to treat hypertensive crisis.

Sympatholitics: Guanethidine, Bretylium tosilate, Reserpine, Raunatinum

They are indirect adrenergic blockers that act on endogenous *norepinephrine* and don't act on adrenergic receptors directly.

Guanethidine (Octadin, Isobarin) is the pharmacologic competitor of NE in vesicles of adrenergic synapse. Practically *Guanethidine* is not applied currently because of serious side effects and contraindications.

Pharmacologic effects of guanethidine:

Hypotensive
Antarrhythmic

Indications for guanethidine use: in nowadays its use is restricted by its adverse effects.

Adverse effects of guanethidine:

Postural hypotension
Bradycardia, tachycardia

Contraindications for guanethidine use:

IHD
Impairment of brain blood circulation
Impairment of coronary blood circulation
Pheochromocytoma

Bretylium tosilate (Ornid) blocks NE release from presynaptic endings that leads to the reduction of its influence on adrenergic receptors. Besides, *Bretylium tosilate* has direct action on cell's membranes of the heart, blocks potassium channels in the membrane cells of the heart, as the antiarrhythmic drug of the third class. At the first phase of *Bretylium tosilate* action is NE release from depots that

causes tachycardia and hypertension. At the second phase of *Bretylium tosilate* action is sympathetic blockage adrenergic neurons that leads to decreasing of BP and heart rate and it may cause postural hypotension. *Bretylium tosilate* doesn't affect the function of postganglionic adrenergic receptors.

Pharmacologic effects of bretylium tosilate:

Hypotensive
Antarrhythmic

Indications for bretylium tosilate use:

Ventricular fibrillation
Ventricular tachycardia refractory to other antiarrhythmic drugs, especially in the patients with acute myocardial infarction
Ventricular arrhythmia
Arrhythmia *torsade de pointes*

Adverse effects of bretylium tosilate:

Postural hypotension
Bradycardia, tachycardia
Chest pain, increased frequency of angina attacks
Dizziness, mental confusion
Psychosis, drowsiness, increased tactile and pain sensitivity
Hyperthermia
Dyspnoea
Nausea, vomiting
Kidney insufficiency
Diarrhea
Nasal congestion

Contraindications for bretylium tosilate use:

Aortic stenosis
Severe pulmonary hypertonia
Uncontrolled heart insufficiency
Acute impairment of brain blood circulation
Severe kidney insufficiency

Drugs that decrease the reserves of NE in adrenergic synapses: *reserpine*, *Rauwolfia alkaloids* (Raunatinum is a combined drug).

Pharmacologic effects of reserpine:

Hypotensive effect is developed gradually in few weeks after enteral introduction and in 2-4 hours after parenteral introduction
Neuroleptic

Indications for reserpine use only as part of combination drugs:

Arterial hypertension (its use is restricted through development of Parkinson syndrome and need a long time for the manifestation of hypotensive effect)
Severe psychosis, shizophrenia (in combined therapy)
Thyrotoxicosis (in combined therapy)
Alcoholic psychosis

The late toxemia of pregnancy

Adverse effects of reserpine:

Drowsiness
Dizziness
Depression
Stupor
Extrapyramidal syndrome
Increased frequency of epileptic seizures
Nightmares
Diarrhea
Nasal congestion
Peptic ulcers of stomach
Liquid retention and edema that doesn't connect with heart insufficiency
Weight gain
Bradycardia, arrhythmia
Decreased libido
Hyperemia of the mucous membranes of the eyes
Rash
Syndrome of disseminated lupus erythematosus

Contraindications for reserpine use:

Severe heart insufficiency
Bradycardia
Nephrosclerosis
Severe cerebral atherosclerosis
Stomach and duodenum ulcer disease
Epilepsy
Parkinson disease
Depression

Pharmacologic effects of Raunatinum:

- Hypotensive effect is developed gradually in 10-14 days

Indications for Raunatinum use, side effects, and contraindications are the same as in *reserpine,* but *Raunatinum* has peculiarities: it has antiarrhythmic effect, calming effect on the CNS, hypotensive effect, neuroleptic effect and side effects are less pronounced than in *reserpine.*

Table 26. Medicinal forms of β-adrenoblockers, Sympatolitics

INN	Trade names	Medicinal forms	
Propranolol	Alindol, Anaprilin, Angilol, Antarol, Avlocardyl, Bedranol, Betadren, Bricoran, Cardinol, Caridorol, Dederal, Deralin,	Tablets; Capsules; Parenteral solution in ampoules (i/v);	0.01, 0.04, 0.08, 0.16; 0.04, 0.08; 0.25% - 1 ml;

	Dociton, Elanol, Eliblok, Inderex, Indicardin, Naprilin, Noloten, Obsidan, Opranol, Prolol, Propanur, Propral, Propranobene, Pylapron, Sloprolol, Stobetin, Tenomal, Tiperal, etc. Betakep TR, Inderal, Obsidan	Eye drops in tube-droppers and in flacons	1% - 1.5 ml; 1% - 5 ml
Sotalol	Berdex, Betapace, Darob, Gilucor, Loritmic, Sotahexa, Sotalex, Tachytalol	Tablets; Parenteral solution in ampoules (i/v)	0.08; 0.16; 1% - 4 ml
Timolol	Blocadren, Blocanol, Temserin, Timacar, Timacor, Arutimol, Glaumol, Glymol, Glucomol, Cusimolol, Nyolol, Ocumed, Ocumol, Ocupres-E, Ocuryl, Ocutim, Optimol, Oftan Timolol, Oftensin, Timohexal, etc.	Tablets; Eye drops in flacons and in tube-droppers	0.005, 0.01, 0.02; 0.1%, 0.25% -5ml; 0.1%, 0.25% - 2.5 ml, 10 ml
Pylocarpine +Timolol	Fotil, Timpilo		0.5%+2% - 5 ml; 0.5%+4% - 5 ml
Nadolol	Anabet, Betadol, Corgard, Nadic, Solgol Corzid	Tablets;	0.04, 0.08;
Nadolol + Bendroflumethiazide		Tablets	0.04/0.08 + 0.005
Pindolol	Betadren, Blocklin, Carvisken, Durapindol, Pectobloc, Pinadol, Pinbetol, Pindomex, Pinloc, Prindolol, Viscen, etc.	Tablets;	0.005;
Pindolol + Clopamid	Viskaldix	Tablets	0.01 + 0.005
Oxprenolol	Captol, Cordexol, Coretal, Laracor, Oxanol, Oxprenololi hydrochloridum, Tracosal, Trasacor, Trasicor, Slow-trasicor, etc.	Tablets	0.02, 0.08, 0.16
Dilevalol		Tablets; Parenteral	0.2; 50 mg

		solution in ampoules (i/v)	
Carteolol	Teoptic	Tablets; Eye drops	2.5 mg; 1% - 5 ml
Atenolol	Apo-Atenolol, Atcardil, Atenobene, Atenol, Atenova, Betacard, Betadur, Blokium, Catenol, Catenolol, Highpoten, Hipres, Myocord, Normiten, Ormidol, Prenormine, Prinorm, Sinarom, Telvodin, Tenobloc, Tenolol, Tenormin, Tensicor, Uniloc, Velorin, Vericordin, etc.	Tablets;	0.025, 0.05, 0.1;
Atenolol+Chlortalidone	Atehexal compositum, Tenoret, Tenoretic	Tablets	50 mg + 12.5 mg, 100 mg + 25 mg
Metoprolol	Beloc, Betaloc, Blocksan, Egiloc, Korvitol, Lopressor, Metocard, Metohexal, Metolol, Metazok, Neobloc, Opresol, Selopral, Specior, Presolol, Vasocardin, Veobloc, etc.	Tablets; Tablets-retard; Parenteral solution in ampoules (i/v);	0.025, 0.05, 0.1; 0.05, 0.1, 0.2; 0.1% - 5 ml
Metoprolol + Felodipine	Logimax	Tablets	47,5/90 mg + 5/10 mg
Betaxolol	Betac, Locren, Betoptic, Betoptima, Betoxolol, Kerione	Tablets; Eye suspension in flacons; Eye drops in flacons-droppers	0.01, 0.02; 0.25% - 5 ml, 10 ml; 0.5% - 5 ml
Bisoprolol	Bisogamma, Concor, Concor Cor	Tablets	0.005, 0.01, 0.0025
Talinolol	Cordanum,	Dragee; Tablets; Parenteral solution in ampoules (i/v);	0.05; 0.2% - 5 ml;
	Codanum-100	Prolonged tablets, dragee	0.1
Acebutolol	Sectral	Tablets	0.2, 0.4
Celiprolol	Cellipres, Celiprol	Tablets	0.1, 0.2
Nebivolol	Nebilet	Tablets	0.005

Labetalol		Tablets; Parenteral (i/v) solution in ampoules	0.1, 0.2; 1% - 5 ml
Carvedilol	Credex, Dilatrend	Tablets	0.00625, 0.0125, 0.025
Guanethidine	Abupressin, Antipres, Azetidin, Declidin, Eutensol, Guanexil, Guanisol, Ipoctal, Ipoguanin, Iporal, Ismelin, Isobarin, Octadin, Octatenzine, Oftalmotonil, Oktatensin, Pressedin, Sanotensin, Visutensil, etc.	Tablets	0.025
Bretylium tosilate	Bretylan, Bretylat, Bretylin, Bretylol, Darenthin, Ornid, etc.	Parenteral solution in ampoules (i/v, i/m)	5% - 1 ml
Rauwolfia alkaloids	Raunatinum, Rauwasan, etc.	Tablets	0.002
Reserpine	Serpasil, Rausedyl, etc.	Tablets; Parenteral solution in ampoules (i/v, i/m);	0.0001, 0.00025; 0.1% - 1 ml; 0.25% - 1 ml
Reserpine+Dihydralazine	Adelphan Adelphane-Esidrex,	Tablets;	10 mg + 100 mg
Reserpine+Dihydralazine+Hydrochlorothiazide	Antihypertonin, Barophane Zidrex, Relsidrex-G, Phensidrex-H, Alsidrex-H, Trirezid, Triniton Trirezid K	Tablets;	0.1 mg +10 mg + 10 mg
Reserpine+Dihydralazine+Hydrochlorothiazide+ Potassium chloride	Brinerdin, Crystepin,	Tablets;	0.1 mg + 10 mg + 10 mg + 30 mg
Reserpine+ Dihydroergocristine+ Clopamide	Normatens, Acenosin Neocristipin	Tablets, Dragee;	0.1 mg + 0.5 mg + 5 mg
Reserpine+ Dihydroergocristine+ Chlortalidone	Sinepres	Dragee;	1 mg + 0.58 mg + 25 mg
Reserpine+ Dihydroergotoxine+ Hydrochlorothiazide		Tablets, Dragee	0.1 mg + 0.6 mg + 10 mg

Table 27*. Pharmacological characteristics of Adrenergic Antagonists

Pharmacological group	**Pharmacological actions**	**Principal therapeutic aplications**	**Untoward effects**	**Comments**
α-blockers:				
non-selective α1,α2 *(phenoxybenzamine, phentolamine, tolazoline)*	Reduction of peripheral vascular resistance and BP, Venodilation	Treatment of catecholamine excess (e.g., pheochromocytoma)	Postural hypotension, Failure of ejaculation	Cardiac stimulation due to initiation of reflexes and to enchanced release of NE via α2 receptor blockade; *phenoxybenzamine* produces long-lasting α receptor blockade, can block neuronal and extraneuronal uptake of amines
α1-selective *(prazosin, terazosin, doxazosin, tamsulosin, trimazosin, alfuzosin, silodosin)*	Reduction of peripheral vascular resistance and BP, Relax smooth muscles in neck of urinary bladder and in prostate	Primary hypertension, Increase urine flow in benign prostatic hypertrophy	Postural hypotension when therapy instituted	*prazosin* and related quinazolines are selective for α1 receptors *tamsulosin* exhibits some selectivity for α1A receptors
β-blockers:				
non-selective (first generation): *nadolol, penbutolol, pindolol, propronolol, oxprenolol, timolol*	Reduction of heart rate, Reduction of contractility, Diminution of cardiac output, Slow conduction atria and AV node, Elongation of refractory period, AV node, Bronchoconstriction,	IHD, angina pectoris, Hypertension, Cardiac arrhythmias, Congestive heart failure, Pheochromocytoma, Glaucoma, Hypertropic obstructive cardiomyopathy,	Bradycardia, Negative inotropy, Diminution of cardiac output, Bradyarrhythmias, Slow AV conduction, Bronchoconstriction, Fatigue, Sleep	Effects depend on sympathoadrenal tone, Bronchoconstriction (of concern in asthmatics and chronic obstructive pulmonary disease), Hypoglycemia (of concern in hypoglycemics and diabetics), Membrane

	Prolonged hypoglycemia, Reduction of plasma level of FFA, Reduction of HDL cholesterol level, Increase of LDL cholesterol level and TG, Hypokalemia, Reduction of intraocular pressure	Hyperthyroidism, Migraine prophylaxis, Acute panic symptoms, Substance abuse withdrawal, Variceal bleeding in portal hypertension	disturbances (insomnia, nightmares), Prolongation of hypoglycemia, Sexual dysfunction in men, Drug interactions	stabilizing effect *(propranolol)*; intrinsic sympathomimetic activity (strong for *pindolol, oxprenolol,* weak for *penbutolol* – long action drug)
β1-selective (second generation): *acebutolol, atenolol, bisoprolol, betaxolol, esmolol, metoprolol*				Membrane stabilizing effect and intrinsic sympathomimetic activity (weak) *(betaxolol)*
non-selective (third generation) vasodilators: *carteolol, carvedilol, bucindolol, labetalol*	Membrane stabilizing effect *(carteolol, carvedilol),* Intrinsic sympathomimetic activity *(bucindolol),* Vasodilation *(labetalol)*			Vasodilation seen in 3rd generation drugs; multiple mechanisms (table 24)
β1-selective (third generation) vasodilators: *celiprolol, nebivolol*				

* - adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12 edition. Medical. 2011. – 2084 P. with amendments of authors

Table 28. Third generation β receptor antagonists with putative additional mechanisms of vasodilatation*

Nitric oxide production	**B2 receptor agonism**	**α1 receptor antagonism**	**Ca^{2+} entry blockade**	**K^{+} channel opening**	**Antioxydant activity**
celiprolol**, nebivolol, carteolol, bopindolol**, nipradilol**	celiprolol**, carteolol, bopindolol**	carvedilol, bucindolol, bevantolol** nipradilol**, labetalol	carvedilol, betaxolol, bevantolol**	tilisolol**	carvedilol

* - adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12 edition. Medical. 2011. – 2084 P.

** - not currently available in the U.S., where most are under investigation for use

UNIT 4. DRUGS AFFECTING the AFFERENT INNERVATION

The drugs affecting the Sensory nerve endings are devided in two groups:

Drugs reducing sensitivity of afferent nerve endings, or defending them from irritant effects of various substances: *local anestetics, adsorbents, enveloping substances, astringents*

Drugs stimulating afferent nerve endings: *irritants, bitterness, emetics, laxatives, expectorants.*

Chapter 8. Local anesthetics

Local anesthetics (LAs) are the plant origin drugs that induce reversible loss of algesthesia (pain sensitivity) and other types of sensitivity due to direct contact with membrane of nerve cells while maintaining the consciousness.

Mechanism of action. Las are the drugs that reversibly connect with certain receptor site within the pores of Na^+ channels in nerves and block ion movement via the pores. LAs decrease permeability of cell membranes for Na^+ ions, block Na^+ ions channels. LAs stabilise cell membranes in phase of polarization. Therefore, LAs block the generation and the conduction of nerve impulses. LAs can bind to other membrane proteins, in particular, they can block K^+ channels, but this requires its higher concentrations.

Different sensitivity of nerve fibers to LAs has great individual variation. Herewith LAs are the dose-dependent drugs, and can act on any part of the nervous system and on every type of nerve fiber, reversibly blocking the transmission of nerve impulse. LAs firstly block pain sensitivity, followed – temperature sensitivity, and further LAs block tactile sensitivity (touch and deep pressure), and finally – motor function. Thereby, the LAs cause the reversible loss of different types of sensitivity: pain, temperature, tactile when applied locally to nerve tissue. Moreover, LAs act on vegetative nerves, namely on autonomic nervous system in case of systemic action. Currently the exact mechanisms responsible for the special action of LAs on the different nerve fibers are not known.

The requirements for local anesthetics:

selective action
short latent period
large latitude of therapeutic action, which ensures the safety of Las use
long-term and strong effect
high effectiveness in all types of anesthesia
they must cause vasoconstriction
they shouln’t irritate tissues in the place of administration

- they should withstand the sterilization

Unfortunately, all known LAs, except *cocaine, bupivacaine, ropivacaine* cause vasodilatation, which leads to a shortening of the duration of the action and to the manifestation of negative side effects, as a result of their systemic action. So, the modern LAs are applied, as combined forms with vasoconstrictors such as *epinephrine*, *norepinephrine*, and *phenylephrine* to prevent absorption in vascular bed.

Classification of LAs

(concerning the origin, the chemical structure and ability to dissolve in water)

Native drugs

cocaine (methylbenzoylecgonine)

II. Syntetic drugs

esters

water-soluble: procaine
tetracaine
benzofuracaine
chloroprocaine

partly water-soluble: benzocaine

amides: lidocaine
articaine
trimecaine
bupivacaine
ropivacaine
mepivacaine
bumecaine
prilocaine

III. Combined drugs:

Pavesthesinum
Bellasthesinum
Anesthesiolum
Anaesthesol
Menovasin
Almagel
Palnmagel A
Remagel A
Heparin ointment
Ultracaine D-C
Emla
Pliaglis
Synera
Ligenten
Dietrin
Xylestesin-F "Forte"

Dentinox
Mydocalm-Richter
Xylodont
Lidocaton
Xylocain adrenaline
Octocaine 50
Oflocaine-Darnitsa
Instillagel
Cathejell with lidocaine
Lidochlor
Supertendin 2000 N
Consol
Alphacaine N
Alphacaine SP
Brilocaine - adrenaline
Septanest with adrenaline
Ubistesine
Citocartin
Primacaine
Septonest with adrenalin
Marcaine Adrenaline
Trimecaine with noradrenaline for injections
Dioxysol
Galagran
Catacel A
Levosin
Mepidont, etc.

There are 3 types of local anesthesia:

terminal (superficial, topical – anesthesia of the mucous membranes and skin)
regional, field block (conductive – via the nerve fibers)
infiltrative (is the injection of LAs directly into tissue, layer by layer, not considering the course of cutaneous nerves).

The advantages of amide LAs before ester LAs:

amide LAs are stable in human tissues in place of administration, consequently they have a long-term action, inasmuch amide LAs are destroyed in the liver by microsomal enzymes after absorption of LAs in vascular beds. Whereas, the ester LAs are rapidly destroyed in place of administration by specific tissue esterases and plasma esterase after absorption into the circulation, and as a result have a short-term action

amide LAs are more potent in comparison with ester LAs because they are stable in acid environment (environment of inflammation), while ester LAs are not stable in these conditions
amide LAs less likely to cause allergic reactions than ester LAs.

Clinical uses of LAs. *Cocaine* does not apply in the clinic because of the toxic effects. Of all known LAs only cocaine reduces the reuptake of catecholamines, specifically NE, in both the central and peripheral nervous systems that provides its high toxicity: vasoconstriction, euphoria. In some contries cocaine is used as 1%, 4%, 10% solution for topical application for topical anesthesia of the upper respiratory tract. Maximal safe dose of cocaine for topical anesthesia in a healthy 70-kg adult are 150mg. Peak of anesthetic effect of cocaine occurs within 2-5 minutes and lasts for 30-45 minutes.

Lidocaine is the standard for all LAs and is used for all types of local anesthesia, namely topical, ophthalmic, mucosal, transdermal, injection. Additionally lidocaine is used in combined preparations such as *Lidoderm* (transdermal path for relief of pain associated with postherpetic neuralgia), *Dentipath* (oral patch for application to superficial dental procedures), *Emla* (for venipunctura, skin graft harvesting, infiltration anesthesia into genitalia), *Pliaglis* (for superficial dermatological procedures such as a filler injections and laser-based treatment), *Synera* (for skin excision, electrodesiccation, shave biopsy of skin lesions). Lidocain is absorbed rapidly after parenteral, enteral administration and from respiratory tracts. Co-administration lidocaine with any vasoconstrictors allow decreasing the rate of its absorption, toxicity, and prolongs its activity. Moreover, lidocaine is also used as antiarrhythmic drug, as well as *trimecaine*. Lidocaine has side effects, especially in high doses. There are drowsiness, tinnitus, dysgeusia, dizziness, twitching, and even seizures, coma, respiratory depression and arrest and cardiovascular depression.Maximal safe dose of lidocaine for topical anesthesia in a healthy 70-kg adult are 300mg. Peak of anesthetic effect of lidocaine occurs within 2-5 minutes and lasts for 30-45 minutes.

Bupivacaine is a popular drug for prolonged analgesia during labor or the postoperative period and in case of indwelling catheters and continuous infusions. But bupivacaine is cardiotoxic and may cause ventricular arrhythmias, myocardial depression after inadvertent intravascular administration. This cardiac toxicity is enhanced by coexisting acidosis, hypercarbia, and hypoxemia.

Articaine is used for dental and periodontal anesthesia. This drug has a rapid (analgesia occurs within 1-2 minutes after administration) and prolonged (1-3 hours) action. Articaine has low toxicity, can not overcome BBB, it binds weakly to plasma proteins, and it is the drug of choice for pregnant women and nursing mothers.

Mepivacaine, *Prilocaine* are the intermediate-acting amide Las and they have pharmacological effects similar to lidocaine. *Mepivacaine* is more toxic in the neonate, and thus it is not used in obstetrical anesthesia. *Prilocaine* has a small vasodilatory effect and may be used without a co-administered vasoconstrictor, it has small CNS toxicity, but its use is limited by methemoglobinemia, which may be treated by the intravenous administration of methylene blue.

The other local anesthetic *benzocaine* which is poorly soluble in the water and is used for terminal anesthesia, it can also elicit methemoglobinemia.

Ropivacaine is less potent and less cardiotoxic than bupivacaine, and more motor-sparing than bupivacaine. The *S*-enantiomer is less toxicy than *R*-isomer. Rupivacaine is suitable for both epidural and regional anesthesia.

Procaine was the first synthetic LA, and it is an ester. In nowadays procaine is bounded to infiltration anesthesia and sometimes for diagnostic nerve block, because procaine has low potency, slow onset, short duration of activity and often causes allergic reactions including cross-allergic reaction with antimicrobial drugs such as sulphonamides and peroral hypoglycemic drugs such as sulfonylureas.

Chloroprocaine is a new ester, chlorinated derivative of procaine. It has rapid onset, short duration of action, fast metabolism, reduced acute toxicity, and it is used for epidural and subarachnoid anesthesia.

Benzofuracaine is a local anesthetic and has central analgesic activity. It may be used in stomatology for infiltration anesthesia, and as an analgesic in patients with pancreatitis, peritonitis, kidney and liver colics, acute pleuritis, and diseases and trauma of peripheral nervous system.

Tetracaine is an ester and it is more potent, has longer duration, more slowly metabolized and has higher toxicity than procaine. Currently tetracaine is widely used in spinal anesthesia in case of need for long duration anesthesia, and as a part of several topical anesthetic preparations. Maximal safe dose of tetracaine for topical anesthesia in a healthy 70-kg adult are 50mg. Peak of anesthetic effect of tetracaine occurs within 3-8 minutes and lasts for 30-60 minutes.

LAs are used primarily for mucous membranes and skin anesthesia. There are *benzocaine, tetracaine, trimecaine, bumecaine, etc*. *Proparacaine* and *tetracaine* are used frequently in ophthalmology. It should be stressed that long-term use of the topical anesthesia to the eye has been associated with retarded healing, pitting, sloughing of the corneal epithelium, and predisposition of the eye to inadvertent injury. Thus, self-treatment with these drugs is dangerous.

For the local anesthesia of mucous membranes of the nose, ear, mouth, throat, tracheobronchial tree, esophagus, genitourinary tract the water solution of many LAs or suspensions of the poorly soluble LAs can be applied. There are *tetracaine, lidocaine, and cocaine*. The shrinking of mucous membranes (one of the effects of LAs) reduces the operative bleeding that is very important during the operation. Epinephrine, topically, as additional vasoconstrictor, as a part of any LAs, has no considerable local effects and can not prolong the term of LAs action applied to mucous membranes due to poor penetration.

In general, topical anesthesia always has the risk of systemic toxic effects in consequence of properties of LAs are absorbed rapidly into the circulation. LAs rate of absorption into circulation depends on the place of application. So, the highest rate of absorption of the LAs occurs from alveolar mucosa, and the smallest - from the laryngeal mucosa, that can be represented as following order: larynx < trachea < bronchi < alveoli. In addition, LAs absorption into the circulation occurs from uretra very quickly, and from the mucosa of the urinary bladder – slowly.

Infiltrative anesthesia. For this type of local anesthesia the *epinephrine* can be used as vasoconstrictor. But, its application should be avoided in those for whom adrenergic stimulation is undesirable, and into tissues supplied by end arteries, videlicet fingers, toes, ears, the nose, the penis because narrowing of blood vessels can lead to gangrene. *Lidocaine, procaine, bupivacaine* are used most frequently for infiltration anesthesia. The main advantage of this type of anesthesia is an absence of disordes of normal body functions. The main disadvantage of this type of anesthesia is the feasibility to use LAs on relatively small areas in minor surgery, and the inability to use LAs on the large areas in major surgery because of possible systemic toxic effects. Infiltrative anesthesia may be applied at one of several levels: subcutaneously, at major nerves, or the spinal roots.

Field block (regional) anesthesia is performed by subcutaneous injection of solution of LAs in order to anesthetize the region distal to the injection. This type of anesthesia can be viewed as a special case of infiltrative anesthesia.

Nerve block anesthesia is the injection of solution of LAs into or around individual peripheral nerves or nerve plexuses that provides the anesthesia of actually the large areas. *Lidocaine, mepivacaine, bupivacaine* are used for this type of anesthesia. The choice of LAs for nerve block anestesia is determined firstly by LAs properties, secondly by purposes of local anesthesia.

Intravenous regional anesthesia is based on using the vasculature to deliver the LAs to the nerve trunks and endings. For intravenous regional anesthesia local anesthetic solution such as *lidocaine, prilocaine* are used without vasoconstrictor. Intravenous regional anesthesia is applied most often for surgery of the forearm and hand, but can be adapted for the feet and legs.

Spinal anesthesia is the most popular forms of anesthesia, and is performed by injection of LAs, such as *lidocaine, bupivacaine, ropivacaine*, into the cerebrospinal fluid in the lumbar space. Spinal anesthesia is a safe and effective technique, especially during surgery involving the lower abdomen, the lower extremities, and perineum.

Epidural anesthesia is administered by injection of LAs into epidural space - the space bounded by the ligamentum flavum posteriorly, the spinal periosteum laterally and the dura anteriorly. Epidural anesthesia can be performed in the sacral hiatus, or in the lumbar, thoracic, or cervical regions of the spine. The primary site of action of this form of anesthesia is on the spinal nerve roots, also on the spinal cord and on the paravertebral nerves. For epidural anesthesia *bupivacaine, lidocaine, chloroprocaine* may be used.

Table 29. The main clinical use of Local anesthetics

Drug	**Types of anesthesia**				**Additional properties**
	Terminal	Infiltrative	Conductive	Spinal	
Procaine		+	+	+	Procaine is used for blokades in case of different diseases of internal organs,

					eczema, atopic dermatitis; Also it can be used in patients with vessel spasms, ulcer disease in GIT, atherosclerosis, arterial hypertension, arthronosos (joint disease), late toxicosis of regnancy with arterial hypertension; Procaine potentiates action of drugs for general anesthesia, it has antishock action, spasmolitic action; Procaine is used in patients with atrial fibrillation as antiarrhythmic drug; Procaine is used as solvent for antibiotics
Tetracaine	+				It has limited use because of the high toxicity
Benzocaine	+				It is used for anesthesia of the mucous membrane of the esophagus and stomach in the form of tablets and powders; as well as a combined preparations in the form of ointments, powders, aerosols, oil solutions for external use, it can be use for local anesthesia for relief pain in case of hemorrhoids, anal fissures, burns of I^{st} and II^{nd} degree, etc.
Lidocaine	+	+	+	+	Lidocaine is used not only as LA, but also it is used as antiarrhythmic drug; It is a solvent for antibiotics; It has significant side effects
Articaine		+	+	+	It is drug of choice for pregnant women and nursing mothers
Trimecaine	+	+	+	+	It is used as a LA and as an antiarrhythmic drug
Bupivacaine		+	+	+	This is one of the most active and long-acting (up to

					7 hours) LA; It has a high cardiotoxicity in getting into general circulation; It can be used for labor pain relief, as it does not overcome the placenta and other biological barriers in the body; It is contraindicated for use in children under 12 years
Ropivacaine		+	+	+	Ropivacaine is used in those with cesarean section; It is contraindicated for use in children under 12 years
Mepivacaine	+	+	+		Mepivacaine is not recommended for subarachnoid administration; It should be used with caution in elderly people
Bumecaine	+				It is used as a LA and as antiarrhythmic drug
Prilocaine		+	+		The risk of methemoglobinemia is higher in case of the use of prilocaine than other LAs; It should be used carefully in children and the elderly people
Chloropro-caine		+	+		It has a rapid onset of action, rapid metabolism, low acute toxicity
Benzofuro-caine		+			Benzofurocaine has a central analgesic properties; As analgesic agent, it is used in patients with pancreatitis, peritonitis, hepatic and renal colic, acute pleuritis, diseases and injuries of the peripheral nervous system; This drug is prone to accumulation

Undesired effects of LAs. LAs have significant effects on the *CNS*, the *autonomic ganglia*, the *neuromuscular junction* and all *muscles* . Herewith, the danger of adverse reactions is proportional to the concentration of LAs in the

bloodstream, and their chiral centers: the *S*-enantiomer is less toxic than the *R*-enantiomer.

Following absorption, LAs may provoke stimulation of *CNS*, and cause tremor and clonic convulsions. With it the more potent LAs cause more easily convulsions. Central stimulation is accompanied by depression and death has occurred as a result of respiratory failure.

In case of systemic absorption the LAs act on *cardiovascular system*, namely, they reduce electrical excitability of myocardium, its conduction and force of contraction. Most LAs dilate blood vessels. But the negative effects of LAs on cardiovascular system can manifest only in high concentration of LAs in vascular bed, and may be in its low doses a very rare. Ventricular tachycardia and fibrillation are the rare consequences of LAs use except for *bupivacaine*. At the same time, such LAs as *lidocaine* and *procainamide* are used as antiarrhythmic drugs.

LAs relax *vascular and bronchial smooth muscles*, notwithstanding the low concentration of LAs and spinal and epidural anesthesia, instillation of LAs into peritoneal cavity can result in increased tone of *GI musculature*.

LAs, for example, *procaine* can block the response of *sceletal muscles* to action of acetylcholine. Besides, high concentation of LAs can block N-cholinoreceptors at *autonomic ganglia*.

Allergic reactions may appear as an allergic dermatitis or a typical asthmatic attack. It is very important to differentiate allergic reactions from toxic side effects of LAs and the effects of co-administered vasoconstrictors and preservatives such as *methylparaben* and an antioxidant such as *sulfite* which added to amide type of LAs with *catecholamine/vasoconstrictor*.

The use of amide type of LAs in patient with *liver diseases* requires caution taking into account their metabolism. The features of metabolism explain a negative side effect of *prilocaine* such as *methemoglobinemia*. The amide LAs are extensively *bound to plasma proteins* therefore change their level entails a change in the metabolism of LAs and thus affect their toxicity. *Age-related changes* in the levels of plasma proteins are essential too. Uptake by lung also is important for distribution of amide LAs in the body.

Table 30. Medicinal forms of Local anesthetics

INN	**Trade names**	**Medicinal forms**	
Cocaine h/cl.		Solution for external use in flacons	1%, 4%, 10%
Procaine	Aethocain, Allocaine, Ambocain, Aminocaine, Anesthocaine, Atoxicain, Cerocain, Chemocain, Citocain, Ethocaine, Genocaine, Herocaine, Isocain,	Poweder; Parenteral solution in ampoules, and in flacons; Parenteral solution in ampoules;	0.25%, 0.5% - 1 ml, 2 ml, 5 ml, 10 ml, 20 ml; 200 ml, 400 ml; 1%, 2% - 1 ml, 2 ml, 5 ml, 10 ml;

	Jenacain, Marecaine, Minocain, Naucain, Neocaine, Pancain, Paracaine, Planocaine, Polocainum, Protocaine, Sevicaine, Syncaine, Syntocain, Topocaine, etc.	Ointment; Rectal suppositories	5%, 10%; 0.1
Tetracaine	Dicain	Powder; Eye drops in flacons	 0.3% -5ml, 10ml
Benzocaine	Aethylis aminobenzoas, Anaesthalgin, Anaesthesinum, Anaesthicin, Anaesthin, Bartel drugs anesthetic, Dentispray, Ethoforme, Norcaine, Parathesine, Rhaetocain, Topanalgin, etc.	Tablets; Ointment; Solution for external use in flacons;	0.3; 5%, 10%; 5%;
Benzocaine + Heparin	Nigepanum,	Rectal suppositories	0.05+0.083;
Anaesthesinum + menthol+ ergocalciferol+ glycerol+propolis+ ethyl alcohol	Amprovisolum	Aerosol	50.0, 80.0, 170.0
Lidocaine	Acetoxyline, Alocaine, Anestacon, Anestecain, Astracaine, Dolicaine, Dulcicaine, Esracaine, Fastocaine, Leostesin, Lidestin, Lidocard, Lidocaton, Lignocain, Lignom, Luan, Maricain, Nulicaine, Octocaine, Remicaine, Solcain, Stericaine, Xycain, Xylesin, Xylocain, Xylocard, Xylocitin, Xylodont, Xylorolland, Xyloton, Xylotox, etc.	Parenteral solution in ampoules, and in flacons; Parenteral solution in syringe pen, capsules-ampoules; Eye drops in flacons, in tubes-droppers; Spray for topical use in balloons and in flacons; Gel for external use	1%, 2% - 5ml, 10ml; 2% - 2 ml; 4% - 5 ml, 10 ml; 10% - 2 ml; 1%, 2% - 50 ml, 100 ml; 2% - 1.8 ml; 2%, 4% - 5 ml; 2%, 4% - 1.5 ml; 10% - 38.0; 10% - 50.0; 1%, 5% - 30.0, 50.0; 2.5% - 15.0
Lidocaine	Lidoderm	Transdermal patch	5%

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Lidocaine	Dentipatch	Transoral Delivery System (TDS)	46.1 mg
Articaine	Articaine h/cl., Ultracaine	Parenteral solution in ampoules	1%, 2% - 5 ml, 20 ml
Trimecaine	Mesdicain, Mesocain	Parenteral solution in ampoules	0.25% - 10 ml; 0.5% - 2.5 ml, 10ml; 1%, 2% - 1 ml, 2 ml, 5 ml, 10 ml; 5% - 1 ml, 2 ml
Bupivacaine	Anekain, Carbostesin, Duracain, Marcain, Narcain, Sensorcain, Svedosan	Parenteral solution in flacons; Parenteral solution in ampoules	0.25%, 0.5% - 20ml; 0.5% - 4 ml
Ropivacaine	Naropin	Parenteral solution in ampoules, in flacons	0.2%, 0.75%, 1% - 10 ml, 20 ml; 0.2% - 100 ml, 200 ml
Mepivacaine	Carbocaine, Isocaine, Mepicatone, Mepidont, Mepivastesine, Polocaine, Scandonest	Parenteral solution in cartridges	1%, 1.5%, 2%, 3% - 1.7 ml, 1.8 ml
Bumecaine	Pyromecaine; Pyromecaine solution; Pyromecaine solution for injections 1% with glucose; Pyromecaine ointment	Parenteral solution in ampoules; Parenteral solution in ampoules; Ointment	0.5% - 1 ml, 3 ml, 5 ml; 1% - 5 ml, 10 ml; 5% - 30.0
Prilocaine	Citanest, Xylonest	Parenteral solution in ampoules	0.5%, 2.0%, 2.5%, 3% - 10 ml, 20 ml
Chloroprocaine	Nesacaine	Parenteral solution in flacons	1%, 2%, 3% - 30 ml, 20 ml
Benzofurocaine		Parenteral solution in ampoules	1% - 2 ml, 5 ml, 10 ml
Benzocaine + papaverine h/cl.	Pavesthesinum	Tablets	0.3 + 0.05
Benzocaine + Extract Belladonnae	Bellasthesinum	Tablets	0.3 + 0.015
Metamizole sodium + benzocaine + Belladonna extract + sodium hydrocarbonate	Bellalgin	Tablets	0.25 + 0.25 + 0.015 + 0.1

Phenylpropanolamine + benzocaine	Dietrin	Capsules	75 mg + 9 mg
Benzocaine + Dermatolum + menthol + zincum oxydum	Anesthesiolum	Rectal suppositories	0.1 + 0.04 + 0.004 + 0.02
Bensocaine + bismuth subgallate + Z zincum oxide + menthol	Anaesthesol	Rectal suppositories	0.1 + 0.04 + 0.02 + 0.004
Menthol + procaine + benzocaine	Menovasin	Solution for external use in flacons	2.5 + 1.0 + 1.0 - 40 ml, 50 ml
Algeldrate + magnesium hydroxide + benzocaine	Almagel	Peroral suspension	0.3 + 0.1 + 0.1 - 170 ml, 200 ml
Algeldrate + magnesium hydroxide + benzocaine	Palnmagel A	Peroral gel	3.0 + 1.35 + 2.0 - 150ml, 180ml, 200ml, 250ml
Algeldrate + magnesium hydroxide + benzocaine	Remagel A	Peroral suspension	0.3 + 0.1 + 0.1 - 5ml
Heparin sodium + benzocaine + benzonicotinic acid	Heparin ointment	Ointment in tubes	100 ME + 0.04 + 0.08mg - 15.0, 25.0, 30.0
Lidocaine + prilocaine	Emla	Emulsion; Cream for topical use in tubes; Transdermal patch	5% (25mg/1.0 + 25mg/1.0) - 5.0, 30.0; 25 mg + 25 mg - 5.0, 30.0
Lidocaine + tetracaine	Pliaglis	Cream for topical anesthesia in tubes	7% (2.1+2.1) - 15.0, 30.0
Lidocaine + tetracaine	Synera	Topical patch	70 mg + 70 mg
Gentamicin + lidocaine + ethonium	Ligenten	Gel for intravaginal and intrauretral administration	6.25 mg + 180 mg + 1.25 mg - 10.0
Lidocaine + norepinephrine	Xylestesin-F "Forte", Xylorolland	Parenteral solution in cartridges	30 mg + 0.048 mg - 1.8 ml
Lidocaine + polidocanol + Chamomillae floridis extract	Dentinox	Gel for topical use in tubes; Solution for external use in flacons	3.4 mg + 3.2 mg + 150 mg - 10.0 3.4 mg + 3.2 mg + 0.15 - 1 ml
Lidocaine + tolperisone	Mydocalm-Richter	Parenteral solution in ampoules	2.5 mg + 0.1 - 1 ml
Lidocaine + epinephrine	Xylodont, Lidocaton, Xylocain adrenaline, Octocaine 50	Parenteral solution in calsules-	5 mg + 5 mcg/ml, 10 mg + 5 mcg/ml, 20 mg + 5 mcg/ml;

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		ampoules, in cartridges	20 mg/12.5 mcg; 2% - 1.8 ml
Ofloxacin + lidocaine	Oflocaine-Darnitsa	Ointment	15.0, 20.0, 30.0, 100.0, 1000.0
Neomycin + polymyxin B + lidocaine	Anauran	Ear drops in flacons	0.5 + 1000000 IU + 4.0
Chlorhexidine + lidocaine	Instillagel, Cathejell with lidocaine, Lidochlor	Gel for topical use	0.05 + 2.0 - 6 ml, 11 ml; 10.0; 12.0
Dexamethasone + lidocaine	Supertendin 2000 N	Parenteral solution in ampoules	4 mg + 40 mg
Dextran + inosine + potassium gluconate + potassium chloride + lidocaine hydrochloride + magnesium sulfate + sodium hydrocarbonate + sodium chloride	Consol	Parenteral solution in flacons	400 ml
Articaine + epinephrine	Ultracaine D-C	Parenteral solution in cartridges	40 mg + 6 mcg – 1.7 ml
Articaine + epinephrine	Alphacaine N; Alphacaine SP	Parenteral solution in cartridges; Parenteral solution in cartridges	40 mg + 1:200000 - 1.8 ml; 40 mg + 1:100000 - 1.8 ml
Articaine + epinephrine	Brilocaine - adrenaline	Parenteral solution	40 mg + 1:200000 - 1.8 ml, 1.7 ml
Articaine + epinephrine	Septanest with adrenalin	Parenteral solution in cartridges	40 mg + 1:200000/ 1:100000 - 1.8 ml
Articaine + epinephrine	Ubistesine	Parenteral solution in cartridges	40 mg + 6 mcg/1 ml - 1.7 ml
Articaine + epinephrine	Citocartin	Parenteral solution in cartridges	40 mg + 1:200000/1: 100000 - 1.7 ml
Articaine + epinephrine	Primacaine	Parenteral solution in cartridges	40 mg + 1:200000/1: 100000 - 1.7 ml
Bupivacaine + epinephrine	Marcaine Adrenaline	Parenteral solution in flacons	2.5 mg/ml + 5 mcg/ml, 5 mg/ml + 5 mcg/ml – 20 ml
Trimecaine + norepinephrine	Trimecaine with noradrenaline for injections	Parenteral solution in ampoules	1 ml, 2 ml
Hydroxymethylhinoxilindioxide + trimecaine	Dioxysol	Aerosol; Solution for	30 ml, 60 ml; 50 ml, 100 ml,

		use in flacons	1000 ml
Hydroxymethylhinoxilindioxide + trimecaine + methyluracil	Galagran; Dioxycol	Powder for topical use; Ointment in banks	2.5, 5.0, 10.0; 30.0, 100.0, 1000
Benzalkonium chloride + trimecaine	Catacel A	Pasta for external use in banks, in tubes	20.0 - 100.0, 500; 30.0 - 300.0
Chloramphenicol + methyluracil + sulfadimethoxine + trimecaine	Levosin	Ointment in banks	50.0, 100.0, 1000.0
Mepivacaine + epinephrine	Mepidont	Parenteral solution in cartridges	2% - 1.8 ml (epinephrine - 1:100000)
Chloroprocaine + epinephrine		Parenteral solution in ampoules	1%, 2%, 3% - 20 ml, 30 ml + (epinephrine -1:100000)

Chapter 9. Sorbents, covering drugs, astringents

Absorbents are the drugs with high surface activity that capable of absorbing of different chemical substances and thus prevent irritation of nerve endings.

Mechanism of action: Effect of absorption is provided by fixation of molecules of different chemical substances on the sorbent surface.

Classification of Sorbents

Neutral absorbents:

Carbo activatus
Charcoal medicinae
Enterosgel
Silicon dioxide
Diosmectite

Special absorbents:

Ion exchange resins

Various substances with absorption properties:

Spherical carbonite
Coke charcoal Spherical
carbon sorbent
Activated carbon fibers

Clinical use of Sorbents

Neutral absorbents are administrated in GIT and use for enterosorption, in other words they are used for extraction of toxic substances (as xenobiotics and endogenous toxins) from GIT.

Special absorbents are used for extraction of toxic substances from blood *(hemosorption),* from plasma *(plasmasorption),* from lymph *(lymphosorption)* and from other liquids of the body.

Pharmacological characteristic of Sorbents

Carbo activatus (activated charcoal) adsorbs toxic substances, prevents their absorption, reduces activity of other drugs in case of their simultaneous administered, and weakens stomach acidity.

Indications for Carbo activatus use:

- Poisonings by chemical substances including organophosporus and chlorophosporus substances, psychoactive drugs
- Dyspepsia, diarrhea, flatulence
- Stomach hyperacidity
- Alkaloid poisoning
- Glycoside poisoning
- Poisoning by heavy metal salts
- Food poisoning, dysentery, salmonellosis
- Burn disease in the stage of toxemia and septicotoxemia
- Kidney insufficiency
- Chronic hepatitis, acute viral hepatitis
- Cirrhosis of liver
- Atopic dermatitis
- Bronchial asthma
- Chronic cholecystitis, pancreatitis
- Allergy
- Metabolism disorders
- Alcohol withdrawal syndrome
- Intoxication in the patient on the background of radiotherapy and chemical therapy
- Preparation for X-ray and endoscopy

Adverse effects of Carbo activatus:

- Dyspepsia, diarrhea, constipation
- Hypovitaminosis, reduction of absorption of lipidsproteins, hormones in GIT with prolonged use of this sorbent
- Thromboembolism, hemorrhages, hypoglycemia, hypocalcemia, hypotermia, arterial hypotension when hemoperfusion through activated charcoal
- Staining of stool in black color

Contraindications for Carbo activatus use:

Hypersensitivity
Stomach and duodenum ulcer
GIT blood bleeding
Simultaneous administered Carbo activatus and antitoxic drugs the effect of which develops after their absorption

Charcoal medicinae (Sorbex) is a plant origin carbo activatus with developed active surface, it is able to adsorb gases and liquid toxic compounds that are formed and accumulated in excess amount in acute and chronic diseases, or these toxic substances come from outside the body. *Sorbex* is nontoxic inert substance. In the body it is not metabolized, it is not absorbed from the intestinal lumen, it is not entered abroad GIT, it is not defined in any biological fluids of the body and it was eliminated from the body through the intestines.

Indications for Sorbex use:

In case of poisoning by household and industrial toxins (alkaloids, heavy metal salts, other substabces), foodstuffs, drugs, alcohol for diminution of their absorption and acceleration of their excretion
Habitation in unfavorable ecological conditions or the action of harmful factors, changing the usual way of nutrition during the holidays, trips, travel
As additional therapy in case of:
GIT disturbances: dyspepsia, flatulence, intestine infections, acute and chronic hepatitis
diseases with syndrome of endogenous intoxication, acute and chronic liver and kidney damage, allergy, autoimmune and cancer, high cholesterol level in blood

Adverse effects of Sorbex:

Simultaneous administration of this drug and food reduces its absorption, thereby Sorbex should be taken before meals (1-1.5 hours), or after meals (1-1.5 hours)
Long-term use (more than 15 days) of Sorbex may cause disorders of absorption of vitamins, hormones, lipids, proteins, that require medical or alimentary correction
Staining of stool in black color
Nausea, vomiting
Long-term use of Sorbex may evoke disturbance of intestine function (diarrhea, constipation) that is easily eliminated by discontinuation of drug receiving and symptomatic therapy
Sorbex is capable to reduce effects of the drugs in case of simultaneous administration due to its absorption properties

Contraindications of Sorbex use:

Individual hypersensitivity
GIT ulcers in acute stage
GIT bleeding
Iliac passion (intestinal obstruction)

Enterosgel – is the hydrogel of methylcilicic acid, enterosorbent that removes toxic substances (midle molecules, products of incomplete metabolism, incorporated radionuclides) from GIT and blood. *Enterosgel* eliminates manifestations of toxemia, dysbiosis, normalizes methabolic processes and intestinal microflora, protects the mucosa of GIT from toxic effects, improves immunity, prevents the development of purulent processes, and owns mediated antimicrobial, hepatoprotective regenerative activity. *Enterosge* is not absorbed in GIT.

Indications for Enterosgel use:

Acute poisoning including ethanol, alkaloids, heavy metal salts
Detoxication on occasion kidney diseases, toxicoinfections, liver diseases, enterocolitis
Diarrhea
Alcohol intoxication
Drud intoxication
Burn disease
Radiation disease
Pyo-septic processes
Dysbiosis

Adverse effects of Enterosgel:

Constipation
Nausea
Reduced absorption of other drugs during their simultaneous administration

Contraindications for Enterosgel use:

Intestine atony
Acute Iliac passion (ileus)
Simultaneous administration with other drugs

Silicon dioxide has adsorbing action due to formation of specific complexes, connection with proteins, enzymes, microbial toxins, bilirubin, bile acids, and microorganisms. *Silicon dioxide* is not absorbed in GIT and can not be accumulated.

Indications for Silicon dioxide use:

Endogenous and exogenous intoxications
Food allergy
Allergic dermatitis
Psorias
Eczemas
Purulent inflammation of soft tissues of the body
Acute intestinal diseases
Diarrhea as a result of salmonellosis, dysentery, food toxic infections

Adverse effects of Silicon dioxide:

Constipation
Dyspepsia

In case of local use – formation of crusts, which impede the wound surface aeration

Reduction of drug effectiveness on occasion simultaneous administration with them

Contraindications for Silicon dioxide use:

Ulcer disease of stomach and duodenum in acute stage

Esophagitis

Ileus

Children under 1 year

Local application in case of clean granulating and aseptic wounds

Simultaneous administration with other drugs

Diosmectite is a plant origin drug, an active sorbent and it is capable to excrete viruses, pathogenic bacteria, toxins, intestinal gases, and salt of bile acids from the body. This drug has a high enveloping activity in respect of gastrointestinal mucosa, prevents water-electrolyte losses. *Diosmectite* interacts with mucus glycoproteins, enhances barrier function of gastrointestinal mucosa, and protects it from negative influence of hydrochloric acid, bile acids, intestinal microbes, their toxins, and other irritants. In therapeutic doses *Diosmectite* does not affect intestinal motility. It is not absorbed in GIT and is excreted from the body in unchanged form.

Indications for Diosmectite use:

Symptomatic treatment of acute and chronic diarrhea in children and adults

As an auxiliary medicine in event of inflammatory diseases of GIT

Adverse effects of Diosmectite:

Rarely – constipation, which is disappeared after reduction of the drug dose

Reduction of drug effectiveness on occasion simultaneous administration with them

Contraindications for Diosmectite use:

Individual hypersensitivity

Ileus

Ion exchange resins – are the solid sorbents that capable to ion exchange. There are cation-exchange resins (cationites) and anion-exchange resins (anionites); amphoteric ion exchange resins that include complex forming groups; the redox resins that contains functional groups capable of altering the ion charges. Besides ion exchange resins can comprise the groups of different classes and they are named polyfunctional resins. According to the structure ion exchange resins are divided into gel (microporous) and macroporous. This diversity of ion exchange resins determines a wide range of their application in modern terms. In the pharmaceutical industry ion exchange resins used for purification of antibiotics, vitamins, hormones, sugar syrup, water, separation of proteins, and in modern medicine – for selective purification of blood plasma.

Table 31. Medicinal forms of Sorbents

INN	Trade names	Medicinal forms	
Activated charcoal, activated carbon, activated coal	Carbactinum, Carbolenum, Carbolongum, Enterosorbentum, Microsorbum-P, Ultra-adsorb	Powder; Tablets; Capsules	0.25, 0,5; 0.2; 110 mg
Charcoal medicinae	Sorbex	Capsules; Powder in packages; Tablets	0.25; 5.0; 0.32, 0.25
Enterosgel		Gel for preparing peroral suspension in packages; Pasta	45.0, 225.0; 70%
Silicium dioxide	**Silics**, Atoxil	Powder in packages for preparing peroral suspension and suspension for external use	1.0, 2.0, 10.0, 12.0
Diosmectite	**Smecta**	Powder in packages for preparing peroral suspension	3.0

Covering drugs are indifferent substances with high molecular mass that form colloid solution with water (mucus), cover a surface of skin or GIT mucosa by thin layer and mechanically protect nerve endings from irritation.

Mechanism of action is connected with the formation of a thin layer of the colloid solution and thus the corresponding reflex response is reduced, intestinal motility is inhibited, GIT absorption is decelerated including drugs and toxins absorption. Covering drugs possess adsorbing, anti-inflammatory, analgesic action, detoxifying properties (slowing absorption of toxic substances); reduce reflex dysphagia, nausea, vomiting, heartburn, and diarrhea.

As covering substances mucus of starch *(mucilago Amyli)* of wheat *(Amylum Tritici)*, of corn *(Amylum Maydis)*, of rice *(Amylum Oryzae)*, of potatoes *(Amylum Solani)* are used,they are prepared with boiling water. Mucus is applied topically, inside, and in enemas. Mucus of starch is added to the mixtures, enemas if they contain substances with a local irritant effect. Mucus is used to slow the absorption of poisons, which came in the GIT, to protect the mucosa in case of poisoning by cauterizing substances (acids, alkalis). Tubers of Orchis *(tuber Salep)*, gum acacia *(Gummi arabicum)*, Marshmallow root *(radix Althaeae)*, Psyllium seeds *(semen Plantaginis majoris)* and Flax seeds *(semen Lini)* are used for preparing mucus. Many plants contain enveloping substances. There are: Geum river *(Geum rivale)*, Oat *(Avéna satíva)*, Plantain leaves *(folia Plantaginis majoris)*, Licorice root *(radices Glycyrrhizae)*, Potentilla erecta (synonyms: Tormentilla erecta, Potentilla laeta, Potentilla tormentilla) rhizomes *(rhizomata Tormentillae)*, Bistorta officinalis rhizomes *(rhizomata Bistortae)*, Sanguisorba

officinalis (great burnet) rhizomes with roots and grass *(rhizomata cum radicibus Sanguisobrae, herbae Sanguisobrae)* etc.

Pharmacological characteristics of Covering drugs

Marshmallow root *(radix Althaeae)* is used in powder, tincture, extract, syrup forms as an expectorant, anti-inflammatory and enveloping drug.

Flax seeds *(semen Lini)* are used as a decoction (1:30), mucus from *Flax seeds (mucilago seminis Lini)* is used externally and inside as enveloping agent and emollient.

Tubers of Orchids (*tuber Salep)* are used for treatment diarrhea, dysentery, stomach and duodenal ulcers, hyperacidic gastritis, enterocolitis and colitis, cystitis, food poisoning, and other poisonings, when the treatment of inflammation of the digestive tract needs enveloping mucus.

Oat *(Avéna satíva)*. Oat groats and flour have a large number of easily digestible, rich in essential amino acids of proteins, carbohydrates, fats and vitamin of B group, so they are widely used in dietary and baby food. They are prepared porridges, soups and mucous broths that are enveloping and dietary agents in acute inflammatory diseases of the GIT (gastritis, enterocolitis), intestinal atony, viral hepatitis, and fatigue, diseases of the nervous system, cardiac arrhythmias and iron deficiency anemia caused by violation of the synthesis of porphyrins. Green grass of oats for the healing properties is not inferior to grains. Its extract has diaphoretic, diuretic and antipyretic effects. Oats have enveloping properties by which is used in acute inflammatory diseases of the GIT and as antiflatulent, and as a laxative.

Plantain leaves *(folia Plantaginis majoris)* have a lot of mucus and the drugs containing them possess enveloping and anti-inflammatory properties and are used for treatment inflamatory diseases of GIT.

Geum River *(Geum rivale)* has enveloping, astringent, analgesic, antiseptic, wound healing, anthelmintic, antacid effects and is used for treatment of diarrhea, tonsillitis, rheumatism and hemorrhoids. In dental practice, this plant is used for treatment of periodontal disease, ulcerative necrotic stomatitis and laryngitis. It is not advisable to apply the *Geum River* in thrombophlebitis and thrombosis.

Licorice roots, the **roots of Glycyrrhiza glabra *(radices Glycyrrhizae)*** is used as an expectorant (especially in children with bronchial asthma), diuretic, enveloping, laxative for constipation, hemorrhoids, stomach ulcer. *Licorice* can be used as an antidote for treatment of poisoning by mushrooms. Furthermore, given that the glycoside glycyrrhizin (found in liquorice) is a source of glucuronic acid, which neutralizes in the human body various toxins (including tetanus toxins), *Licorice* is used in case of gallstones and liver diseases. *Licorice* extract soothes pain, but we must remember that glycyrrhizin may violate electrolytic-water balance (water retention, decrease urinary sodium excretion and increase potassium excretion) and cause edema, lower content of vitamin C in the adrenal glands.

Potentilla erecta rhizomes *(rhizomata Tormentillae)* are used in event of GIT diseases (gastritis, dyspepsia, enteritis, enterocolitis), externally – in case of inflammatory diseases of oral cavity and throat.

Bistorta officinalis rhizomes *(rhizomata Bistortae)* are known as a strong astringent and are used in diarrhea (per oral use), and for external use in treatment of wounds, blood bleeding, abscesses, urinary bladder diseases.

Sanguisorba officinalis (great burnet) rhizomes with roots and grass *(rhizomata cum radicibus Sanguisorbae, herbae Sanguisorbae)* due to the high content of tannins are used as drugs to stop the stomach, uterine and intestinal bleedings, for strengthen the gums in periodontal disease, hemorrhoids, in lambliasis cholecystitis, diarrhea. This plant is a good anti-inflammatory, astringent and diaphoretic agent. *Sanguisorba officinalis* has strong antibacterial properties and is used for treatment of inflammation of the mouth and throat for lubrication of gums in case of gingivitis, stomatitis, in gynecology on occasion of trichomonas disease. An external application of decoction of *Sanguisorba officinalis* rhizomes with roots and grass makes quick therapeutic effect in acute purulent conjunctivitis.

Covering effects are also aluminum products (Almagel, Maalox, Gastal, Fosfalugel, Sucralfate, Gastrogel, Carbaldrate, etc.) bismuth preparations (Vicair, De-Nol). These drugs are used in inflammatory diseases of GIT, in case of stomach hypersecretion, stomach ulcer and duodenal ulcer. In the application they prevent the absorption of vitamins, cause constipation, violate digestive. Due to ability of these drugs to reduce gastric acidity, they are called antacids. Antacids are not recommended to be used together with any drugs through the obstacle of their absorption.

In dentistry the starch and white clay, which have expressed adsorbent properties are used as enveloping agents.

Table 32. Medicinal forms of Covering (enveloping) drugs

INN	Trade names	Medicinal forms	
Tuber Salep		Powder in the containers	45.0
Radices Althaeae		Powder in bottles; Powder in the packets	19.6 1.47
Folia Plantaginis mayoris		Shredded raw in packs, in filter packets	50.0 1.5
Semen Lini		Raw in packs	1000
Geum rivale		Shredded raw in packs	100.0
Avéna satíva		Raw in packs	100.0
Radices Glycyrrhizae		Powder in banks	600.0, 800.0
Rrhizomata Tormentillae		Shredded raw in packs	50.0
Rhizomata Bistortae		Shredded raw in packs	50.0
Rhizomata cum radicibus Sanguisorbae		Shredded raw in packs	100.0

Herbae Sanguisorbae		Raw in carton packs	100.l0
Aluminum preparations:			
Aluminum hydroxide+magnesium oxide+D-sorbitol	**Almagel**	Oral suspension in flacons	170 ml, 200 ml: each 5 ml of drug contains 0.3 Aluminum hydroxide, 0.1 Magnesium hydroxide with the addition of D-sorbitol
Algedrate*+Magnesium hydroxide	**Maalox**	Oral suspension in flacons; Chewable tablets	250 ml
Aluminum hydroxide+ magnesium hydroxide+ magnesium carbonate	**Gastal**	Tablets	0.45+0.45+0.3
Aluminium phosphate (алюмінію фосфат+ гель пектину+ гель агар-агару)	**Fosfalugel**, Alfogel, Gefal, Phosphalugel	Gel for taking inside in plastic bags	8%, 55% - 16.0
Sucralfate	Alsucral, Ancrusal, Andapsin, Keal, Sucrabest, Sucrafil, Sucras, Sucrat, Ulcon, Venter etc.	Tablets Granules in sachets; Gel for oral administration in sachets; Oral suspension in sachets and flacons	0.5, 1.0; 0.5, 1.0; 20% -5 ml; 10 ml, 250 ml
Original Silicea Gastrogel		Gel for oral administration in plastic flacons	2.8%-500 ml
Carbaldrate		Oral suspension in vials; Lozenges (lingual tablets, dispersible tablets)	250 ml 355 mg
Bismuth preparations:			
Bismuth subnitrate + Magnesium carbonate + Sodium hydrocarbonate + Frangulae cortex + Rhizomata Calami	**Vicair**	Tablets	0.35+0.4+0.2+ 0.025+0.025
Bismuthate tripotassium dicitrate	**De-Nol**, Biskolcitrate, Bisnol, De-Noltal, Duosol, Pylocide, Trimo, Tripotassium dicitrabismutate, Trybimol, Ulceron, Ventrisol	Tablets	0.12

Astringents protect sensitivity nerve endings of mucous and skin from negative influence of irritant agents.

Classificstion of Astringents

I. Drugs of plant origin:

Tanninum
Oak bark (cortex Quercus)
Alder cones (fructus Alni)
St John's wort (herba Hyperici)
Vaccinium myrtillus/ European blueberry (fructus Myrtilli)
Bidens tripartita / Three-lobe Beggarticks / Three-part Beggarticks (herba Bidentis)
Salvia leaves (folia Salviae officinalis)
Matricaria Chamomilla / Chamomile flowers (flores Chamomillae) Rotocanum

II. Drags of nonorganic origin (salts of metals):

Bismuthi subnitras

III. Combined drugs:

Vicalinum
Vicair
Alcidum

Mechanism of action of astringents is associated with precipitation of tissue proteins in their contact with the mucous membranes or damaged skin to form a dense film of circulating albuminates, which protects the sensitive nerve endings in tissues from the influence of irritating agents. It reduces or stops pain sensitivity. Founded membrane is shrinked, it takes less surface and mechanically compresses blood vessels, resulting in capillary walls are compacted, their lumen is narrowed, exudation is reduced, bleeding is stopped, enzyme activity in the tissues are reduced, the formation of inflammatory mediators is slowed, and thus anti-inflammatory action of astringents is implemented. Antimicrobial action of them due to the fact that the dense protein membrane protects the tissue against the penetration of microorganisms and denaturation of protein structures of microbes leads to the violation of metabolism of microbial cells and bacteriostatic effect.

Pharmacological characteristics of Astringents

Tannin (Taninum) is used as an astringent and local anti-inflammatory drugs in inflammatory processes of the mouth, nose, throat as a rinse and as a lubricating in burns, ulcers, fractures, bedsores. It is forbidden to use of tannin inside (as oral and rectal) through its interaction with proteins of the mucous membrane of the digestive tract, indigestion, of thrombosis in the cracks of the rectum. Tannin forms stable insoluble compounds with salts of alkaloids, heavy

metals, but with some alkaloids (morphine, cocaine, atropine, nicotine, physostigmine) tannin forms unstable compounds. Thus, tannin (0.5% aqueous solution) is used for gastric lavage in poisonings be substances listed above.

Oak bark (*cortex Quercus*) in the form of decoctions has astringent and tannic characteristics; it has the ability to denature proteins, providing anti-inflammatory effect in the external and internal use. An oral decoction of Oak bark enhances motility of the stomach and reduces its secretion, reduces the enzymatic activity and gastric acidity, slows absorption of the mucous membrane with respect stomach contents. All parts of this plant have a disinfecting effect. Gallic acid and its derivatives have effect, similar to the effect of bioflavonoids: compact vascular tissue membranes, increase their strength and reduce permeability, also have antiradiation property and antihemorrhagic property. Antimicrobial and antiprotozoal actions are associated with both gallic acid derivatives, and to the presence of oak bark catechins. Oak bark reduces sweating, binds cations. *Indications:* stomatitis, gingivitis, tonsillitis, halitosis, burns, frostbite, infected wounds, sores, blisters, sweating feet, hemorrhoids. In folk medicine, a decoction of oak bark is used to treat diarrhea, dysentery, gastric ulcer and duodenal ulcer, bleeding from the digestive tract, hemorrhoids, polymenorrhea, mushroom poisoning, copper salts poisoning. *Contraindications:* hypersensitivity.

Alder cones *(fructus Alni)* have astringent, disinfectant, anti-inflammatory, desensitizing and hemostatic properties. *Indications:* acute and chronic enteritis, enterocolitis, colitis, dyspepsia. *Contraindications:* idiosyncrasy. Not recommended for use for children under 5 years.

St John's wort *(herba Hyperici)* has astringent, anti-inflammatory and mild antibacterial activity, it accelerates tissue regeneration, stimulates the secretion of bile and gastric juice. *Indications:* externally prescribed for the prevention and treatment of oral inflammation (gingivitis, stomatitis), and internally in the liver diseases and bile ducts diseases (biliary dyskinesia, chronic hepatitis, cholecystitis) and in diseases of the GIT, accompanied by diarrhea and flatulence (acute and chronic colitis, gastritis with secretory insufficiency). *Contraindications:* idiosyncrasy.

Vaccinium myrtillus/ European blueberry *(fructus Myrtilli)* have astringent, antiseptic, anti-inflammatory (in diarrhea, enterocolitis), hypoglycemic, haemostatic, restorative, detoxification, multivitamin, anti-anemic actions. *Indications:* diarrhea, gout, rheumatism, diabetes mellitus, weak twilight vision, hemorrhoidal bleeding. In folk medicine, a decoction of the fruit is used in pyelitis, cystitis, urethritis, kidney stones and gallstones, atony of the bladder, stomach ulcers, intestinal colic and hemorrhoids (astringent, diuretic, uroseptyc actions), also in case of rheumatism, gout, psoriasis, mouthwashes for treatment of stomatitis, pharyngitis, tonsillitis; it is used externally for treatment of eczema, dermatitis, burns. Blueberry Shoots have hypoglycemic properties and are used in milder forms of diabetes mellitus. *Contraindications:* hypersensitivity.

Bidens tripartita / Three-lobe Beggarticks / Three-part Beggarticks *(herba Bidentis)* has astringent, enveloping and antacid properties, it reveals a

diuretic, diaphoretic, anti-inflammatory, anti-allergic, antibacterial and choleretic effect, improves digestion, normalizes impaired metabolism, lowers BP. *Indications:* internally it is used in diseases of the urinary system, catarrhal diseases (acute respiratory infections, flu, etc..); externally it is used in pediatric patients with diathesis, allergic skin diseases, pyoderma, psoriasis, eczema, atopic dermatitis and other skin diseases. *Contraindications:* individual intolerance to substances contained in the medicinal product. Allergic reactions are possible (rash, itching, redness and swelling of the skin).

Salvia leaves *(folia Salviae officinalis)* possess astringent, enveloping and antacid properties. *Indications:* Salvia leaves are used for treatment of stomatitis, gingivitis, tonsillitis, ulcerative processes of the mouth, inflammation of the upper respiratory tract and skin, light burns and frostbite, as well as gastritis and gastric ulcer and duodenal ulcer with secretory insufficiency and low acidity of gastric juice. *Side effects:* at high individual sensitivity to local Salvia may develop allergic reactions (redness, itching and swelling of the skin). In lactating women Salvia can inhibit lactation. *Contraindications:* Salviae is contraindicated in hypersensitive to biologically active substances (BAS) contained in it. Internal use of Salvia drugs are contraindicated in inflammatory kidney diseases and in patients with a strong cough and in young children and in women during lactation. Children aged from 1 to 12 years and women who are breastfeeding, Salvia is prescribed only for external use.

Matricaria Chamomilla / Chamomile flowers *(flores Chamomillae)* have astringent, antispasmodic, anti-inflammatory, aseptic, sedative and some analgesic activity. Infusion of Chamomile when taking increases the secretion of digestive glands, has a choleretic effect, inhibits fermentation, and relieves spasms of the intestine. *Mechanism* of spasmolytic action is explained by M-cholinolytic properties of plant glycosides. Chamomile essential oil strengthens and deepens breathing, accelerates heart rate, dilates blood vessels of the brain, and has disinfectant and anti-inflammatory properties due to the presence of a chamazulene. Preparations of Chamomile accelerate the regeneration of the epithelium in experimental ulcers and delay the development of experimental inflammation.

Rotocanum has a local astringent, anti-inflammatory, antiseptic action, promotes regeneration of damaged mucosa, and has haemostatic properties. *Apply* in dental practice in adults with inflammatory diseases of the mouth mucous membrane (aphthous stomatitis, periodontal disease, ulcerous-necrotic gingivitis and stomatitis) and in gastroenterology. Possible *side effects* – there are allergic reactions. *Contraindications:* hypersensitivity to the components of Rotocanum.

Bismuthi subnitras has astringent, and skin-protective, antimicrobial, absorbent, antacid, anti-inflammatory properties. *Bismuthi subnitras* coagulates the proteins to form dense albuminate membranes on the surface of the mucous membrane of the digestive tract, has vasoconstrictor effect, reduces local inflammation, and inhibits the growth and development of Helicobacter pylori. Intensity of antacid action is low. Drugs *are used* in inflammatory diseases of the

skin and mucous membranes (dermatitis, ulcers, erosions, eczema), for the treatment of gastro-duodenitis, gastric ulcer and duodenum ulcer, reflux esophagitis, enteritis, colitis. *Side effects:* headache, swelling of the eyelids and gums, vesicles and pigmentation on the tongue, nausea, vomiting, methemoglobinemia. *Interaction:* Bismuthi subnitras is compatible with cholinolytic, antispasmodic agents – often used for stomach ulcers and duodenal ulcers. It is not compatible with tetracyclines through the formation of complexes that are not absorbed. Limitations for use are hypersensitivity and renal failure.

Vicalinum has astringent, antacid, laxative and antispasmodic action. *Magnesium carbonate* and *sodium bicarbonate* reduce gastric acidity and pepsin activity. *Bismuth subnitrat* forms a protective membrane on the mucosa of the stomach, and has anti-inflammatory, antibacterial, restorative effects. *Acorus calamus* and *Khellin* which are contained in the *Vicalinum*, have antispasmodic action, and *Frangulae* – laxative action. *Indications:* peptic ulcer and duodenal ulcer, hyperacidic gastritis. *Side effects:* may be diarrhea, allergic reactions. *Contraindications:* hypersensitivity to the components of *Vicalinum*, hypoacidic gastritis, renal failure.

Vicair has astringent, antacid, laxative and antispasmodic action. *Magnesium carbonate* reduces gastric acidity and pepsin activity. *Bismuth subnitrat* forms a protective membrane on the mucosa of the stomach, reveals anti-inflammatory, antibacterial, restorative effects. *Acorus calamus* and *Frangulae* are contained in *Vicair*; commit at first – antispasmodic action, and at second – laxative action, thus contributing to the improvement of the intestinal passage. *Indications:* gastric ulcer and duodenal ulcer, hyperacidic gastritis with a tendency to constipation. *Side effects:* diarrhea, allergic reactions. *Contraindications:* hypersensitivity, hypoacidic gastritis, chronic renal failure, infancy. *Interaction* with other drugs: in patients receiving M-cholinoblockers or H2 histamine receptors blockers the need to use *Vicair* is reduced; it reduces absorption of tetracyclines; in combination with other drugs that keep bismuth, *Vicair* increases the concentration of bismuth in blood.

Alcidum has antiulcer effect due to *Glycyrrhizae spissum* and *Chamomile blossoms*; antacid action – through *alkaline magnesium carbonate, aluminum hydroxide, sodium bicarbonate; subnitrat bismuth* as a part of this drug has astringent, antiseptic and absorbent effects; *aluminum hydroxide* has antacid effect and it has absorbent and astringent properties, at the same time forming a protective layer on the gastric mucosa, resulting in reduced acidity and peptic activity of gastric juice; *alkaline magnesium carbonate* and *Buckthorn bark* provides a laxative effect for constipation that can occur under the influence of *bismuth subnitrat* and *aluminum hydroxide*. *Alcidum* is used for the treatment of gastric ulcer and duodenal ulcer in the acute stage, acute and chronic gastritis. *Side effects:* painting stool in gray-black. *Contraindications:* severe renal impairment; the control of plasma electrolytes is needed; it is not compatible with antibiotics through a decrease in their absorption.

Table 33. Medicinal forms of Astringents

INN	Trade names	Medicinal forms	
Tannin	Tanninum	Powder; Alcohol solution for topical use	 4% - 25 ml
Cortex Quercus		Shredded raw material in packages; Broth; Powder; Gathering	100.0
Fructus Alni		Shredded raw material in packages	40.0, 50.0, 100.0
Herba Hyperici		Raw material in boxes; In briquettes; Tincture in flacons	30.0, 100.0; 75.0; 25-100 ml
Fructus Myrtilli		Raw material in cardboard boxes	100.0
Herba Bidentis		Shredded raw material in packages; In briquettes; In filter-packages	50.0, 75.0, 100.0; 75.0; 2.0
Folia Salviae officinalis		Shredded raw material in filter- packages; Alcohol solution in flacons for external use; Shredded raw material in filter- packages	1.0, 5,0; 1%-10 ml; 50.0
Flores Chamomillae, flores Chamomillae + semen Foeniculum vulgare + semen Coriandrum sativum (0,6:1:1)	 Azulan; Babynos	Shredded raw material in filter- packages, packages; The liquid extract in flacons; The liquid extract in flacons	0.5; 50.0, 100.0, 150.0, 200,0; 25 ml; 30 ml
Calendulae officinalis floridis extract + Chamomillae recutitae floridis extract + Achillea millefolii herbae extract (2:1:1)	**Rotocanum**	The liquid extract in bottles	25 ml, 50 ml, 110 ml

Bismuthi subnitras		Substance powder; Ointment	25 kg; 10%-25.0
Bismuth subnitrate + Magnesium carbonate + Sodium hydrocarbonate + Calami rhizomata + Frangulae cortex + Rutoside + Khellin	Vicalinum	Tablets	
Bismuth subnitrate + Magnesium carbonate + Sodium hydrocarbonate + Calami rhizomata + Frangulae cortex	Vicairum, Vicair	Tablets	
Extractum Glycyrrhizae spissum + Extractum Chamomilla recutita + Alkaline magnesium carbonate + Aluminum hydroxide + Sodium bicarbonate + Bismuth subnitrate + Frangulae cortex + fructus Coriandri + fructus Foeniculi	Alcidum	Tablets	

Irritants contain substances that are readily soluble in fats, easily penetrate the skin, mucous membranes and irritate nerve endings. This is followed by the arrival of nerve impulses in different parts of the central nervous system and the emergence of relevant reflex reactions, changing the function of various parts of the nervous system, including the vital centers (respiratory and vasomotor) of medulla oblongata, hypothalamus, where the formation of enkephalins, which reduce the intensity of pain. Local reactions arise in place of irritation of skin or mucosal. There are: redness as a result of the expansion of arterioles and capillaries; swelling as a result of penetration of plasma through the capillary walls into the surrounding tissue; tingling, burning, heat from the impact of *Irritants* and tissue BAS on sensitive nerve endings. In other words, the occurrence of local reactions is explained by reflex reactions, including axon-reflexes, i.e. reflexes that are closed within the peripheral sensory nerve fibers. These reflexes begin in cutaneous receptors; they are distributed via sensory nerve fibers and in fibers that innervate arterioles, and causing their extension. The products of decomposition (BAS: histamine, serotonin etc.) that are released from the tissue during application of *Irritants* to the skin or mucosa, leading to chemical and mechanical tissue damage. Thereby, the local reaction is explained by neural and humoral factors and is used in the treatment of subacute and chronic joint disease, myositis, neuralgia, and neuritis of peripheral nerves, because vasodilation and increased blood delivery of nutrients lead to activation of metabolic processes in inflammatory tissues, acceleration of washout of products of inflammation, i.e. to the anti-inflammatory effect.

Chapter 10. Irritants

Classification of Irritants

I. Drugs of plant origin:

Drugs that contain essential oils:

Folia Menthae piperitae
Menthol
Menthol solution in menthyl isovalerate (Validolum)
Folia Eucalypti viminalis
Semen Sinapis
Fructus Capsici
Extract Salviae sclareae (Salmus)
Oleum Terebinthinae rectificatum
Spiritus Acidi formici

Bitterness:

Tinctura amara
Herba Centaurii
Herba et folia Artemisiae absinthii
Succus Plantaginis
Radices Taraxaci
Folia Menyanthidis trifoliatae
Rhizomata Calami

II. Synthetic drugs:

Chloroform
Finalgon
Solutio Ammonii caustici 10%

III. Drugs that contain venoms of bees and snakes:

Apiphor
Apisartron
Ungapiven (Bees venom)
Vipraxin pro injectionibus
Najaxin
Viprosal
Nizhvisal

Thus, Irritants have folloving **Pharmacological effects:**

Local irritanting effect due to release of BAS, vasodillatation, exudation, and improvement of microcirculation

Analgesic effect is explained by the fact that:

the interference of pain impulses from the affected organ and the site of application of irritating substance in segments of the spinal cord, that eliminates the dominant focus of the pathological process, hyperalgesia, and muscle tension;

washout of BAS from the area of skin irritation, rising flow of afferent impulses that affect the brain, alter the metabolism of neurotransmitters,

promote the release of antinociceptive factors (β-endorphins, enkephalins, and others);
reduction of liberation of pain mediators (substance P, somatostatin, cholecystokinin);
increase of the secretion of hypothalamic releasing hormone, ACTH, thyroid-stimulating hormone, increased secretion of glucocorticoids;
inhibition of inflammatory response;
pain impulses from the area of skin irritation entering the rear horn segments of the spinal cord, they switch on the side horn segments of the spinal cord, excite cores of preganglionic sympathetic nerve fibers;
sympathetic impulses improves blood flow to the lungs, skeletal muscles, reduces inflammation

Stimulatory effect on the vital centers (respiratory and vasomotor) of medulla oblongata that leads to deepening of respiration and increase BP

Expectorant effect through glands of the bronchial mucosa

Antiviral and immunostimulatory effects as a result of increase of interferone synthesis

Trophic effects as a result of application of Irritants on the skin i.e. the change of metabolism in the defined tissues. For spinal cord segmental structure and innervation is characterized: one segment innervates internal organs and the corresponding area of the skin. Projection areas of the internal organs on the skin surface are called *zones of Zakharyin-Head* and irritating effect of *Irritants* the relevant areas of the skin causes cutano-visceral reflexes leading to vasodilatation in the corresponding internal organ, improves its blood circulation, promotes washout of degradation products and toxins that is manifested in anti-inflammatory effect. This mechanism underlies the treatment of inflammatory diseases of the respiratory tract via chafing and the use of mustard plasters

A distracting effect: the flow of impulses in the CNS from arteficial fire (due to action of irritants) reduces the flow of impulses from the pathological focus and thus anesthesia comes. Perhaps that BAS from pathological focus reflexively influence on the hypothalamus and stimulate the synthesis of enkephalins, which reduce the intensity of pain. This effect of irritating drugs is used in the treatment of angina pectoris (stenocardia), arthritis and other diseases associated with pain syndrome

Reflectory redistribution of blood, restoration of normal blood delivery of organs and tissues of the body. Thus, application of mustard plasters on the foot contributes to reduction of cerebral blood delivery in case of hypertensive crisis, as a result it diminishes risk of stroke, on occasion of catarrhal diseases it promotes vasodilatation in respiratory tract and improves their trophy, that allow to use *Irritants* for treatment of bronchitis and pneumonia.

Pharmacological characteristics of Irritants

Folia Menthae piperitae *(Peppermint leaves)* contain essential oil, flavonoids, ursolic acid and oleanolic acid, betaine, carotene, hesperidine, tannins, organic acids, trace elements (microelements). This complex of BAS has choleretic, sedative and weak hypotensive effects. Drugs with peppermint leaves enhance the secretion of digestive glands, stimulate the appetite, inhibit the processes of decay and fermentation in GIT, reduce smooth muscle tone of the intestine, bile duct and urinary tract, increase the secretion of bile. *Indications:* in the treatment of GIT diseases (nausea of various origins, intestinal colic, flatulence, gastrointestinal spasms); liver diseases (cholecystitis, hepatitis, cholangitis, cholelithiasis); as a light sedative agent. *Side effects:* inefficient use of peppermint leaves can cause pain in the heart; in some cases may manifest allergic reactions (urticaria, pruritus, contact dermatitis). *Contraindications:* hypersensitivity to BAS, which are included in the drugs; spasmophilia, croup, asthma; children under 3 years.

Menthol is obtained from mint oil; it stimulates receptors in the mucous membranes, skin and subcutaneous tissue. Inunction it into the skin and application to the mucous membranes causes irritation of nerve endings, which is accompanied by a feeling of cold, mild burning and tingling. Menthol has a local analgesic effect, weak antiseptic properties. *Indications:* externally it is prescribed as an analgesic (distracting) remedy for treatment of neuralgia, myalgia, arthralgia, in case of itching dermatoses, as well as it is used in migraine, inflammatory diseases of the upper respiratory tract (rhinitis, pharyngitis, laryngitis, tracheitis etc.). Menthol is prescribed inside as a sedative agent, often in combination with tincture of Valerian, Belladonna; sometimes – in mild forms of angina pectoris due to the possibility of Menthol reflexively cause expansion of coronary vessels through stimulation of the receptors of oral mucosa. *Side effects:* possible reflex apnea on occasion of nasal lubrication by Menthol in small children. *Contraindications:* small children.

Menthol solution in menthyl isovalerate *(Validolum)* stimulates receptors of mucous membranes, has a calming effect on the CNS, has a moderate reflex vasodilating properties. Validolum is used to relieve mild attacks of stenocardia, in case of neuroses, hysteria, also as antiemetic in sea and air sickness. *Adverse reactions:* rarely occurs slight nausea, watery eyes, dizziness, that disappear on their own.

Folia Eucalypti viminalis *(Eucalyptus leaves)* exhibit antibacterial, antiviral, antifungal, antiprotozoal and anti-inflammatory effects. The degree of manifestation of these effects depends on the content of essential oil. At oral administration of eucalyptus leaves cause expectorant, mucolytic, broncholytic effects, when it is applied to the skin – astringent, antiexudative, antipruritic, anesthetic effects, and in high concentrations – local irritating action. Infusion of the *Eucalyptus leaves* due to the presence of essential oil and a small amount of bitterness in the structure stimulates the secretion of digestive glands, improves

digestion. Oral infusion of *Eucalyptus leaves* has sedative effect due to aldehyde of isovaleric acid. Chlorophyllipt that is contained in the leaves of Eucalyptus, has antimicrobial, especially antistaphylococcal activity, stimulates regenerative processes. Components of essential oil with organic acids, tannins and trace elements as manganese, zinc, selenium, increases the resistance of body tissue to hypoxia of different origin. *Indications:* in combined therapy for acute and chronic infectious and inflammatory processes of different localization: rhinitis, stomatitis, gingivitis, laryngitis, bronchitis, pneumonia, hypersecretion of stomach glands, enterocolitis, goiter, cholecystitis, pielonephritis, vaginitis, colpitis, cervical erosion, burns, dermatitis, sciatica (radiculitis), neuritis, myositis, trophic ulcers, nervous disorders, mild form of insomnia, low back pain. *Side effects:* possible allergic reactions; in high doses – nausea, vomiting, diarrhea, muscle cramps; in case of frequent inhalation use – dry mucous membranes of the respiratory system. *Contraindications:* hypersensitivity to the components of *Eucalyptus*, atrophy of the mucous membranes of the respiratory tract. *Warning:* it is not desirable to use *Eucalyptus* at elevated secretion of digestive glands, to avoid the the contact of the drug with eyes, before applying to check sensitivity to *Eucalyptus* by its smell.

Semen Sinapis *(Mustard seeds)* are rich in fatty oils (oleic, erucic, stearic and linolenic acids), steroids (brassicasterol, campesterol, sitosterol, cholesterol, metylenholesterol) thioglycoside sinalbin, saponins, and glycoside sinigrin.
Traditional medicine recommends the *use* of *Mustard seeds* to enhance the functions of GIT, for the treatment of arterial hypertension, atherosclerosis, diseases of liver and gall bladder, digestive disorders, neuralgia, rheumatism, pneumonia, bronchitis, gout, hemorrhoids. *Mustard seeds* are also used as a laxative and to reduce fever. The *Official medicine uses mustard plasters* which are made of mustard powder, they are well warmed, facilitate breathing, promote blood flow in space applications. For this purpose they are used in pneumonia, bronchitis, rheumatism, angina pectoris, hypertensive crisis, the risk of stroke. *Contraindications:* tuberculosis, kidney diseases. *Caution* should be exercised to use large doses of mustard, which can lead to shortness of breath, bradycardia and even loss of consciousness. It is undesirable to use high doses of mustard in patients with hyperacidic gastritis, stomach and duodenal ulcers, acute enterocolitis. Given the fact that Mustard is a poisonous plant, you need to consider its dosage carefully.

Fructus Capsici *(fruits of Cayenne pepper)* have a distracting and irritant effect. Apply externally for rubbing in case of neuralgia, radiculitis, myositis, lumbago, rheumatic pains in the joints, to treat frostbite. Alcohol tincture of fruits of Cayenne pepper is used to excite the appetite, has antibacterial properties so it is useful in acute disorders of GIT. There is evidence of antiviral activity of fruits of Cayenne pepper. In addition, fruits of Cayenne pepper are multivitamin concentrate and they particularly rich in rutin and ascorbic acid, thus positively affect metabolism, and make it easier during of radiation sickness. *Side effects:* for external use, itching and flaking of the skin are possible. *Warning:* cannot be

applied to damaged skin, mucous membranes. *Contraindications:* hypersensitivity, gastric and duodenal ulcers, acute and chronic gastritis, colitis, enteritis, hepatitis, cholecystitis.

Extract Salvia sclarea *(extract of Clary sage, Salmus)* has a local anti-inflammatory, antiseptic and local irritanting action, improves tissue trophic, has analgesic effects on receptors of sensory nerves, and reduces sweating. *Indications:* it is used as bathes, as reflex distracting agent for treatment of the peripheral nervous system diseases (mononeuritis, polyneuritis, sciatica, lumbago, in case of recovery period after injury), for treatment of CNS diseases (neurasthenia, fatigue); diseases of the muscular and skeletal systems (rheumatoid arthritis, primary deforming osteoarthritis, spondylosis, bursitis, restricted movement of joints). *Side effects:* balneology reactions (asthenia, palpitations, dizziness, headache, tachypnea, tachycardia, increased BP), allergic reactions. *Contraindications:* hypersensitivity; asthma; diabetes mellitus (severe course); tuberculosis; expressed heart failure; vascular crises; expressed atherosclerosis of the vessels of a brain, heart, kidneys; coronary artery disease; skin diseases (acute phase); cancer; rheumatoid arthritis (active phase).

Oleum Terebinthinae rectificatum *(oil of turpentine, Turpentine)* is applied externally as distracting and irritating agent. When applied to wounds and ulcers in weak concentrations it contributes to their healing, activating of granulation, improving blood circulation, acting as antiseptic; Turpentine promotes blood clotting; if it was introduced subcutaneously Turpentine oil causes aseptic abscess, which is used for exacerbation of chronic processes; in case of resorptive action Turpentine oil moderately stimulates the CNS, stimulates respiration, improves reflex excitability. *Indications:* for aggravation of chronic diseases; as an expectorant, antiseptic, anti-inflammatory agent, as well as laxative and anti-fermentative agent. *Side effects:* in patients with hypersensitivity to *Turpentine* may occur local allergic reactions (itching, swelling, and redness, burning, rash); in some cases may occur generalized allergic reactions (dyspnea, palpitations, decreased BP, dizziness, seizures, loss of consciousness). *Contraindications:* severe kidney and liver diseases and skin diseases of various origins. *Caution:* do not allow to enter Turpentine ointment on mucous membranes and eyes. If the ointment accidentally gets in the eyes, you should rinse thoroughly them with plenty of running water. *Not recommended* for use in children. It is not known whether Turpentine penetrates into breast milk or pass through the placenta during pregnancy because Turpentine for pregnant and lactating women is not recommended.

Spiritus Acidi formici *(1.4% formic acid in 70% or 96% ethyl alcohol)* has bactericidal, local irritanting, anti-inflammatory, analgesic actions, it dilates blood vessels, improves blood circulation in the tissues. *Indications:* arthritis, arthralgia, myalgia, neuralgia, to treat acne. *Side effects:* local allergic reaction. *Contraindications:* oral administration, applying to the mucous membranes and damaged skin.

Tincture amara *(bitter tincture)* has properties inherent in its components. Tincture amara is used to stimulate appetite, improve digestion.

Herba Centaurii *(grass of Centaury)* increases appetite, secretion of gastric juice, accelerates GIT motility, has a mild laxative effect and has anthelmintic properties. *Indications:* decreased appetite, indigestion (burping, nausea, vomiting, flatulence), atonic constipation, hepatitis, cholecystitis, the recovery period after severe infections, helminthiasis (infestation by whipworm). *Side effects:* possible allergic reaction. *Contraindications:* gastric and duodenal ulcers, hypersensitivity to Herba Centaurii. Grass of Centaury is part of the combined herbal preparations Canephron and Bittner Balsam.

Herba et folia Artemisiae absinthii *(grass and leaves absinthe Wormwood)* stimulate the function of the GIT glands, increase the secretion of gastric juice, bile, exhibit anti-inflammatory, antiseptic properties. *Indications:* it is used as a bitter for stimulation of appetite and improve digestion, increase of secretory activity in patients with decreased secretion of the stomach. *Side effects* are not established. *Contraindications:* cholelithiasis; are not recommended for children under 12 years and for women during pregnancy and lactation.

Succus Plantaginis *(Plantain juice)* has anti-inflammatory, analgesic, wound healing, haemostatic, ants-allergic effects; it stimulates secretion and regulates digestion, increases appetite. *Indications:* anorexia, gastritis with decreased secretion, functional dyspepsia which occurs on a background of low gastric acid secretion. *Side effects:* allergic reactions. *Contraindications:* hypersensitivity to the components of *Plantain juice*, children under 12 years, increased acidity of gastric juice, stomach and duodenal ulcers. *Disclaimer:* it is used only in cases of low or normal stomach acidity; pregnant and lactating women can use the drug with Plantain juice only if the benefits of the use outweigh the potential risk. *The interaction* of Plantain juice with antacids and H2-blockers reduce the effectiveness of the drug last.

Radices Taraxaci *(Dandelion roots)* in folk medicine is used as drugs to increase appetite and stimulate digestion, reducing putrefactive and fermentative processes in the digestive tract. Bitterness that is contained in Dandelion root, irritates taste buds and stimulates the reflex secretion of gastric juice. Dandelion root tincture is *useful* for cholelithiasis, hypoacidic gastritis and chronic constipation, also as an expectorant for treatment of respiratory diseases, as sedative and hypnotic – in disorders of CNS, for treatment of kidney diseases, spleen, gall bladder (as cholagogue) diseases, and hemorrhoids. As part of the mixed teas Dandelion root is used to treat early stages of diabetes mellitus (moderately reduces blood glucose levels), it improves metabolism, and it has anti-atherosclerotic properties. External infusion of Dandelion root is rubbed in the skin for treatment of acne, boils (furuncles), medicamental dermatitis. Powder Dandelion root improves wound healing, burns, ulcers. Studies revealed antituberculosis, antiviral, fungicidal, antihelmintic, anti-cancer activities of Dandelion. *Caution:* not recommended the use of drugs with Dandelion root for acute conditions with occlusion of the biliary tract; *carefully* – in hyperacidic

gastritis, stomach and duodenal ulcers. *Side effects:* in large doses Dandelion root can cause vomiting and diarrhea. *Contraindications:* individual intolerance.

Folia Menyanthidis trifoliata *(leaves of Menyanthes trifoliata, Bog-bean, Buckbean)* contain bitter that irritates taste receptors of the mucous membranes of the mouth and tongue, reflexes an increase of the secretion of gastric glands, improves appetite, and digestion. Leaves of Bog-bean have also antiseptic and antipyretic effects. It is applied at hypoacidic gastritis, constipation, flatulence, for the treatment of headaches, trigeminal neuralgia, rheumatism, diseases of the liver and gall bladder, dysentery, pulmonary tuberculosis, scurvy, fever, malaria, dyspepsia, migraine, helminthiasis; in dentistry – for treatment of periodontitis, stomatitis, gingivitis, toothache; external leaves of Bog-bean are used as an antiseptic for the wash of venous (trophic) ulcers, wounds that heal poorly, diseases of the skin and mucous membranes.

Rhizomata Calami *(Calamus rhizome, rhizome of Acorus calamus, rhizome of Sweet Flag, Calamus, rhizome of Beewort)* in official medicine *is used* for gastritis with low acidity, to improve appetite and digestion, in case of cholecystitis, colic, diseases of kidney and urinary bladder; also it is used as an expectorant, disinfectant and antiflatulent; Calamus rhizome is used for treatment of diseases of the male and female reproductive organs, thyroid disease, diabetes mellitus, acute respiratory diseases, besides as a sedative agent in patients with mental illness; in dentistry – to treat periodontal diseases, stomatitis, pharyngitis, and tonsillitis;. Calamus rhizome in the form of baths is also used in children with rickets and eczema and in adults with violation of the peripheral circulation. *Contraindications:* pregnancy, increased acidity of the stomach, and acute exacerbation of chronic gastric ulcers, nasal bleeding, acute inflammation of the kidney diseases, and arterial hypertension. In large doses it can cause vomiting.

Chloroform in modern medicine is used externally due to the presence irritating activity on the skin for rubbing in patients with neuralgia, myositis (usually mixed with methyl salicylate, turpentine and other irritating agents). Very rarely chloroform in mixture with tincture of Valerian may be appointed in case of vomiting, hiccups, and as antismoke mixture (solution of ammonia and ethanol) in patients with lesions of the respiratory tract by irritant arsines (organic arsenic compounds).

Finalgon contains in its composition Nonivamide and Nicoboxil. Nonivamide is a synthetic analogue of Capsaicin; it has analgesic effect by stimulating peripheral nociceptive nerve fibers when applied to the skin. Nicoboxil reveals a direct vasodilatative action, accelerates enzymatic reactions, activates metabolism; vasodilation leads to hyperemia, improves blood circulation in the tissues, thus achieving a warming effect. *Indications:* arthritis, myalgia, arthralgia, sports injuries, bruises and injuries of ligaments, lumbago, neuritis, bursitis, tenosynovitis, violations of peripheral blood circulation (in the complex therapy). *Side effects:* allergic reactions, excessive redness and burning of the skin, irritation at the site of application of the drug. *Contraindications:* hypersensitivity, dermatitis, open wounds, the skin with impaired permeability, causing the skin in

the neck, abdomen and inside thighs, drawing on the mucous membranes; pregnancy and lactation.

Solutio Ammonii *(solution of Ammonia caustic)* **10%** operates in the field of sensory (afferent) nerve endings, inhalation of it reflex stimulates the respiratory center due to the effects on receptors of the upper airway (endings of trigeminal nerve); when it is taken inside has emetic effect. *Indications*: solution of Ammonia caustic is used for excitation breath in patients with loss of consciousness, for call vomiting; externally – in the form of lotions it is used in patients with insect bites; in surgical practice – it is used for hand washing. *Side effects:* in large doses solution of Ammonia caustic causes reflex stop of breathing. *Caution:* when it is taken inside can only be used in diluted form because of the high risk of burns of the esophagus and stomach. When using ammonia solution should be wary of getting vomit into the respiratory tract.

Apiphor – tablets for making solution for external use, or rectal suppositories and ointment containing lyophilized bee venom. Apiphor *is used* for electrophoresis in the treatment of arthritis, myositis, deforming spondylarthrosis, sciatica, peripheral vascular diseases (endarteritis, thrombosis without purulent process), keloid scars after burns and operations; and rectal suppositories of Apiphor *is used* for treatment of metabolic disorders, diabetes mellitus, conditions after stroke and myocardial infarction, arrhythmias, angina, coronary artery disease, atherosclerosis, arterial hypertension, furunculosis, radiculitis, hemorrhoids, to improve the condition of rectal mucosa, in diseases of the genital and urinary systems, pathological menopause, infertility, for regulation of menstrual cycle. *Side effects:* may be hives, runny nose, severe itching, sneezing, chills, headache, nausea, vomiting, flushing, edema, pyrexia, pain, itching at the site of application. *Contraindications:* individual intolerance, decompensated liver and/or kidney failure, pancreatitis, blood diseases, mental illness, adrenal insufficiency, chronic heart failure of I-II degrees, diabetes mellitus, cancer, cachexia, sepsis, acute purulent diseases, tuberculosis and other infectious diseases in the acute stage, and pregnancy. *Caution:* during treatment by this drug the status of skin and kidney function drug should be monitored; it must *be used with caution* during menstruation, in childhood or old age; after rubbing wash the hands thoroughly.

Apisartron – ointment containing bee venom, methyl salicylate, allyl isothiocyanate, emulsifiers, Vaseline and water; it has a local irritating effect due to stimulation of peripheral nerve endings, reveals a direct vasodilating effect, which leads to improvement of blood supply to the tissues, accelerates the decay of products of metabolism that cause pain; and methyl salicylate, allyl isothiocyanate cause flushing of the skin, providing soothing and warming effects. Apisatron helps to enhance metabolism, to increase the elasticity of the connective tissue and muscles, reducing muscle tone. This drug is *used* for rubbing in rheumatism, myalgia, neuritis, neuralgia, disturbance of peripheral circulation, pain syndrome in injuries of muscles, tendons, ligaments, in bruises and sprains, to warm up the muscles before and during exercise. *Side effects:* possible allergic reactions.

Contraindications: individual intolerance, chronic renal failure, liver disease, skin tumors, inhibition of hematopoiesis, mental illness, acute arthritis, children under 12 years. *Disclaimer:* Apisatron should not be applied to damaged skin, avoid contact of the drug with the eyes, mucous membranes and open wounds.

Ungapiven *(Bees venom)* – ointment with bee venom, which has anti-inflammatory, local irritating, analgesic effects and stimulates the endocrine and immune systems, and *is used* as an analgesic and anti-inflammatory drug for treatment of arthritis, arthrosis, osteochondrosis, radiculitis, myalgia, myositis, lumbago, peripheral vascular disease, keloid scars after burns and operations. *Side effects:* possible allergic reactions, chills, headache, nausea, vomiting, redness, swelling, pain at the site of application. *Contraindications:* individual intolerance, decompensated liver and/or renal failure, chronic heart failure of I-II degrees, diabetes mellitus, cancer, cachexia, sepsis, acute purulent diseases, tuberculosis and other infectious diseases in the acute stage, and pregnancy. *Disclaimer:* this drug must be used with caution during menstruation, in childhood or in elderly, it can not be applied to damaged skin, avoid contact with eyes, mucous membranes and open wounds; after rubbing the hands should be thoroughly washed; during the application one should monitor the renal function and skin condition.

Vipraxin pro injectionibus contains poison of adder *(Vipera berus L.)* and is used as an analgesic and anti-inflammatory agent in case of neuralgia, arthralgia, myalgia, chronic non-specific mono- and polyarthritis, myositis. *Side effects:* may occur allergic reactions, pain at the injection site. *Contraindications:* individual intolerance, tuberculosis, fever, cachexia, cerebral insufficiency and/or coronary circulation insufficiency, heart diseases, predisposition to angiospasm, organic liver and kidney diseases, pregnancy, lactation. *Disclaimer:* given the fact that this drug is thermolabile the syringe must be cooled to prevent loss of drug activity.

Najaxin is clear, colorless liquid that contains poison of central asian cobra, procaine and sodium chloride and is used for the relief of pain in the case of sciatica, neuralgia, neuritis of various origins. Najaxin increases the effects of opioid analgesics and local anesthetics. *Side effects:* possible allergic reactions. *Contraindications:* individual intolerance, tuberculosis, fever, cachexia, cerebral insufficiency and/or insufficiency of coronary circulation, heart diseases, predisposition to angiospasm, organic liver and kidneys, pregnancy, lactation.

Viprosal is ointment with poison of adder, with the addition of camphor, salicylic acid, Turpentine oil, Vaseline, glycerine, emulsifier and water. Viprosal has local irritating and analgesic effects, causing irritation of sensory receptors of the skin and subcutaneous tissue, dilates blood vessels, and improves tissue trophism. *Assign externally* for rheumatic pain, neuralgia, radiculitis, lumbago, myositis, arthritis. *Side effects:* possible allergic reactions. *Contraindications:* individual intolerance, pustular disease and skin damage at the site of application, pregnancy, lactation, fever, cachexia, severe lack of cerebral and coronary circulation, a tendency to angiospasm, severe renal and/or liver dysfunction. *Warning:* to avoid the application of Viprosal to open wounds and mucous

membranes; in case of appearance of side effects you should stop using the drug; the need of its use for children is determined individually.

Nizhvisal is ointment containing venom viper, salicylic acid, camphor, spruce oil or Turpentine and has analgesic, absorbing, anti-inflammatory effects. Neurotropic component of viper venom has analgesic effect, and its enzymatic component with hyaluronidase activity accelerates the healing process. It is used for pain relief and anti-inflammatory effect when injuries, lumbago, radiculitis, rheumatic pain, myalgia, sciatica. *Side effects:* possible allergic reactions, burning at the site of application. *Contraindications:* hypersensitivity, pustular skin diseases, violation of the integrity of the skin at the site of application of the drug. *Caution:* avoid getting the drug on the mucous membranes, and in the case of a hit should be abundantly rinse with water.

Table 34. Medicinal forms of Irritants

INN	Trade names	Medicinal forms	
Folia Menthae piperitae	Infusum foliorum Menthae piperitae,	Infusion;	5.0 : 200 ml;
	Briketum foliorum Menthae piperitae,	Briquettes;	8.0;
	Oleum Menthae piperitae,	Oil;	
	Menthae piperitae Aqua Menthae piperitae	Tincture in flacons;	15 ml, 25 ml;
		Tooth drops in flacons-droppers;	10 ml;
		Shredded raw in packs	50.0
Menthol	Mentholum	Powder;	
		Alcohol oral solution for sublingual administration in flacons;	5% y 70% alcohol; 1%, 2% - 10 ml;
		Oil solution in flacons for intranasal administration;	1%, 2% - 10 ml;
		Menthol pencil in a plastic pencil case;	
		Menthol oil in flacons;	1%, 2% - 10 ml;
		Oinment in jars and tubes;	5.0, 25.0, 50.0, 30.0, 50.0;
0.5 part of Menthol : 5 parts of boric acid : 94.5 parts of Vaselinum;		Peroral solution in flacons;	40 ml;

0,15 Menthol + 20 ml tincture of Eucalyptus + 90% Ethyl alcohol up to 40 ml;	Eucatolum;	Liquid for external use in flacons;	40 ml;
2,5 Menthol + 1,0 procaine + 1,0 Anaesthin + 70% Ethyl alcoho up to 100 ml;	Menovasinum;	Ointment in glass jars;	15.0, 25.0, 40.0;
18.0 Menthol racemic (or 22.5 Peppermint oil) + 10.0 Camphor + 10.0 Eucalyptus oil + 1.0 Clove oil + Paraffin and Vaseline up to 100.0;	Geucamenum;	Aerosol in balloons;	35 ml, 45 ml;
0.06 (or 0.09) Menthol + 0.61 (or 0.915) Camphor oil (or Castor oil) + 0.002 (or 0.003) Furacilinum + 10.0 (or 15.0) Olive oil + 2 ml (or 3 ml) Ethyl alcohol;	Camphomenum;	Mixture for inhalations in flacons;	40 ml;
0.71 Menthol + 35.7 ml tincture of Eucalyptus + 357 ml Glycerin + 96% Ethyl alcohol up to 100ml;	Mixtio pro inhalationibus;	Pocket inhaler;	
0.3 Camphor + 0.17 Menthol + 0.08 Methyl salicylate + 0.1 Eucalyptus oil;	Inhacamfum;	Ointment in tubes;	10.0, 25.0;
10.0 Camphor + 3.0 Clove oil + 3.0 Mustard oil + 7.0 Eucalyptus oil + 14.0 Menthol + 8.0 Methyl salicylate + 4.0 tincture of Capsicum + 3.0 Thymol + 3.0 Chloral hydrate +1.0 Cinnamon alcohol + 4.4 Paraffin + Spermaceti and Vaseline up to 100.0;	Efcamonum;	Peroral solution in flacons;	15 ml, 20 ml, 25 ml, 30 ml, 40 ml;
Tincture Convallariae 100 ml and tincture Valerianae 100 ml + tincture Belladonnae 5 ml + Menthol 0.2 ;	drops of Zelenin;	Peroral solution in flacons;	25 ml, 50 ml;
Tincture Convallariae 10 ml and tincture Valerianae 10 ml + 1 ml 1% solution of Nitroglycerin + 2 ml Validolum;	drops of Votchal;	Aerosol	30.0, 45.0

Irritants

Camphore + Menthol + Chlorbuthanol + Eucalyptus oleum	Cametonum		
Menthol solution in menthyl isovalerate	Validolum	Tablets; Capsules; Peroral solution in flacons-droppers	0.06; 0.05, 0.1; 5 ml, 15 ml
Folia Eucalypti viminalis	 INSTI; Eucaliminum	Shredded raw in packs; Granules for making oral solution; Mixture for inhalations in flacons; Tincture in flacons; Solution for topical application and inhalation	50.0, 100.0, 500.0; 25 ml, 30 ml, 40 ml, 50 ml; 40 ml; 1% - 25 ml, 50 ml
Semen Sinapis		Powder, Patch	
Fructus Capsici	 Unguentum contra congelationem; Capsitrinum; Linimentum Capsici ammoniatum, Linimentum Capsici camphoratum, Emplastrum Capsici, "Еспол" (Unguentum "Espolum"), Nicoflex -crème	alcohol tincture (90%) in flacons; Ointment in flacons; Liquid in glass vials; Liniment in vials; Liniment in vials; Patch; Ointment in tubes; Crème in tubes	1:10 - 50 ml, 100 ml; 30.0, 60.0; 100 ml; 40 ml; 80 ml; 12 x 18 sm; 10 x 18 sm; 6 x 10 sm; 30.0; 50.0
Extract Selviae sclarea	Salmus	Concentrate	10 kg
Oleum Terebinthinae rectificatum	Carmolis; Doctor Mom, Salvisar, Alvipsal, Muv, Nigvisal	Gel for external in tubes; Liniment; Ointment; Ointment, Ointment, Ointment; Parenteral solution in ampoules (s/c)	72.0, 145.0; 20% - 25.0, 20% - 30.0; 20.0; 15.0, 25.0; 30.0, 50.0; 5 ml, 10 ml

Drugs affecting the Afferent innervation

Spiritus Acidi formici		Solution for external use in flacons	1.4%
Herbae Centaurii 60.0, Folium Menyanthidis 60.0, Rhizomata Calami 30.0, Herba Artemisiae absinthii 30.0, fruits of Coriander 15.0 and 40% Ethyl alcohol pu to 1 l	Tincture amara	Tincture in flacons	25 ml
Herba Centaurii Herbae Centaurii 18mg, Radicis Levistici 18mg, Foliorum Rosmarini 18mg	Original Grosser Bittner Balsam, Canephron	Shredded raw in packs; Balsam for oral administration in vials; Peroral solution in flacons; Dragee	100.0; 50 ml, 100 ml, 250 ml; 50 ml, 100 ml;
Herba et folia Artemisiae absinthii		Shredded raw in packs	50.0
Succus Plantaginis	Plantaglucidum	Liquid for oral administration in vials; Granules in vials and packages	100 ml; 50.0; 2.0
Radices Taraxaci		Shredded raw in packs; Powder	100.0
Folia Menyanthidis trifoliata		Shredded raw in packs	100.0
Rhizomata Calami		Shredded raw in packs	100.0
Chloroform		Fluid for external use in glasses; Complex liniment in vials	100 ml; 25 ml
Nonivamide+Nicoboxil	Finalgon, Betalgon	Ointment in tubes	20.0
Solutio Ammonii caustici 10%		Solution in vials with ground stoppers and ampoules	10ml, 40ml, 100ml; 1 ml
Bees venom	Apiphor, Apiphor -1, Apiphor -2	Tablets for making solution for external use; Ointment; Suppositories	0.001
Bees venom 3 mg + methyl salicylate 10.0 + allyl isothiocyanate 1.0	Apisartron	Ointment in tubes	20.0, 30.0, 50.0, 100,0

Irritants

Bees venom	Ungapiven, Bees venom	Ointment in tubes	30.0
Vipraxin pro injectionibus, Viper venom		Parenteral solution in ampoules (i/s, s/c, i/m)	1 ml
Viper venom 1mg + procaine 4 mg	Najaxin	Parenteral solution in ampoules (s/c, i/m)	1 ml
Viper venom 1IU + salicylic acid 10 mg + Camphora 30 mg + Therpentine 30 mg/100.0	Viprosal	Ointment in tubes	25.0, 50.0
Venenum vipirae 16 IU + Camphor 3.0 + salicylic acid 1.0 + Therpentin oleum 8.0/100.0	Nizhvisal	Ointment in tubes	25.0, 50.0

UNIT 5. DRUGS AFFECTING the CENTRAL NERVOUS SYSTEM

Chapter 11. General anesthetics

General anesthetics (GAs) depress the CNS to permit the surgery operations and unpleasant procedures. General anesthesia is a reversible depression of CNS function with the loss of response and perception of all external stimuli.

The features of the use of General anesthetics are:

Decrease in systemic arterial blood pressure due to vasodilatation, myocardial depression, blunting of baroreceptor control, reduction in central sympathetic tone

Reduction or elimination ventilatory drive and reflexes that maintain airway patency

Loss of passive and active regurgitation due to the loss of gag reflex and cough reflex, and decrease of lower esophageal sphincter tone

During surgery the *hypothermiais* is developed in patients as a result of low environment temperature, exposed body cavities, cold intravenous fluids, altered termoregulatory control, reduced metabolic rate

Peripheral vasoconstriction is activated to defend against heat loss

Total body oxygen consumption is decreased by 30%

Nausea and vomiting in the post-operative period are caused by an action of general anesthetics on chemoreceptor trigger zone and brainstem vomiting center, which are modulated by serotonin, histamine, acetylcholine, and dopamine.

Pharmacological effects of GAs:

Amnesia

Immobility in response to harmful stimulation

Abatement of autonomic responses to harmful stimulation

Analgesia

Unconsciousness

Mechanism of anesthesia.

At the *cellular level* GAs generates two main physiologic effects. *First*, the inhalational anesthetics cause hyperpolarization of neurons that may be important in synaptic connection, whereas diminished excitability in postsynaptic neurons may reduce probability of initiation of an action potential in response to neurotransmitter release. *Second*, both inhalational anesthetics and intravenous anesthetics in anesthetizing concentrations have significant effects on synaptic transmition and far less effects on action potential formation or distribution.

At the *molecular level* GAs modulate ligand-gated ion channels, receptors, and signal transduction proteins: K^+ channels, Cl^- channels, GABA (gamma-aminobutyric acid) receptors, NMDA (N-methyl-D-aspartate) receptors, Glycine receptors, N-cholinoreceptors, GABA-receptors proteins.

So, inhibition of NMDA receptors leads to *anesthetic effect* and produces *unconsciousness*; the increase of sensitivity of GABA receptors to GABA enhances *inhibitory neurotransmission and depressing nervous system activity*; the ability of some GAs *to inhibit noxious stimuli and to elicite sedative effects* is mediated by their actions on GABA receptors; Glycine receptors mediate the *inhibition of responses to noxious stimuli* by GAs; GAs increase the capacity of glycine to activate Glycine receptors that leads to *inhibition of neurotransmission in the spinal cord and brainstem*; N-cholinoreceptors could mediate *analgesia or amnesia*; the molecular interactions inhalation GAs with specific protein complex involved in synaptic neurotransmitter release explain the ability of inhalation GAs to cause presynaptic inhibition in the hippocampus and promote to the *amnesic effect* of them; inhalation anesthetics activate K^+ channels that are located in both pre-synaptic and post-synaptic sites, and in first case they cause *hyperpolarization* of the pre-synaptic terminal, thereby *reducing neurotransmitter release*, and in the second case they induce *resting membrane potential*.

In summary, it should be noted that modern data support the view that *intravenous GAs* act predominantly through GABA receptors and possibly through the interactions with other ligand-gated ion channels – NMDA receptors, two-pore K^+ channels. The halogenated inhalational GAs have a variety of molecular targets. Nitrous oxide, ketamine, xenon inhibite NMDA receptors and/or activate the two-pore-domain K^+ channels.

Classification of General anesthetics

Non-inhalational (intravenous, parenteral) anesthetics:

drugs of short action (less than 10-15 min.): ketamine, propanidid, propofol, methohexital, etomidate;

drugs of average duration of action (20-30 min): thiopental sodium, hexobarbital;

drugs of long action (60 min and more): sodium oxybate.

II. Inhalational anesthetics:

liquid volatile substances: ether for anesthesia, halothane, isoflurane, enflurane, desflurane, sevoflurane;

gas-like substances: nitrous oxide, xenon.

Pharmacological characteristics of Non-inhalational (intravenous, parenteral) anesthetics

Through lipophilic properties of general anesthetics they easily overcome BBB and penetrate into the brain and spinal cord providing general anesthesia.

These drugs accumulate in fatty tissue, prolonging recovery if multiple doses are given. The sensitivity of the patients to GAs depends on the physiological and/or pathological condition of the patients such as age, body mass, comorbidities, cardiac output, serum protein levels, liver and/or kidney insufficiency, the combination with other drugs, etc. Each general anesthetic has its own unique properties, adverse effects, advantages and application features.

Ketamine is an arylcyclohexylamine. Ketamine is typically administrated intravenously but may be introduced intramuscularly, oraly and rectaly. It is metabolized in the liver and is excreted with the bile and urine. In case of intravenous introduction of ketamine the onset of anesthesia after single bolus is 20-60 seconds and the duration of anesthesia is 5-10 minutes.

Ketamine after single bolus induces the general anesthesia, although it does not produce the classic anesthetic state, but it causes profound analgesia, slight hypnotic effect and partial loss of consciousness with mild amnesia. Muscle relaxation is poorly expressed. Swallowing, laryngeal, cough reflexes are expressed and even are increased. Ketamine slightly increases general blood pressure, causes tachycardia, salivation, increased intraocular and intracranial pressure. Besides, ketamine has psychomimetic effects.

Mechanism of analgesic action of ketamine is based on activation of μ-opioid receptors of talamus and activation of κ-opioid receptors of spinal cord, and activation of serotonine receptors of middle brain, talamus and cortex. *Mechanism of hypnotic action* of ketamine is based on the blockage of cholinergic receptors, and N-methyl-D-aspartat (NMDA) receptors, and activation of GABA. *Mechanism of cardiac effects* is provided by sympathomimetic action of ketamine mediated by inhibition of central and peripheral catecholamine reuptake. Furthermore, ketamine has direct negative inotropic and vasodilating activities that are overpowered by its sympathomimetic action. *Mechanism of psychomimetic effects* of ketamine is a capacity to activate dopaminergic systems of the brain and to stimulate σ-opioid receptors, serotonine receptors of the brain.

Side effects of ketamine: it increases blood pressure, heart rate, and cardiac output, myocardial oxygen consumption; induces cataleptic state, is accompanied by nystagmus, pupillary dilatation, salivation, lacrimation, spontaneous limb movements with increased general muscle tone; it increases cerebral blood flow, intracranial pressure, intraocular pressure; during the introduction in the anesthesia and during the removal from the anesthesia can occur delirium, characterized by hallucinations, vivid dreams, delusions; ketamine as NMDA receptor agonist may cause neurotoxicity is known as Olney's lesions.

Prevention of ketamine-induced delirium may be by benzodiazepines; spontaneous limb movements with increased general muscle tone, hallucinations, vivid dreams, delusions may be prevented by tranquilizers or neuroleptics; increased salivation can be prevented by cholinoblockers; anticholinergics, benzodiazepines, barbiturates and central α2 adrenergic agonists such as clonidine suppress neurotoxicity of ketamine, conversely, coadministration of NMDA-

antagonists with α2 adrenergic antagonists, like yohimbine could theoretically potentiate neurotoxicity.

The advantages of ketamine over other parenteral GAs: it induces profound analgesia, increases blood pressure, heart rate, cardiac output, ketamine produces less severe respiratory depression than other GAs, is a potent bronchodilatator due to its sympathomimetic activity.

Thus, *ketamine* is the parenteral anesthetic which *is the best suited* for the patients with the risk of development significant hypotension during anesthesia, for the patients with high risk of bronchospasm during anesthesia; for children undergoing short painfull procedures considering that delirium symptoms occur less frequently in children.

But, *ketamine is not good anesthetic* for the patients with risk of miocardial ischemia, for the patients with intracranial pathology or cerebral ischemia, for the patients with open eye injuries.

Propanidid is a propyl ester of phenylacetic acid. In case of its intravenous single bolus onset of anesthesia arises in 20-40 seconds without stage of excitement and lasts 4-10 minutes. In human body *Propanidid* rapidly is hydrolyzed by plasma cholinesterase. Propanidid is excreted by kidney and is not accumulated.

Side effects of Propanidid: spontaneous limb movements, tremor; slight decrease in general blood pressure, tachycardia; laryngeal spasm; transient tachypnea, followed by a brief apnea; nausea, vomiting, headache, salivation, phlebitis, thrombophlebitis, and anaphylactic shock due to its ability to increase histamine release.

Propanidid is suited the best for the short painful procedures, examinations, reposition of bone fragments, and removal of stitches.

Contraindications for Propanidid use: kidney and liver insufficiency, shock.

Propofol is the most frequently used parenteral anesthetic in USA. *Propofol* is 2,6 disopropylphenol, insoluble in aqueous solutions. Propofol as lipid emulsion causes pain on injection, hyperlipidemia and risk of patient infection due to possible contamination of open containers with this anesthetic. Untapped propofol emulsion must be discarded. Presently there is water-soluble analog of propofol – *Fospropofol*. It is a prodrug form which is converted to propofol *in vivo*. Fospropofol does not induce adverse effects that inherent to propofol lipid emulsion. *Propofol* is metabolized in the liver and is excreted by kidney. Propofol is highly protein bound.

The *mechanism of sedative and hypnotic action* of propofol is mediated by its activation of GABA receptors that lead to increase chloride conduction and hyperpolarization of neurons. Propofol produces cardionegative effects: bradycardia, dose-dependent arterial hypotension due to both vasodilatation and mild depression of myocardial contractility, suppression of cerebral blood flow, cerebral oxygen consumption, intracranial and intraocular pressure. There is evidence of anticonvulsant activity of propofol and the possibility of its use for the treatment of epileptic status in humans.

Side effects of Propofol: transient choreiform movements, opisthotonus, respiratory depression, airway obstruction, apnea, bradycardia, moderate arterial hypotension. Propofol causes pain on injection, but have considerable anti-emetic effect. It may elicit allergic reaction rarely. Propofol transiently depresses activity in newborns. Propofol rarely can produce "profocol infusion syndrome" which was described in prolonged, higher-dose infusions. Profocol infusion syndrome includes the metabolic acidosis, hyperlipidemia, rhabdomyolysis, and enlarged liver.

Side effects of Fospropofol are similar to that of Propofol, but they are less expressed, and it has not "profocol infusion syndrome". Fospropofol has slower onset of sedation due to the need for hydrolysis of the prodrug.

Propofol is the best suited for the patients with cerebral ischemia, but no evidences about its neuroprotective effect.

Propofol should be used with caution in patients with hypotension or unstable pressure, in patients with hypovolemia, in astmatics, in pregnant women by reason of pass through the placental barrier. Patients given propofol should be monitored to adequate oxygenation and ventilation. Taking into account propofol painful injection it should be administered with lidocaine and into a large vein to prevent phlebitis and/or thrombosis.

Both *Propofol* and *Fospropofol* can be used in patients with adequate airway and cardiorespiratory function.

Three derivatives of barbituric acid are used for general anesthesia the most widely. There are sodium thiopental, thiamylal, and methohexital.

Barbiturates are precipitated as the free acid if they are used with other drugs in acid solutions during anesthetic induction, therefore the administration of other drugs should be delayed until the barbiturates has cleared the intravenous tubing. Veno-irritant effect of barbiturates can be reduced by injection into larger veins and by prior intravenous injection of lidocaine. In pediatric practice barbiturates can be given per rectum. After single dose barbiturates are redistributed from the brain to other tissues that limit anesthetic duration. But after multiple doses anesthetic duration of barbiturates becomes longer and they may accumulate. All three anesthetic barbiturates are eliminated by hepatic metabolism and renal excretion of inactive metabolites; a small fraction of sodium thiopental is transformed to the longer-acting hypnotic pentobarbital. In patients with cirrhosis can result in prolongation of the action of barbiturates. Three derivatives of barbituric acid that are used for general anesthesia are highly protein bound. In patients with the diseases that lead to low levels of serum protein concentration the initial free concentration and hypnotic effect of an induction dose of the barbiturates will be increased.

Sodium thiopental *is* most frequently used for inducing anesthesia and does not elicit pain on injection, but has anti-analgesics effect and reduces the pain threshold. Thiopental has been used as a protectant against cerebral ischemia, but for this purpose the large doses are required that elicits prolonged sedation and limits such use. Thiopental is effective in case of status epilepticus. Besides, this

general anesthetic supports ratio of myocardial oxygen supply to demand in patients with ischemic heart disease. Sodium thiopental in single induction may elicit mild transient depression of newborn activity. Thiopental does induce precipitation of neuromuscular blockers or other drugs during anesthetic induction. ***Thiamylal*** is used only in veterinary medicine. Prolonged infusions or large doses of sodium thiopental and thiamylal can cause unconsciousness continuing a few days due to their slow excretion and large volumes of distribution. ***Methohexital*** is used for inducing anesthesia during short surgical, diagnostic and therapeutic procedures with minimal pain. It causes mild pain on injection to a greater degree than thiopental. Methohexital has much more rapid clearance, and it accumulates less during prolonged infusions than other barbiturates. Methohexital can increase ictal activity and seizures.

Side effects of the barbiturates: suppression of electroencephalogram (EEG), reduction of cerebral metabolic rate and cerebral oxygen consumption in dose-dependent manner, decrease of cerebral blood flow and intracranial pressure, anticonvulsant effect; dose-dependent decrease of general blood pressure, as a result of vasodilation, especially in patients with hypovolemia, cardiomyopathy, valvular heart disease, ischemic heart disease, cardiac tamponade, β adrenergic blockade, direct decrease in cardiac contractility, and as a compensatory response - increase of heart rate, though barbiturates abate the baroreceptor reflex; depression of respiratory center, diminution the minute ventilation and tidal volume, and reduce sensitivity of respiratory center to carbon dioxide; increase of histamine release from mast cells during induction anesthesia; barbiturates can induce fatal attacks of porphyria in patients with porphyria that are manifested by severe abdominal pain, nausea, vomiting, psychiatric disoders, neurologic anomalies; inadvertent intra-arterial injection of thiobarbiturates can induce a severe inflammatory and necrotic reaction that threaten limb survival; barbiturates particularly Methohexital can produce cough, hiccup, muscle tremors, twitching, hypertonus.

Etomidate is a carboxylated imidazole derivative that has anesthetic and amnestic properties, but that has no analgesic and myorelaxants properties. Etomidate is poorly soluble in water and is formulated as a solution in propylene glycol. Etomidate is used as parenteral solution and may be given rectally. Etomidate does not induce precipitation of neuromuscular blockers or other drugs during anesthetic induction.

In the main Etomidate is used for anesthetic induction of patients with hypotension. Induction doses of Etomidate have a rapid onset and short duration of action and are accompanied by pain on injection and myoclonic movements. Therefore it is injected with lidocaine to reduce pain and with premedication by benzodiazepines or opiates for relieving myoclonic movements. Etomidate is the best general anesthetic for patients with ischemic heart disease, cardiomyopathy, cerebral vascular disease, hypovolemia.

Methabolism of Etomidate takes place in liver and elimination of it is both renal and biliary. Etomidate has a high binding with plasma proteins.

Side effects of Etomidate: Etomidate produces hypnosis and hasn't analgesic effect; decreases a cerebral blood flow and intracranial pressure, reduces a cerebral metabolism, this general anesthetic increases the EEG activity and may cause seizures; it has a small effects on heart work: small increase in heart rate, little or no decrease in blood pressure and cardiac output, little effect on coronary perfusion pressure; to a lesser degree depresses the respiratory center; induces hiccups, nausea, vomiting; it does not stimulate histamine release; single induction of Etomidate may reduce cortisol levels, but can not cause adrenocortical suppression.

Sodium oxybate (Sodium oxybutyrate) is a synthetic analog of natural metabolite which is in the brain, it is sodium salt of γ-hydroxybutyric acid (GOBA). As a general anesthetic Sodium oxybutyrate has low activity and it requires high doses to achieve anesthetic effect, it has hypotoxicity, easily overcomes the BBB, decreases a blood pressure level and may cause hypokalemia. Sodium oxybutirate has hypotermic effect, anticonvulsive effect; it increases the resistance to radiation, brain tissues hypoxia, and starvation. Sodium oxybutyrate has a sedative, anxiolytic, antihypoxic, myorelaxant effect, and mild analgesic effect. Sodium oxybutyrate is excreted basically by the lungs as carbon dioxide. Sodium oxybutyrate can be used intravenously and peroral for general anesthesia. The basic place of its action is tissue metabolism, first of all – the carbohydrate metabolism.Synaptic component of mechanism of its action is an increase of acetylcholine and a dopamine level, decrease of serotonin level, and it does not influence the level of epinephrine, norepinephrine, opioid peptides, GABA, glutamate in brain tissues. This general anesthetic blockes N-cholinoreceptors, GABA, postsynaptic adrenergic receptors, dopamine receptors, M-cholinoreceptors, and activates inhibitory α-adrenergic receptors, and GABA receptors. Overdose may depress respiratory center. Sodium oxybutirate can be used for the induction and basic anesthesia in case of delivery, brain hypoxia and shock.

Pharmacological characteristics of Inhalational anesthetics (gases and volative liquids)

One of the disadvantages of inhalational anesthetics is a low degree of safety. They are dangerous in clinical use. Each of them has a unique side-effect profile. The choice of inhalational anesthetic in clinic use is difficult. Advantages of inhalational anesthetics are rapid removal from the body and out of the anesthesia. The recovery from anesthesia for the inhalational anesthetics with low blood and tissue solubility reflects the anesthetic introduction despite duration of anesthetic administration. The recovery from anesthesia is the function of duration of anesthetic administration for the inhalational anesthetics with high blood and tissue solubility. The ability of the inhalational anesthetic to be accumulated in fatty tissue prevents blood and alveolar partial pressures from a rapid fall.

Ether for anesthesia is the volatile highly flammable liquid, dangerously explosive. Advantages of Ether for anesthesia are: the large latitude of therapeutic action, rapid recovery from anesthesia, and simple control of the depth of anesthesia. The main place of its distribution is the brain. The ether for anesthesia is mainly eliminated by the lungs in an unchanged form and the remains of it are eliminated by kidney, skin and GIT. The ether for anesthesia has analgesic effect, which is saved in after recovery from anesthesia; depresses of the cortex activity; it does not influences blood pressure, increases the heart rate; causes myocardial depression, but produces epinephrine and norepinephrine release, it does not change sensitivity of myocardium to catecholamines; the ether for anesthesia does not damage internal organs; it has myorelaxant effect, impoves the action of neuromuscular blockers. The disadvantages of ether for anesthesia are long-term introduction of anesthesia with a severest phase of excitation due to induction of subcortical activity and depression of cortex activity; irritation of the mucous membranes that cause inflammatory process in respiratory ways, vomiting; it depresses the renal function and may provoke proteinurua; ether for anesthesia may elicit acidosis, ketonemia. Premedication by atropine in case of ether for anesthesia use prevents bradycardia, cardiac arrest, and apnoe.

Halothane is the volatile liquid at the room temperature and it must be stored in a sealed container. Halothane and its mixtures with air or oxygen are neither flammable nor explosive. Halothane is soluble in fat and other body tissues, it has high blood; gas partition coefficient and high fat; blood partition coefficient, is accumulated during prolonged administration. About 80% of halothane is eliminated by lungs in unchanged form in the first 24 hours, and remainder of it is biotransformed by hepatic enzymes. In the rare cases halothane may cause fulminant halothane-induced hepatic necrosis as a result of modification of several proteins in the liver. Halothane does not irritate the respiratory tract; it diminishes bronchial secretion and causes bronchodilatation, inhibits both laryngeal and swallowing reflexes, reduces salivation, relaxes masticatory muscles, and accelerates the rate of breathing. Halothane potentiates the effects of non-depolarizing neuromuscular blocking agents. However the analgesic effect of halothane is weak.

Halothane is used for maintance of anesthesia and is well tolerated for inhalation induction, especially in children, in whom preoperative administration of intravenous catheter can be difficult. Side effects of halothane appear to be diminished in children, and low cost of it allows using halothane widely in developing contries. Bronchodilatory properties of halothane are allowed to use it in patients with status asthmaticus as a last resort. Due to uterine smooth muscle relaxation effect of halothane, it is used for manipulation of the fetus (version) in the prenatal period and for delivery of retained placenta postnatally.

Side effects of halothane. From the *cardio-vascular system* halothane causes dose-dependent reduction in general blood pressure, as a result of direct myocardial depression, decreased cardiac output, and on the molecular level these side effects of halothane are explained by depression of depolarization-induced

intracellular calcium transients. Hypotension is accompanied by bradycardia or may be normal heart rate because of damped baroreceptor reflex function diminishes chronotropic and inotropic responses to a decrease in general blood pressure. But the cardio-vascular adverse effects vanish after several hours of halothane administration due to progressive sympathetic stimulation. Halothane increases cerebral blood circulation and skin perfusion as a result of alteration of specific vascular beds, redistribution of blood flow; it increases perfusion to poorly ventilated regions of the lung and elevares alveolar oxygen gradient; halothane inhibits kidney and visceral perfusion, nevertheless coronary blood flow is largely preserved during haloten anesthesia. Necessary to consider the possibility of halothane to increase sensitivity of myocardium to arrhythmogenic effects of epinephrine, as endogenous adrenal production and exogenous administration. On the side of *respiratory system* halothane has bronchodilatory effect; it causes frequent and shallow breathing, decrease of alveolar ventilation, and inhibition of ventilatory response to carbon dioxide due to halothane depression of central chemoreceptor mechanisms, inhibition of peripheral chemoreceptor response to arterial hypoxemia. From *CNS* halothane may increase intracranial pressure and may suppresses cerebral metabolism. Halothane relaxes *skeletal muscles* by central depressant effects, potentiates the effects of non-depolarizing muscle relaxants, can provoke specific *fatal syndrome* with malignant hyperthermia, severe muscle contraction, and increase in metabolic rate in genetically sensitive patients. Halothane inhibits *uterine contractions* during parturition, prolonging labor and increasing blood loss. Halothane elicits reversible reduction of *renal* blood flow and glomerular filtration, hepatic and visceral blood flow on account of reduced general blood pressure. Halothane-induced hepatic necrosis as a result of immune response to hepatic proteins that become trifluoroacetylated as a consequence of halothane metabolism (see above) is rare: 1 in 10,000 patients receiving halothane.

Isoflurane is halogenated inhalation anesthetic similar to halothane for most of the pharmacokinetic and pharmacodynamic parameters. But isoflurane has a blood/gas partition coefficient lower than halothane or enflurane; therefore induction with isoflurane and recovery from isoflurane are faster than with halothane, and changes in anesthetic depth can be achieved more rapidly with isoflurane than halothane or enflurane. About 99% of inhaled isoflurane is eliminated by the lungs in unchanged form; the remainder of it is metabolized in liver. Isoflurane is typically used for maintenance of anesthesiaafter induction of other agents. Isoflurane is safe anesthetic for the patients with ischemic heart disease. If it is used together with opioids or nitrous oxide isoflurane concentration may be reduced.

Side effects of isoflurane: decrease in general blood pressure due to the decreased systemic vascular resistance, vasodilatation without reduction of cardiac output; isoflurane improves cardiac blood flow and decreases myocardial oxygen consumption; it causes tachycardia in response to reduced blood pressure, although isoflurane as well as halothane attenuates baroreceptor function; rapid changes in isoflurane concentration may cause tachycardia and hypertension as a result of

isoflurane-induced sympathetic stimulation; isoflurane suppresses ventilation, tidal volume, it elicits bronchodilatation, irritates an airway, stimulates an airway reflex during induction anesthesia, producing coughing and laryngospasm; isoflurane increases cerebral blood flow, but lower than halothane or enflurane; isoflurane has moderate risk of an increase in intracranial pressure; it reduces cerebral metabolic rate and cerebral metabolic oxygen consumption in a dose-dependent manner; isoflurane relaxes the skeletal muscles, uteine smooth muscles and enchances the effects of both non-depolarizing and depolarizing muscle relaxants; isoflurane reversibly reduces renal blood flow and glomerular filtration; splanchnic and hepatic blood flow is reduced according elevated doses of isoflurane as systemic arterial pressure decreases. Isoflurane is not recommended for analgesia or anesthesia for labor and vaginal delivery.

Enflurane like other inhalation anesthetic is volatile, nonflammable and non-explosive in mixtures of air or oxygen. Enflurane has high blood/gas coefficient, induction of anesthesia and recovery from it are relatively slow. A small part of enflurane is metabolized in the liver, and most of it is excreted through lungs with expired air. As with isoflurane, enflurane *is used* for rather than induction of anesthesia. Opioids and nitrous oxide reduce required concentration of enflurane for anesthesia. Enflurane is rarely used for anesthesia in developed countries.

Side effects of enflurane: concentration-dependent decrease in arterial blood pressure, depression of myocardial contractility, peripheral vasodilatation, minimal effects on heart rate; rapid shallow breathing, decrease in minute ventilation, more significant depression of ventilatory responses to hypoxia and hypercarbia than do either halothane or isoflurane, bronchodilatation; improving of cerebral blood circulation due to cerebral vasodilatation, increase of intracranial pressure, reduction of cerebral metabolic oxygen consumption; seizures may occur in case of high concentration of enflurane and in hypocapnia during anesthesia; skeletal muscle relaxation and enhancement of non-depolarizing muscle relaxant effects; relaxation of uterine smooth muscle; reduction of renal blood flow, glomerular filtration rate, and urinary output; reduction of splanchnic and hepatic blood flow in proportion to reduced arterial blood pressure.

Enflurane *does not use* in the patients with seizure disorders, and for obstetric anesthesia.

Desflurane is a highly volatile liquid at room temperature. It has a very low blood/gas partition coefficient and also is not very soluble in fat or other peripheral tissues. More than 99% on desflurane is eliminated unchanged through the lungs. A small amount of absorbed desflurane is metabolized by liver enzymes. Desflurane provides a very rapid induction of anesthesia and the time of awakening. Therefore *desflurane is a widely used anesthetic* for outpatient surgery for maintance of anesthesia. Lower concentrations of desflurane are used in case of co-administration with nitrous oxide or opioids.

Side effects of desflurane: irritation of tracheobronchial tree can provoke coughing, salivation, bronchospasm, although desflurane like other inhalational

agents is bronchodilatator; a concentration-dependent acceleration in respiratory rate, and a diminution in tidal volume, may become apneic, a concentration-dependent decrease in arterial blood pressure, moderate negative inotropic effect, systemic vasodilatation, transient tachycardia results from desflurane-induced stimulation of the sympathetic nervous system; a decrease in cerebral vascular resistance and cerebral metabolic oxygen consumption, an increase in cerebral blood flow, a raise in intracranial pressure under condition of normocapnia and normotension, but under condition of hypocapnia deflurane causes a vasoconstriction; skeletal muscle relaxation and it improves the effects of non-depolarizing and depolarizing neuromuscular blocking agents.

Desflurane is not used for inductive of anesthesia due to its irritant properties.

Sevoflurane can undergo an exothermic reaction with desiccated Carbon dioxide absorbent to produce airway burns or spontaneous ignition, explosion, and fire. Thereby, sevoflurane is not used with an anesthesia machine in which the Carbon dioxide absorbent has been dried by prolonged gas flow through the absorbent. Sevoflurane has a low solubility in blood and other tissues. That ensures the rapid induction of anesthesia, rapid changes in anesthetic depth, and rapid output from anesthesia. Sevoflurane *is a widely used anesthetic* for outpatient, especially for children, due to the rapid recovery profile and due to the absence irritant effect on the airways. Sevoflurane is a preferable agent in patients who are inclined to myocardial ischemia because it does not provoke tachycardia.The greater part of absorbed sevoflurane is excreted in unchanged form and insignificant part of it is metabolized in the liver.

Side effects of sevoflurane: a concentration-dependent decrease in arterial blood pressure, systemic vasodilatation, a concentration-dependent decrease in cardiac output; a concentration-dependent reduction in tidal volume and increase in respiratory rate, and an increase in partial pressure of carbon dioxide in the blood, sevoflurane like other inhalational agents is bronchodilatator; its cerebral vasodilatation is less than of isoflurane and desflurane, an increase in intracranial pressure, delirium in children; skeletal muscle relaxation; and it improves the effects of non-depolarizing and depolarizing neuromuscular blocking agents like other inhalational anesthetics; transient renal injury.

Nitrous oxide is very insoluble in blood and other tissues; as a result it provides rapid equilibration between delivered and alveolar anesthetic concentration, rapid induction of anesthesia and rapid anesthesia recovery. Nitrous oxide is eliminated in unchanged form by the lungs and with minimal diffusion through the skin. Nitrous oxide can oxidize cobalt form of vitamin B12 to cobalt, thereby inhibiting methionine synthetase and synthesis of methionine, DNA, RNA, myelin, and it can produce vitamin B12 deficiency, megaloblastic anemia, and peripheral neuropathy. That's why nitrous oxide is not used in patients with vitamin B12 deficiency, anemia, chronic alhocolism, malnutrition, and it is not used as chronic analgesic although nitrous oxide has a significant analgesic effect or as a sedative agent. Analgesic effect of nitrous oxide is a function of the

activation of opioidergic and adrenergic neurons in CNS. Nitrous oxide is used as an adjunct to other inhalational or intravenous anesthetic to reduce their doses.

Side effects of nitrous oxide: stimulatory effects on sympathetic nervous system; the cardiovascular effects of nitrous oxide are dependent on concomitant administration with other anesthetic agents, an increase in venous tone of both the peripheral and pulmonary vasculature; an increase in respiratory rate and a decrease in tidal volume, depression in ventilatory response to hypoxia; an increase in cerebral blood flow and intracranial pressure.

If nitrous oxide is co-administered with halogenated inhalational anesthetic, it elicits an increase in heart rate, arterial blood pressure, cardiac output, and if nitrous oxide is co-administered with opioids, it causes a decrease in arterial blood pressure and cardiac output. Nitrous oxide is not used in patients with pulmonary hypertension.

Nitrous oxide has two major problems. *Firstly:* on discontinuation of nitrous oxide administration, nitrous oxide gas can diffuse from blood to the alveoli, diluting oxygen in the lungs and provoke an effect called *diffusional hypoxia*. In order to prevent diffusional hypoxia, 100% oxygen rather than air should be administered after the cessation of supply of nitrous oxide for 4-5 minutes. *Secondly:* nitrous oxide can exchange with nitrogen in any air-containing cavity in the human body. Furthermore, nitrous oxide can enter the cavity faster than nitrogen escapes, and therefore increasing the volume and pressure in this cavity. Thereby, nitrous oxide can expande a Pneumothorax, an obstructed middle ear, an aire embolus, an obstructed loop of bowel, an intraocular air bubble, a pulmonary bulla, and intracranial air. As a result, nitrous oxide cannot be used in these clinical setting.

Xenon is an inert gas. It has minimal cardiorespiratory side effects, has analgesic and anesthetic effects due to influences on receptors and potassium channels in the CNS. At the same time, xenon is a rare gas and must be extracted from air and cannot be manufactured. This renders xenon very expensive. Its use is limited. Xenon is extremely insoluble in blood and other tissues, provides rapid induction of anesthesia and rapid anesthesia recovery. Xenon is well tolerated in the patients of advanced age. *Side effects* of xenon: a slight decrease in respiratory rate, an increase in tidal volume, minimal respiratory depression; reduction in cerebral metabolism and cerebral blood flow.

Table 35. Medicinal forms of General anesthetics

INN	Trade names	Medicinal forms	
Ketamine	Kalipsol, Ketaject, Ketalar, Ketanest, Ketaset, Ketolar, Velonarcon, Vetalar, etc.	Parenteral solution for i/v, i/m injections in ampoules, in flacons	1% - 5 ml; 5% -2 ml, 10 ml 1% -20 ml; 5% - 5 ml, 10 ml; 10% - 10 ml
Propanidid	Epontol, Fabantol, Fabantal, Sombrevin, etc.	Parenteral solution for i/v injections in ampoules	5% - 10 ml

Propofol	Diprivan, Pofol, Recofol	Isotonic water emulsion in ampoules; Isotonic water emulsion in flacons; Isotonic water emulsion in syringes	1% - 20 ml; 1% - 20 ml, 50 ml, 100 ml; 1% - 50 ml
Methohexital	Brietal	Powder in flacons for i/v injections	0.5
Etomidate	Amidate, Hypnomidate, Radenarcon, etc.	Parenteral solution for i/v injections in flacons	0.2% - 10ml
Hydroxydione sodium succinate	Hydroxydione Sodium succinate, Pregnocin-natrium, Presuren, Viadril	Powder in flacons and ampouls for i/v injections	0.5
Thiopental sodium	Farmotal, Nesdonal, Penthiobarbital, Pentothal sodium, Thiopenten, Thiopentobarbital, Thiopentone, Thiotal, Trapanal, etc.	Powder in flacons for i/v injections	0.5, 1.0
Hexobarbital	Cyclobarbitalum soluble, Evipan sodium, Hexobarbitone soluble, Noctivane, Novopan, etc.	Powder in flacons for i/v injections	1.0
Sodium oxybate	Natrium oxybutyricum	Parenteral solution for i/v, i/m injections in ampoules; concentrate for peroral solution in flacons; Syrup in flacons	20% - 5 ml, 10 ml; 66,7% - 37,5 ml; 5% - 400 ml
Ether for anesthesia	Anesthetic Ether, Ether Anaesthesicus	Liquid in a tightly sealed flacons	140 ml, 150 ml
Halothane	Narcotan, Fluothane, etc.	Liquid in a tightly sealed flacons	50 ml, 250 ml
Isoflurane	Forane	Liquid in vials	100 ml, 250 ml
Enflurane	Ethrane	Liquid in flacons	125 ml, 250 ml
Desflurane		Liquid in flacons	125 ml, 250 ml
Sevoflurane		Liquid in flacons	125 ml, 250 ml
Nitrous oxide	Nitrogenium oxydulatum, Oxydum nitrosum, Protoxyde d'Azote, Stickoxydal	Gas in tanks	10 l
Xenon		Gas in tanks	10 l

Chapter 12. Opioid analgesics

Opioid analgesics – are the drugs that stop pain and cause euphoria, abuse, and addiction.

Pain is the primary clinical imperative and a component of all clinical pathology.

Nociceptive system – there is the system which provides the sensation of pain in humans.

Nociceptors –are the peripheral sensory (touch) neurons that are activated by damaging stimuli. Nociceptors are activated by mechanic or temperature stimuli, by action of chemical substances (algogenic substances – producing pain). Nociceptors have various sensitivity to different types of stimuli. There are the specific *"silent"* nociceptors that are responded on the stimuli only after their damage or in case of inflammation of nearby organs. Peripheral nerves endings of nociceptors are located in the skin, subdermal fat layer, periosteum, joints, muscles, internal organs.

The higher echelon of perception of nociceptive information is the cortex of the brain. Somatosensory areas and regions of the cortex of the brain evaluate the painful signals; they form feeling of the pain. Association areas of the brain cortex take part in formation of complex emotional and affective symptoms of pain and associated mental experiences.

Antinociceptive system (ANS) is a hierarchical set of neural structures on different levels of CNS with their own neurochemical mechanisms, which can stop the activity of nociceptive system. The opiatergic regulation acts in ANS, and it is based on the interaction of ligands-opioids with opioid receptors. **Ligands** are the agents that are connected with biological acceptors, for example, receptors, ion channels, etc. In this case there are opioids both endogenous and exogenous.

Structures of ANS:

ANS structures of middle brain, medula oblangate, spinal cord

They inhibit nociceptive upstream excitation.

There is the system of downstream abscopal control of pain.

The transmitters of ANS are opioids and serotonin.

ANS structures of hypotalamus

They have various actions on nociceptive system:

downstream abscopal control for the nociceptors of spinal cord neurons
upstream abscopal control for the pituitary nociceptive neurons
activating influence on the system downstream abscopal control

3. ANS structures of the brain cortex

These areas activate ANS of the first and second levels. ANS release biological active endogenous opioid substances are the "internal opioids" – internal ligands. They are named ***endorphins, enkephalins, dynorphins***, ***nociceptins*** *or* ***orphanins, endomorphins***. They are aminoacids, and are

named neuropeptides, or opioid peptides. At the same time endorphins, endomorphins exercise maximum affinity for the type μ, enkephalins – type δ, dynorphin – type κ.

Endogenous opioid peptides are produced in the body and exercise their opioid effects. Discovery of opioid receptors led to the discovery of their endogenous ligands.

Exogenous opioids enter the body from the outside and bind to opioid receptors. The first discovered opioid was morphine, an alkaloid of opium poppy. Currently we know a large number of exogenous opioids, which are ligands to opioid receptors. By origin we distinguish natural, synthetic and semi-synthetic opioids. Many of them are used in medicine as analgesics and anti-cough drugs.

In human body opioids connect with specific receptors and block nociceptive system activity in neurons. This leads to stop the pain. But in human body there are **non-opioid peptides**, such as neurotensin, seritonin, catecholamines.

Interaction of nociceptive and antinociceptive systems:

Hyperalgesy – high pain sensitivity in case of:
increase of excitement of nociceptive system;
reduction of excitement of antinociceptive system.

Hypoalgesy – low pain sensitivity in case of:
reduction of excitement of nociceptive system;
increase of excitement of antinociceptive system.

Pain tolerance – depends on interaction of both: nociceptive system and antinociceptive system.

Both of this systems form general system of pain.

There are *4 main types of opioid receptors: μ, δ, κ, NOP. σ*-receptors (sigma) previously attributed to opioid, because it is considered that the antitussive effect of many opioid is realized through action on these receptors, as well as the first selective σ-opioid agonists were derivatives of opioids. However, it was found that σ-receptors are not activated by endogenous opioid peptides, and very different from other opioid receptors both in function and in genetic structure. It has been suggested the existence of *ε*-opioid (epsilon) receptors. Currently there are several selective agonists and antagonists of the alleged ε-receptors, but attempts to detect the gene of these receptors have been unsuccessful.

Opioid receptors were named using the first letter of the first ligand that was found to bind to them: for μ-receptor – morphine; for κ-receptor – ketocyclazocine; δ-receptor was named after the mouse vas deferens tissue in which the receptor was first characterised; the nociceptin receptor or OLR (opiate-like receptor)1 was later identified and cloned based on homology with the cDNA.

Table 36*. Types of opioid receptors and their Locations, Functions and Presumed Endogenous ligands

Receptor	**Subtypes**	**Location**	**Function**	**Presumed Endogenous ligands**
delta (δ) DOP	δ_1, δ_2	□ brain ○ pontine nuclei ○ amygdala ○ olfactory bulbs ○ deep cortex □ peripheral sensory neurons	□ analgesia □ antidepressant effects □ convulsant effects □ physical dependence perhaps of mu-opioid receptor-mediated respiratory depression	enkephalins, β-endorphin
kappa (κ) KOP	κ_1, κ_2, κ_3	□ brain ○ hypothalamus ○ periaqueductal gray ○ claustrum □ spinal cord ○ substantia gelatinosa □ peripheral sensory neurons	□ analgesia □ sedation □ miosis □ inhibition of ADH release □ dysphoria	dynorphin A, dynorphin B, α-neo-endorphin
mu (μ) MOP	μ_1, μ_2, μ_3	□ brain ○ cortex (laminae III and IV) ○ thalamus ○ striosomes ○ periaqueductal gray ○ rostral ventromedial medulla	**μ_1**: □ analgesia □ physical dependence **μ_2**: □ respiratory depression □ miosis □ euphoria □ reduced GIT motility □ physical	β-endorphin, enkephalins, endomorphin-1, endomorphin-2

		□ spinal cord ○ substantia gelatinosa □ peripheral sensory neurons □ intestinal tract	dependence μ3: □ possible vasodilation	
Nociceptin receptor NOP	ORL_1	□ brain ○ cortex ○ amygdala ○ hippocampus ○ septal nuclei ○ habenula ○ hypothalamus □ spinal cord	□ anxiety □ depression □ appetite □ development of tolerance to μ agonists	nociceptin/ orphanine FQ

* - adopted from Corbett AD, Henderson G, McKnight AT, Paterson SJ (2006). «75 years of opioid research: the exciting but vain quest for the Holy Grail». *Br. J. Pharmacol.* 147 Suppl 1: S153–62 with autor's changes and additions.

Opioid receptors are expressed in the brain and spinal cord. Besides, opioid receptors also are expressed widely in peripheral tissues, including vascular, cardiac, airways, lungs, GIT, immune/inflammatory cells.

Table 37*. Actions and selectivities of some opioids at*: μ, δ, κ* receptors.

Opioid ligands	**Receptor types**		
	μ	***δ***	***κ***
Agonists			
Morphine	+++		+
Fentanyl	+++		
Sufentanil	+++	+	+
Trimeperidine	++		
Codeine	±		
Methadone	+++		
Buprenorphine	±		– –
Butorphanol	±		+++
Nalbuphine	– –		++
Nalorphine	– –		++
Pentazocine	±		+
Tramadol	++	++	++

Antagonists			
Nalmefene			+
Naloxone	– – –	–	– –
Naltrexone	– – –	–	– – –
Endogenous peptides			
Met-enkephaline	++	+++	
Leu-enkephaline	++	+++	
β-endorphin	+++	+++	
Dynorphin A	++		+++
Dynorphin B	+	+	+++
α-neoendorphin	+	+	+++
Endomorphin-1	+++		
Nociceptin/ orphanine FQ	–	–	–

+ agonist; – antagonist; ± partial agonist.

* - adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12th edition. Medical. 2011. – 2084 P. with autor's changes and additions.

Classification of Opioids according mechanism of action

1. Agonists:

Morphine
Fentanyl
Sufentanil
Omnoponum (Papaveretum) – is the mixture of hydrochloride salts of opium alkaloids
Trimeperidine
(Promedolum) Codeine
Dimenoxadol
Methadone

2. Agonists-antagonists and Partial agonists:

Buprenorphine
Butorphanol
Nalbuphine
Nalorphine
Pentazocine

Antagonists:

Nalmefene
Naloxone
Naltrexone

Others (opioid analgesic with opioid and non-opioid mechanism of action)

Tramadol

Mechanism of action of opioid analgesics is based on intracellular events, including:

inhibition of adenylyl cyclase activity
reduced opening of voltage-gated Ca^{2+} channels
stimulation of K^+ current through channels including G protein-activated inwardly rectifying K^+ channels
activation of Protein kinase C and Phosphoinositide-specific phospholipase C.

Mechanism of opioid-induced analgesia. After systemic delivery opioid analgesics act in the brain, spinal cord and in the periphery. Opioid analgesics act on opioid receptors in CNS and block the nociceptive responces, alter nociceptive transmission. Direct introduction of opiates to a peripheral nerve can produce a local anesthetic-like action at high concentrations. But, analgesic effects are limited if opiates do not readily penetrate the brain. And yet the local injection of opiates into peripheral sites under condition of inflammation where there is exaggerated pain response (e.g. hyperalgesia) can cause a normalizing effect upon exaggerated threshold.

In general opioids have good absorption from GIT and rectal mucosa, nasal mucosa, transdermally. Opioids are metabolized in the liver by the microsomal enzymes and are eliminated through kidney and liver.

Pharmacological effects of Opioid analgesics depend of opiate receptor preferences.

Pharmacological effects of Opioid agonists:

Analgesia
Euphoria
Sedative
Oppression of breath
Oppression of cough reflex
Miosis, increase accommodative powder and lower intraocular pressur
Increasing of muscle tone
Nausea & vomiting (stimulation of the trigger zones of medula oblangata)
Stimulation of the vagus nerve and elicit bradicardia
Arterial hypotension
Increasing of intracranial pressure
Decreasing of motility of GIT and increasing of the tone of sphincters of GIT (constipation), gallbladder, urinary bladder
Constipation
Urine retention
Decreasing of stomach acidity
Spasms of intestine, gall bladder, sphincter Oddi, urine bladder (colic)
Decreasing of kidney function, kidney blood circulation
Increasing of plasma prolactin, ADH (antidiuretic hormone), STH (somatotropic hormone) secretion

Block release of gonadotropin-releasing hormone (GnRH) and corticotrophin-releasing hormone (CRH) that leads to reduce release of LH (luteinizing hormone), FSH (folicule stimulating hormone), ACTH and β-endorphin.

In males - decreasing of plasma cortisol, gonadotropins, testosterone, adrenal androgens

- In females - decreasing of LH secretion and FSH

In both males and females - cause endocrinopathies, including hypogonadotrophic hypogonadism: decrease libido, in males reduce secondary sex characteristics; in females lead to menstrual cycle irregularities. These changes are reversible with removal of the opiates.

Decreasing of uterus tone, decreasing of strength, duration, frequency of uterine contractions

Increasing of histamine secretion: vasodilatation, bronchoconstriction, erythema, sweating, feeling of warmth

Immunomodulative effect

Adverse effects of Opioid analgesics:

Withdrawal (abstinence) syndrome as a result of tolerance

Cross tolerance

Physical and psychical dependence

Restlessness, tremor, hyperactivity

Oppression of breath

Nausea & vomiting

Increasing of intracranial pressure

Constipation

Urine retention

Itching of the nose wings, urticaria

Dysphoria

Cerebral and spinal ischemia

In case of short-time or long-time use opioids may exert **some adverse effects**: desensitization, internalization of opioid receptors (down-regulation) tolerance (loss of drug effect), dependence, addiction.

The **clinical use of opioid analgesics** is determined by their ability to activate or block different types of opioid receptors (tabl. 29, 30). So, selective agonists of MOP produce analgesia, affect mood and rewarding behavior, and alter respiratory, cardiovascular, GIT, and neuroendocrine function. KOP agonists, with rare exceptions, can not be used for long-term therapy because they produce dysphoric and psycotomimitic effects. DOP agonists have not yet been used in the clinic. NOP agonists have not analgesic effects. The selectivity of opiates is disappeared in case of their use in high doses. The doses of opiates should increase to overcome tolerance. The agonists-antagonists of opioid receptors frequently interact with more than one receptor and can activate one

type of opioid receptors and block other type of opioid receptors. These agents have less addictive potential, less respiratory depression than opioid agonists. Indeed, in practice, for the same degree of analgesia, the same intensity of adverse effects occurs.

Indications for opioid analgesics use:

Analgesia in cases of tissue injury, nerve injury in some pathological conditions and diseases, that lead to pain
Diarrhea
Cough
Acute pulmonary edema
Anesthesia & premedication

Contraindications for opioid analgesics use*:

Pregnance, lactation
Children (up to 2 years) and old age
Breath insufficiency, bronchial asthma, lung insufficiency
Hepatic and renal insufficiency
Traumatic brain injury, hemorrhagic stroke, convulsive state, psychostimulant poisoning, drug
Idiosyncrasy to morphine
Cachexia, fever, myxedema
The syndrome of "acute abdomen."

* - The contraindications for opioid analgesics use are relative, not absolute.

Caution!

Do not use with antipsychotics, sedatives, hypnotics (depression of CNS and depression of breath center) & MAO inhibitors (hyperpyrexia, hypertension)

Do not use in patients with hepar insufficiency and insufficiency of breath.

Indications for opioid agonists-antagonists and antagonists use

Drug addiction
Drug overdose
Side effects of opioid agonists.

Peculiarities of opioid analgesics use. Given many adverse effects, *morphine* currently is rarely used, mainly during prolonged severe pain. *Omnopon* rarely causes the severe adverse effects in comporison with morphine. *Codein* is used mainly for relief of cough. In the application of *pentazocine* one should consider its ability to increase blood pressure. One should take into account, that medicinal form of *nalbuphine* contains sodium disulfide which can induce an attack of breathlessness in patients with

bronchial asthma. *Buprenorphine* produces euphoria and addiction to a lesser degree. *Butorphanol* does not have a marked influence on GIT sphincter tone and GIT motility and tone of other smooth muscles. It increses pressure in lung artery, general BP, and intracranial pressure, besides, has positive intropic effect. *Trimeperidine* has moderate spasmolitic effect on smooth muscles of bronhi and renal ducts, and in less degree increases the tone of intestine and bile ducts. At the same time trimeperidine increases the tone of myometrium, badly passes through the placental barrier in usually therapeutic doses, and can be used for analgesia during labor. *Fentanyl* due to its short action is used for neuroleptanalgesia together with neuroleptics (droperidol or haloperidol).

Dimenoxadol has analgesic and antitussive activity, moderate spasmolitic effect on GIT and bronhi, and is used also for pain relief in parturition. *The opioid antagonists* basically are used in case of acute intoxication by opiates, and in case of abstinent syndrome in newborns whose mothers used drugs during pregnancy. *Tramadol* is the drug with mixed mechanism of action: opioid and non-opioid. It is an agonist of μ, δ, κ receptors, and it inhibits neuronal recapture of serotonin and norepinephrine. In fact tramadol is a racemic mixture of *RS(+/-)* enantiomers. In addition it has an analgesic effect and weak antitussive effect and sedative effect. *Methadone* is used for control opiates abuse, of opioid dependence. It has cross-tolerance with other opioids including heroin and morphine, offering very similar effects and a longer duration of effect. Oral doses of methadone can stabilise patients by mitigating opioid withdrawal syndrome. Higher doses of methadone can block the euphoric effects of heroin, morphine, and similar drugs. As a result, properly dosed methadone by patients can reduce or stop altogether their use of these substances. Methadone is approved for different indications in different countries. Common is approval as an analgesic and approval for the treatment of opioid dependence. It is not intended to reduce the use of non-opioid drugs such as methamphetamine, or alcohol. The principal effects of methadone maintenance are to relieve narcotic craving, suppress the abstinence syndrome, and block the euphoric effects associated with opiates.

In summary, it can be noted that opioid analgesics provide symptomatic relief of pain, but underlying disease remains. The decision to control pain by repeated introductions of opioid analgesics must be made cautiously. In cases of pain is due to chronic nonmalignant diseases, conservative treatment of pain should begin with use of non-opioid analgesics, local nerve blocks, antidepressants, electrical stimulation, acupuncture, hypnosis, and behavioral modification.

Table 38*. Pain management with opioids, and Equivalent doses of opioid analgesics

This is only an approximate guide (doses may not correspond with those given in clinical practice); patients should be carefully monitored after any change in medication and dose titration may be required		
Analgesic	**Route**	**Dose**
Codeine	PO	100 mg
Diamorphine	IM, IV, SC	3 mg
Dihydrocodeine	PO	100 mg
Hydromorphone	PO	2 mg
Morphine	PO	10 mg
Morphine	IM, IV, SC	5 mg
Oxycodone	PO	6.6 mg
Tramadol	PO	100 mg
PO = by mouth; IM = intramuscular, IV = intravenous, SC= subcutaneous		

* - adopted from British National Formular 2013, www.bnf.org

Table 39. Buprenorphine patches are *approximately* equivalent to the following 24-hour doses of oral morphine

morphine salt 12 mg daily	≡	*BuTrans*® ‘5’ patch	
morphine salt 24 mg daily	≡	*BuTrans*® ‘10’ patch	7-day patches
morphine salt 48 mg daily	≡	*BuTrans*® ‘20’ patch	
morphine salt 84 mg daily	≡	*Transtec*® ‘35’ patch	
morphine salt 126 mg daily	≡	*Transtec*® ‘52.5’ patch	4-day patches
morphine salt 168 mg daily	≡	*Transtec*® ‘70’ patch	
Note: Conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine			

* - adopted from British National Formular 2013, www.bnf.org

Table 40. 72-hour Fentanyl patches are *approximately* equivalent to the following 24-hour doses of oral morphine

morphine salt 30 mg daily	≡	fentanyl '12' patch
morphine salt 60 mg daily	≡	fentanyl '25' patch
morphine salt 120 mg daily	≡	fentanyl '50' patch
morphine salt 180 mg daily	≡	fentanyl '75' patch
morphine salt 240 mg daily	≡	fentanyl '100' patch
Note: Conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine		

***** - adopted from British National Formular 2013, www.bnf.org

Table 41*. Summary of Drug Target and Site of Action of Common Drug Classes and Relative Efficacy by Pain State

Drug cases (representative agents in parentheses)	**Drug action**	**Site of action**[a]	**Relative efficacy in pain strategy**[b]
NSAIDs (ibuprofen, aspirin, acetominophen)	Nonspecific COX inhibitors	Peripheral and spinal	Tissue injury >> acute stimuli = nerve injury = 0
COX 2 inhibitors (celecoxib)	COX 2 selective inhibitors	Peripheral and spinal	Tissue injury >> acute stimuli = nerve injury = 0
Opioids (morphine)	μ receptor agonist	Supraspinal and spinal	Tissue injury = acute stimuli ≥ nerve injury > 0
Anticonvulsants (gabapentin)	Na^+ channel block, $\alpha_2\delta$ subunit of Ca^{2+} channel	Supraspinal and spinal	Nerve injury > tissue injury = acute stimuli = 0
Tricyclic antidepressants (amitryptiline)	Inhibit uptake of 5-HT/NE	Supraspinal and spinal	Nerve injury ≥ tissue injury >> acute stimuli = 0

* adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12th edition. Medical. 2011. – 2084 P.

a - Studies based on local delivery in preclinical models, e.g., intracranial microinjection or intraventricular injections, lumbar intrathecal delivery or topical/sq application at injury site.

b - Pain state are defined by principal models: acute: hot plate/tailflick/acute mechanical compression; tissue injury: intraplantarinjection of irritants, focal thermal injury; nerve injury: compression/ligation of sciatic nerve or its branches or of nerve roots; systemic delivery of chemotherapeutics.

Table 42. Medicinal forms of Opioid analgesics

INN	Trade names	Medicinal forms	
Morphine	MS Contin, Doltard, MSIR, Avinza, Kadian, Oramorph, Roxanol, Kapanol	Powder in flacons; Tablets; Parenteral solution (s/c, i/m, i/v) in ampoules	0.3; 0.01; 1% - 1 ml
Fentanyl	Fentonest, Leptonal, Sublimaze, Actiq, Durogesic, Sentonil, Duragesic, Fentora, Matrifen, Haldid, Onsolis, Instanyl, Abstral, Lazanda, etc.	Parenteral solution (i/m, i/v) in ampoules	0.005% - 1 ml, 2 ml, 10 ml
Morphine hydrochloride + Papaverine hydrochloride + Codeine; Morphine+Narcotine + Papaverine hydrochloride + Codeine + Tebaine	Papaveretum; **Omnopon**	Parenteral solution (s/c) in ampoules; Tablets	1%, 2% - 1ml
Trimeperidine	Promedolum	Tablets; Parenteral solution (s/c, i/m, i/v) in ampoules and in ampins	0.025; 1%, 2% - 1 ml
Codeine	Tussamag with codeine	Powder; Tablets; Syrup; Peroral solution;	 0.015; 0.1% - 5 ml; 2%
Caffeine+Codeine+Acetylsalicylic acid+Paracetamol;	Parcocet, Perdolan;	Tablets;	
Caffeine+Codeine+Paracetamol+Propyphenazone;	Caffetin;	Tablets;	
Caffeine+Codeine+Paracetamol+Propyphenazone+Phenobarbital;	Plivalgin;	Tablets;	
Caffeine+Codeine+Paracetamol+Metamizole sodium+Phenobarbital;	Pentalgin-N;	Tablets;	
Caffeine+Codeine+Naproxen+Metamizole sodium+Phenobarbital;	Pentalgin-N, Pyralgin		
Codeine+Ipecacuanha syrup;	Neo-Codion;	Syrup;	
	Paracodamol; Panadein; Co-codamol; Cought control tablets;	Tablets;	0.1% - 125 ml, 140 ml,180 ml

Codeine+Sodium hydrocarbonate + Glycyrrhizae radix + Thermopsidis herba; Codeine+Sulfogaiacol+Grindelia extract; Dihydrocodeine	Neo-Codion; HC Continus	Tablets; Tablets Tablets	
Dimenoxadol	Dimenoxadoll hydrochloridum, Dimenoxadol hydrochloride, Estocin, Lokarin, Propalgyl	Powder; Tablets; Parenteral solution (s/c, i/m) in ampoules	 5, 15, 30, 60 mg 2% - 2 ml
Methadone; L-Methadone	Phenadone, Amidone, Anadon, Dolophine, Physeptone, Symoron, Methadose Heptadone, Levo-Polamidone, Polamidone,	Tablets	40 mg
Buprenorphine	Bupranal, Bupremen, Buprenex, Bupresic, Buprex, Lepetan, Nopan, Norfin, Norphine, Sangesic, Temgesic	Tablets; Parenteral solution (s/c, i/m, i/v) in ampoules	0.0002; 0.03% - 1 ml, 2 ml
Butorphanol	Stadol, Beforal, Moradol, Torate, Torbugesic, Torbutrol, Torgesic, Verstadol	Parenteral solution (i/m, i/v) in ampoules, in ampin; Aerosol for intranasal introduction	0.2%- 1 ml, 2 ml; 1%
Nalorphine	Lethidrone, Nalline, *N*-allyl-normorphine, Norfin, Tidigesic, etc.	Parenteral solution (s/c, i/m, i/v) in ampoules; Sublingual tablets; Parenteral solution (s/c, i/m, i/v, in the umbilical vienna) in ampoules	for adults - 0.5% - 1ml; for newborns - 0.05% - 0.5 ml in the umbilical vienna; 0.2 mg; 0.03% -1 ml
Nalbuphine	Nubain	Parenteral solution (s/c, i/m, i/v) in ampoules and in flacons	1%, 2% - 1 ml; 1%, 2% - 10 ml

	Dolapent, Fortal, Fortalgesic, Fortral, Fortvin, Lexit, Magadolin, Pentagin, Sosegon, Sosenyl, Sosigon, Talvin, etc.	Tablets; Parenteral solution (s/c, i/m) in ampoules	0.05; 3% - 1 ml
Nalmefene	Revex	Parenteral solution (s/c, i/m, i/v) in ampoules; Tablets	0.01% - 1 ml, 2 ml 25mg
Naloxone	Narcan, Nalone, Narcanti, Intrenon, Narcan neonatal	Parenteral solution (i/m, i/v) in ampoules	0.04% - 1ml; 0.002% - 2 ml
Naltrexone	Revia, Depade, Vivitrol, Nalorex,	Capsules; Tablets	0.05 0.05
Tramadol	Conzip, Ryzolt, Ultracet, Ultram, Ralivia, Zytram XL, Tramal	Tablets; Capsules; Tablets retard; Peroral solution in flacons; Rectal suppositories; Parenteral solution (s/c, i/m, i/v) in ampoules	0.05; 0.05; 0.1, 0.15, 0.2; 10ml, 20ml, 30ml, 50 ml, 100 ml; 0.1; 5% - 1ml, 2ml; 10% - 1ml

Chapter 13. Non-opioid analgesics (nonsteroid anti-inflammatory drugs – NSAIDs)

Traditional NSAIDs (tNSAIDs) act by inhibition the prostaglandines G/H synthase enzymes that known as the COX (see the Chapter 3). This inhibition of COX 2 is a facilitator of antipyretic, analgesic, and anti-inflammatory action of tNSAIDs. Simultaneously, inhibition of COX 1 leads to adverse effects in GIT.

All of known **NSAIDs have anti-inflammatory, analgesic, and antipyretic effects**. The *inflammatory response* is characterized by transient local vasodilatation, increased capillary permeability, infiltration of leukocytes and phagocytes cells, tissue degeneration, and fibrosis and is accompanied by pain and often - fewer. In these conditions prostanoid biosynthesis is greatly increased in inflamed tissues. Inhibitors of COX that depress prostanoid formation are effective and widely used anti-inflammatory drugs.

Inflammatory mediators increase the sensitivity of nociceptors and potentiate *pain perception*. The main components of this inflammatory "mixture" are bradykinin, H^+, neurotransmitters such as serotonin and ATP, neutrophins (nerve growth factor), LTs, and PGs, cytokines, some of neuropeptides, are involved in eliciting pain. PGE2 and PGI2 decrease the threshold to stimulation of nociceptors, exerting *peripheral sensitization*. The basic of peripheral component

of analgesic activity of NSAIDs is reversal of peripheral sensitization. Besides, NSAIDs have central component of reducing pain. These drugs have central action in spinal cord and brain, the more so because both COX 1 and COX 2 are expressed in the spinal cord. and release PGs in response to peripheral pain stimuli. Centrally active PGE2, also PGD2, PGI2, and PGF2α facilitate to *central sensitization,* an increase in excitability of spinal dorsal horn neurons that lead to hyperalgesia and allodynia. Necessary to consider that chronic inflammatory diseases may evoke persistent modification of the architecture of the nociceptive system, and long-lasting changes in its responsiveness. This mechanism promotes chronic pain.

In human body hypotalamus regulates body temperature. The temperature is lelvated in response to an infection, tissue damage, inflammation, graft rejection, or malignancy. All these conditions increase formation of cytokines that act as endogenous pyrogens. The *initial phase of the thermoregulatory response* is mediated by ceramide release in neurons in the anterior hypothalamus. The late response is mediated by coordinate induction of COX 2 and microsomal PGE synthase-1 in the blood vessel edndotelium in hypothalamus to form PGE2 which can cross BBB and act on EP3 and EP1 receptors on termosensitive neurons. This motivates hypothalamus to raise body temperature by increasing in heat generation and decreasing in heat lost. NSAIDs suppress this process by inhibition PGE2 synthesis.

Mechanism of action of NSAIDs are the inhibition of PG production and thereby inhibition of first enzyme in the PG synthesis – COX, also known as PG G/H synthase. This enzyme converts AA to the unstable intermediates PGG2 and PGH2, and causes release of the prostanoids, TxA2, and series of PGs. COX 1 is expressed in most cells, is a dominant (but not exclusive) source of prostanoids for maintance functions, such as gastric epitelial cytoprotection and hemostasis. COX 2, induced by cytokines, is more important source of prostanoid formation in inflammation and possibly in cancer. So, both enzymes COX 1 and COX 2 promote to formation of autoregulatory and homeostatic prostanoids, and can facilitate to prostanoid formation in human inflammation and pain (see above).

NSAIDs do not inhibit lipoxygenase (LOX) pathway of AA methabolism and consequently do not suppress LT formation.

Indications for NSAIDs use:

Pain of mild and moderate intensity
Fever
Inflammation in some tissues
Musculoskeletal disoders, such as rheumatoid arthritis, and osteoarthritis, ankylosing spondylitis
Gout
Mild arthropaties
To close inappropriately patent ductus
As an antiplatelet drugs in patients with cardiovascular diseases and atherosclerosis

Systemic mastocytosis

Bartter syndrome (hypokalemic, hypochloremic, metabolic alkalosis with normal BP and hyperplasia of the juxtaglomerular apparatus) – in complex therapy

Cancer chemoprevention

Alzheimer's disease

Adverse effects of NSAIDs use:

GI system: abdominal pain, nausea, diarrhea, anorexia, gastric erosions/ulcers*, GI hemorrhage**, perforation/obstruction*

Platelets: inhibited platelet activation*, propensity for bruising*, increased risk of hemorrhage*

Renal: salt and water retention, edema, worsening of renal function in renal/cardiac and cirrhotic patients, decreased effectiveness of antihypertensive medications, decreased effectiveness of diuretics, decreased urate excretion (especially with aspirine), hyperkalemia

Cardiovascular: closure of ductus arteriosus, myocardial infarction**, stroke**, thrombosis**

CNS: headache, vertigo, dizziness, confusion, hyperventilation (salicylates);

Uterus: prolongation of gestation, inhibition of labor

Hypersensitivity: vasomotor rhinitis, angioneurotic edema, asthma,urticaria, flushing, hypotension, shock

Aspirin resistance: the precise mechanism of this phenomenon is not clear;

*Bronchospasm****

Reye's syndrome (salicylates)*:* is a severe and often fatal disease, is characterized by acute encephalopathy, liver dysfunction, and fatty infiltration of the liver and other viscera. The etiology and pathophysiology of it are not clear, but relationship between aspirin and Reye's syndrome exists

*Cardiac insufficiency, arrhythmogenesis*******

* - side effects decreased with COX 2-selective NSAIDs

\- with the exception of low-dose aspirin

\- there is no this side effect in case of COX 2-selective NSAIDs

\- side effects increased with COX 2-selective NSAIDs

Contraindications for NSAIDs use:

Children and adults under 20 years (high risk of Reye's syndrome)

cautiously apply in old patients, in patients with cardiovascular diseases, GI diseases, Helicobacter pylori infection, heavy alcohol consumption, or other risk factors for mucosal injury, including glucocorticoid use

Hypersensitivity

Pregnancy

Lactation

Bronchial asthma, obstructive bronchitis

Drug interactions. Angiotensine-converting enzyme (ACE) inhibitors act by partly prevention of breakdown of kinins that stimulate PG production. So, NSAIDs reduce the effectiveness of ACE inhibitors. By virtue of hyperkalemia

(the side effect of both NSAIDs and ACE inhibitors) may arise bradycardia, syncope. Corticosteroids and selective serotonin reuptake inhibitors (SSRIs) in case of combined use with NSAIDs may increase the frequency or severity of GI disorders. Anticoagulants may enhance the risk of hemorrhages when are used together. NSAIDs are highly bound to plasma proteins and may displace other drugs (warfarin, sulfonylurea hypoglycemic drugs, methotrexate, etc.) from their binding sites that require the regulation of the drug dosage to prevent toxicity.

Table 43*. Classification and some features of NSAIDs

Class/Drug	**Pharmaco kinetics**	**Comments**	**Compared to Aspirin**
Salicylates			
Aspirin (acetyl ester)	Peak C_p[a] 1hour Protein binding 80-90% Metabolites[b] - salicyluric acid $T_{1/2}$[c], therapeutic dose - 2-3 hours $T_{1/2}$, toxic dose - 15-30 hours	Permanent platelet COX1 inhibition in dose less than 300mg/day (acetylation). Main side effects: GI, increasing bleeding time, hypersensitivity. Avoid in children with acute febrile illness. Antidote for Aspirin is Sodium bicarbonate (sodium hydrogen carbonate), carbo activates	
Diflunisal (defluorophenyl)	Peak C_p 2-3 hours Protein binding 99% Metabolites - glucuronide $T_{1/2}$ 8-12 hours	Not metabolized to salicylic acid. Competitive COX inhibitor. Excreted into breast milk.	Analgesic and anti-inflammatory effects 4-5 times more potent. Antipyretic effect weaker. Fewer platelet and GI side effects.
Para-amonophenol derivative			
Acetaminophen	Peak C_p 30-60 min Protein binding 20-50% Metabolites - glucuronide conjugates (60%); sulfuric acid conjugates (35%)	Weak nonspecific inhibitor at common doses. Potency may be modulated by peroxides. Overdose leads to production of toxic metabolite and liver	Analgesic and antipyretic effects equivalent. Anti-inflammatory, GI and platelet effects less than

	T 2 hours	necrosis. The risk of liver necrosis is elevated with hereditary deficiency of glucose-6-phosphate dehydrogenase. It does not form the toxic metabolites in children to 12 years old due to immaturity of cytochrome P450 enzyme system. Antidote for acetaminophen is acetylcysteine, carbo activatus.	aspirin at 1000 mg/day
Acetic acid derivatives			
Indomethacin	Peak C_p 1-2 hours Protein binding 90% Metabolites - *O*-demethylation (50%); Unchanged (20%) $T_{1/2}$ 2.5 hours	Side effects (3-50% of patients): frontal headache, neutropenia, thrombocytopenia; 20% discontinue therapy	10-40 x more potent. Intolerance limits dose
Sulindac (sulfoxide prodrug)	Peak C_p 1-2 hours; 8 hours for sulfide metabolite; extensive enterohepatic circulation Metabolites - sulfone and conjugates (25%) $T_{1/2}$ 7 hours; 18 hours for metabolite	20% suffer GI side effects; 10% get CNS side effects	Efficacy comparable
Etodolac (pyranocarbolic acid)	Peak C_p 1 hours Protein binding 99% Metabolites - hepatic metabolites $T_{1/2}$ 7 hours	Some COX 2 selectivity *in vitro*	100mg etodolac has similar efficacy to 650 mg of aspirin, but may be better tolerated
Tolmetin (heteroaryl acetate derivative)	Peak C_p 20-60 min Protein binding 99% Metabolites - oxidized to carboxylic acid/other	Food delays decreases peak absorption. May persist longer in synovial fluid to give a biological efficacy longer than its plasma $T_{1/2}$	Efficacy similar. 25-40% develop side effects. 5-10% discontinue

	derivatives, then conjugated $T_{1/2}$ 5 hours		drug
Ketorolac (pyrrolizine carboxylate)	Peak C_p 30-60 min Protein binding 99% Metabolites - glucuronide conjugate (90%) $T_{1/2}$ 4-6 hours	Commonly given parenterally (60mg i/m followed by 30mg every 6 hours, or 30mg i/v every 6 hours). Available as ocular preparation (0.25%); 1 drop every 6 hours	Potent analgesic, poor anti-inflammatory
Diclofenac (phenyllacetate derivatives)	Peak C_p 2-3 hours Protein binding 99% Metabolites - glucuronide and sulfide (renal 65%, bile 35%) $T_{1/2}$ 1-2 hours	Available as topical gel, ophthalmic solution, and oral tablets combined with misoprostol. First-pass effect; oral biovailability, 50%. High doses and prolonged use of the drug increases the risk of stroke	More potent. 20% develop side effects. 2% discontinue use. 15% develop elevated liver enzymes
Fenamates (N-phenyl-anthranilates)			
Mefenamic acid	Peak C_p 2-4 hours Protein binding - High Metabolites - conjugates of 3-hydroxy and 3-carboxyl metabolites (20% recovered in feces) $T_{1/2}$ 3-4 hours	Isolated cases of homolytic anemia. May have some central action	Efficacy similar. GI side effects (25%)
Meclofenamate	Peak C_p 0.5-2 hours Protein binding - 99% Metabolites - hepatic metabolism; fecal and renal excretion $T_{1/2}$ 2-3 hours		Efficacy similar. GI side effects (25%)
Flufenamic acid	*Not available in U.S.*		
Propionic acid derivatives			
Ibuprofen	Peak C_p 15-30 min Protein binding 99% Metabolites -	10-15% discontinue due to adverse effects. Children's dosing Antipyretic: 5-10mg/kg	Equipotent

	conjugates of hydroxyl and carboxyl metabolites $T_{1/2}$ 2-4 hours	every 6 hours (max: 40mg/kg/day) Anti-inflammatory: 20-40mg/kg/day in 3-4 divided doses	
Naproxen	Peak C_p 1 hour Protein binding 99% (less in elderly) Metabolites - 6-demethyl and other metabolites $T_{1/2}$ 14 hours	Peak and anti-inflammatory effects may not be seen until 2-4 weeks of use	More potent *in vitro*; usually better tolerated; variably prolonged $T_{1/2}$ may afford cardioprotection in some individuals
Fenoprofen	Peak C_p 2 hours Protein binding 99% Metabolites - glucuronide, 4-OH metabolite $T_{1/2}$ 2 hours		15% experience side effects; few discontinue use
Ketoprofen	Peak C_p 1-2 hours Protein binding 98% Metabolites - glucuronide conjugates $T_{1/2}$ 2 hours		30% develop side effects (usually GI, usually mild)
Flurbiprofen	Peak C_p 1-2 hours Protein binding 99% Metabolites - hydroxylates and conjugates $T_{1/2}$ 6 hours	Available as a 0.03% ophthalmic solution	
Oxaprozin	Peak C_p 3-4 hours Protein binding 99% Major metabolites - oxydates and glucuronide conjugates $T_{1/2}$ 40-60 hours	Long $T_{1/2}$ alows for daily administration; slow onset of action; inappropriate for fever/ acute analgesia	
Enolic acid derivatives			
Piroxam	Peak C_p 3-4 hours Protein binding	May inhibit activation of neutrophils, activity of	Equipotent; perhaps better

	Metabolites - hydroxylates and then conjugated $T_{1/2}$ 45-50 hours	proteoglycanase, collagenases	tolerated 20% develop side effects; 5% discontinue drug
Meloxicam	Peak C_p 5-10 hours Protein binding 99% Metabolites - hydroxylation $T_{1/2}$ 15-20 hours		Some COX 2 selectivity, especially at lower doses
Nabumetone (naphthyl alkanone)	Peak C_p 3-6 hours Protein binding 99% Metabolites - *O*-demethylation then conjugation $T_{1/2}$ 24 hours	A prodrug, rapidly metabolized to 6-methoxy-2-naphthyl acetic acid; pharmacokinetiks reflect active compound	Shows some COX 2 selectivity (active metabolite does not) Fewer GI side effects than many NSAIDs
Diaryl heterocyclic NSAIDs (COX 2 selective)			
		Evidance for cardiovascular adverse events	*Decrease in GI side effects and in platelet effects*
Celecoxib [diaryl substituted pyrazone; (sulfonamide derivative)]	Peak C_p 2-4 hours Protein binding 97% Metabolites - carboxylic acid and glucuronide conjugates $T_{1/2}$ 6-12 hours	Substrate for CYP2C9, inhibor of CYP2D6 Coadministration with inhibitor CYP2C9 or substrates of CYP2D6 should be done with caution	see the text for an overview of COX 2 inhibitors
Paracoxib Etoricoxib Lumaricoxib	*Not approved for use in U.S.*		

* adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12th edition. Medical. 2011. – 2084 P. with autor's changes and additions.

a - Time to peak plasma drug concentration (C_p) after a single dose.

b - The majority of NSAIDs undergo hepatic metabolism, and the metabolites are excreted in the urine.

c - Typical $t_{1/2}$ is listed for therapeutic doses; if $t_{1/2}$ is much different with the toxic dose, this is also given.

Classification of NSAIDs according mechanism of action

1. Selective COX 1 inhibitors:

Acetylsalicylic acid in dose less than 300 mg

Selective (Specific) COX 2 inhibitors:

Lornoxicam
Meloxicam
Nimesulide
Nabumetone
Etodolac

Highly selective COX 2 inhibitors:

Celecoxib
Parecoxib
Valdecoxib
Etoricoxib
Rofecoxibe

Nonselective (Nonspecific) COX inhibitors (COX 1 and COX 2):

Acetylsalicylic acid in dose more than 300 mg
Diclofenac sodium
Indometacin
Ibuprofen
Piroxicam

Classification of NSAIDs according their action on articular cartilage metabolism

Inhibitors of glycosaminoglycan biosynthesis:

Acetylsalicylic
acid Indometacin
Ibuprofen
Fenoprofen
Phenylbutazone

No effect on glycosaminoglycan biosynthesis:

Meloxicam
Piroxicam
Diclofenac
sodium Sulindak

Stimulators of glycosaminoglycan biosynthesis:

Paracetamol
Tiaprofenic acid

Classification under the influence of some NSAIDs on the metabolism of articular cartilage is presented in connection with the use of these drugs mainly in the pathology of joints. When inflammation of the articular cartilage is excessive

destruction of molecules of glycosaminoglycans (GAG) and collagen fibers, resulting in an articular cartilage becomes thinner and is unable to effectively perform its biological functions. Unlike corticosteroids, NSAIDs differently affect the biosynthesis of GAG, the processes of cell proliferation, collagen biosynthesis, and catabolic processes in cartilage. And if you do not consider the effects of NSAIDs on the metabolism of articular cartilage, can worsen the articular syndrome.

In summary, tNSAIDs and COX 2 selective inhibitors have anti-inflammatory, analgesic, and antipyretic activity due to inhibition of PG biosynthesis. Nonselective inhibitors of COX (tNSAIDs) induce GIT adverse effects. Selective inhibitors of COX 2 were synthesized to reduce these GIT adverse effects, but have never been shown advantages in efficiency of COX 2 selective inhibitors over tNSAIDs. Besides, COX 2 selective inhibitors most have been eliminated from the market due to cardiovascular and hepatic toxicities. They provide an increased risk of heart attack and stroke. The mechanism of the cardiovascular hazard is based on acceleration of atherogenesis directly via inhibition of PGI2 and indirectly by virtue of elevate in BP due to inhibition of COX 2-derived PGE2 and PGI2. The patients with risk of cardiovascular diseases or prone to thrombosis (including Leiden mutation or concomitant therapy, such as oral contraceptives, smoking, alcohol abuse, etc.) should be treated by analgesics that do not interfere with platelet action.

The NSAIDs with more rapid onset of action, shorter duration of action are preferable for a temperature control in case of acute viral diseases, and of a pain control after minor musculoskeletal injuries, or headache. At the same time NSAIDs with a longer duration action may be preferable for management of postoperative and arthritic pain.

Table 44. Medicinal forms of NSAIDs.

INN	Trade names	Medicinal forms	
Acetylsalicylic acid	Аспро, Acesal, Aceticyl, Acetol, Acetophen, Acetosal, Acetylin, Acetylsal, Acetysal, Acylpyrin, Aspirin, Aspisol, Asposal, Aspro, Astrin, Ataspin, Bayaspirin, Bebaspin, Benaspir, Bispirine, Caprin, Cetasal, Citopyrine, Clariprin, Darosal, Durasal, Easprin, Endosalil, Endospirin, Eutosal, Genasprine, Helicon, Isopirin, Istopirin, Monasalyl,	Tablets;	0.1, 0.25, 0.5

	Novosprin, Panspiril, Polopiryna, Prodol, Rodopyrin, Ruspirin, Salacetin, Saletin, Temperal, Vicapirine, Zorprin, etc. Aspirin cardio; Thrombo ASS; Aspilite, Aspirin "York", Aspirin "Quolity", Aspirin-Milton, Aspirin UPSA, Bufferan, Bufferin, Novandol, NU-seals 75 cardio-aspirin	Tablets; Tablets; Tablets	0.1, 0.3; 0.05, 0.1; 0.325
Acetylsalicylic acid, lysine salt - Lysine acetylsalicilat	Acelysin, Aspisol-Aspirinum solubile, Aspidol, Delgesic, Draspir, Egalgic, Flectadol, Injesprin, Laspal, Laboprin, Lasdol, Lisaspin, Lysoprin, Salisyn, Solpirin, Solusprin, Venopirin etc.	Powder for per oral solution; Powder for injections (i/m, i/v) in flacons	1.6, 2.6; 1.0; 2.0
Sodium salicylate	Enterosalyl, Glutosalyl, Nadisal, Natrii salicylas, Salicine, Saliglutin, Salitin, etc.	Tablets; Parenteral solution (i/v) in ampoules	0.25, 0.5; 10% - 5.0 ml, 10 ml
Salicylamide	Algamon, Salamide, Saliamid, Salopur, Urtosal, etc.	Tablets	0.25, 0.5
Methylii salicylas; Camphor + Methyl salicylate + Terbinthinae oleum + Eucalypti oleum; Methyl salicylate + menthol + vaseline + paraffin; Methyl salicylate + Analgin + petroleum + cachalot fat; Hyoscyami oleum + Methyl salicylate + Capsici tinctura; Hyoscyami oleum + Methyl salicylate + Chloroform; Hyoscyami oleum + Methyl salicylate + Chloroform	Methylis salicylas, Methylium salicylicum; Sanitas; Boum-Benge; Naphthalginum Capsinum; Linimentum Methylii salicylatis compositum; Salinimentum	Ointment; Liniment; Ointment; Liniment; Liniment; Liniment; Liniment	10% - 25.0; 50.0; 20.0, 25.0, 35.0, 40.0; 100.0; 50.0, 100.0, 50.0; 30.0, 40.0, 50.0, 80.0
Metamizole sodium	Analginum, Algocalmin, Algopyrin,	Tablets;	0.05, 0.1, 0.15, 0.5;

	Analgetin, Baralgin M, Devalgin, Dipyrone, Ilvagin, Metamizole sodium, Metapyrin, Methylmelubrin, Minalgin, Nebagin, Neomelubrin, Nobol, Novaldin, Novalgin, Novamidazophen, Novaminosulfon, Novapyrin, Optalgin, Pantalgan, Pyralgin, Pyretin, Pyridone, Pyrisan, Ronalgin, Spasdolgin, Sulpyrin, Toralgin, Totalgine, Vetalgin, etc.	Calsules; Rectal suppositories; Parenteral solution (i/m) in ampoules; Peroral solution in flacons	0.25; 0.1, 0.2, 0.3; 25%, 50% - 1 ml, 2 ml; 50% - 1 ml, 20 ml, 50 ml
Phenylbutazone;	Butadionum, Alindor, Antadol, Arthril, Arthrizon, Artrizin, Artropan, Azobutil, Butalan, Butapirazol, Butartril, Butazolidin, Butazone, Butofar, Butosal, Butylpyrin, Colbutan, Curosoladin, Delbutan, Deltabutanyl, Dibutone, Diphenylbutazon, Elmedal, Eributazone, Fenibutasan, Fenibutazona, Fenylbutazon, Mephabutazon, Merizone, Nadozone, Novophenyl, Panazone, Phebutan, Phenbutazol, Phenopyrine, Phenylbutazone, Rheumaphen, Rubatone, Sedazole, Todalgil, Zolaphen, etc.;	Tablets; Ointment;	0.03, 0.05, 0.15; 5% - 20.0;
Phenylbutazone + aminofenazon;	Pyrabutol;	Dragee;	0.125 + 0.125;
Phenylbutazone + aminofenazon	Rheopyrin	Dragee, Parenteral solution (i/m) in ampoules	0.125 + 0.125; 5 ml
Acetaminophen	Paracetamol; Abesanil, Acamol,	Tablets;	0.125, 0.2, 0.325, 0.5, 0.008;

	Acelifen, Acemol, Acetalgin, Acetaminophen, Acetaminophenol, Actasol, Adol, Aldolor, Algotropyl, Alvedon, Aminadol, Aminophen, Amphenol, Apamide, Apanol, Bartell drugs analgetic apap, Bindard, Biocetamol, Calpol, Celifen, Cetadol, Cetanil, Chemcetaphen, Daleron, Dapirex, Datril, Deminofen, Dexa-mol, Dimindol, Dolamin, Dolanex, Dolipram, Dolo, Dolomol, Dominophen, Dynafed, Efferalgan, Erocetamol, Febricet, Febridol, Febrinil, Febrinol, Fendon, Ifimol, Lekadol, Lupocet, Medipyrin, Mexalen, Minoset, Myalgin, Napa, Napamol, Naprinol, Nasprin, Nysacetol, Opradol, Pacemol, Pacimol, Pamol, Panadol, Panadon, Paracetamol, Paracinol, Paramol, Perfalgan, Prohodolum, Pyranol, Pyrimol, Pyrinazin, Rolocin, Sanidol, Strimol, Tempramol, Tralgon, Tylemin, Tylenol, Ushamol, Valadol, Valgesic, Valorin, Volpan, Winadol, etc.	Powder for peroral solution; Peroral suspension; Peroral solution in flacons; Syrup; Rectal suppositories; Parenteral solution in (i/m, i/v) ampoules; Eye films	0.08, 0.15, 0.24; 2.4% - 70 ml; 10 0ml; 300 ml; 5% - 100 ml; 10% - 15 ml; 2.4%- 60 ml; 100 ml; 3% - 90 ml; 2.4% - 50 ml; 100 ml; 2.5% - 60 ml; 100 ml; 120 ml; 3.2% - 30 ml; 120 ml; 4% - 60ml; 120ml; 0.05, 0.08, 0.1; 0.125, 0.15, 0.25, 0.3, 0.5; 15% - 2 ml
Indomethacin	Algometacin, Articin, Artrizinal, Artrocid, Bonatol, Cidalgon, Cinodocin, Cosmocalm, Dolopas, Dolovin, Elmetacin, Fortarthrin, Inacid,	Tablets; Dragee; Capsules; Capsules retard; Rectal	0.005, 0.01, 0.025, 0.025; 0.025, 0.03, 0.05; 0.075; 0.05, 0.1;

	Indacin, Indocid, Indometacin, Indomethacin, Indomin, Indopal, Indren, Inteban, Melitex, Metacen, Mataril, Matartril, Methacid, Mathindol, Metindol, Nuricon, Peralgon, Phenotacin, Rumacid, Reumadolon, Reumatin, Sadoreum, Valicent, Vellopan, etc.	suppositories; Parenteral solution (i/m) in ampoules; Gel in tubes; Ointment; Eye suspension	3% - 2ml; 1%, 10% - 50.0; 100.0; 5%, 10% - 30.0; 40.0; 0.1%, 1%
Diclofenac-natrium	Voltaren, Ortophen, Aflamin, Almiral, Apo-Diclo, Arthrex, Batafil, Betaren, Bioran, Blesin, Clofenac, Delimon, Diclac, Diclo, Diclobene, Dicloberl, Diclofen, Diclofenac, Diclogen, Diclogesic, Diclomax, Diclomelan, Diclonac, Diclonat, Dicloran, Diclorium, Diclovit, Difisal, Dignofenac, Diklofenak, Diphen, Diralon, Ecofenac, Effecton, Feloran, Forgenac, Inflanac, Linobol, Naklof, Naklofen, Neodol, Novo-Difenac, Olfen, Panamor, Prophenatin, Remetan, Rewodina, Rheumavek, Rumaphen, Sanfinac, Skip, Sofarin, Sorelmon, Ultrafen, Umeran, Valetan, Veral, Vernac, Voltaren, Voltarol, Vonafec, Votaxil, Votrex, Youfenac; Dicloberl retard, Diclonat P retard, Difisal-SR, Rewodina retard, Rumaphen-SR, Feloran retard, Voltaren retard 100;	Tablets; Rectal suppositories; Parenteral solution (i/m) in ampoules; Ointment in tubes; Eye drops in - dropper – flacons; Tablets;	0.015, 0.025; 0.05; 2.5% - 3 ml; 2% - 30.0; 0.1% - 1 ml; 0.1;

	Voltaren Emulgel	Gel	1%
Aceclofenac	Airtal	Tablets	0.1
Ibuprophen	Advil, Algofen, Anflagen, Artofen, Artril, Bren, Brufanic, Brufen, Bufigen, Burana, Children's Motrin, Deef Relief, Dolgit, Ebufac, Iborufen, Ibalgin, Ibumetin, Ibuprofen, Ibupron, Ibusan, Ibutad, Ibutop, Inflam, Ipren, Lamidon, Marcofen, MIG 200, Mortifen, Motrin, Napacetin, Nobfen, Nuprin, Nurofen, Paxofen, Profen, Profinal, Rebugen, Relcofen, Reumafen, Ruprin, Seclodin, Sednafen, Solpaflex	Tablets; Dragee; Tablets retard; Capsules retard; Syrup in flacons; Sispension for peroral introduction; Peroral solution in flacons; Cream in tubes; Gel	0.2, 0.4, 0.6, 0.05, 0.1; 0.2; 0.8; 0.3; 100 ml, 200 ml; 2% - 60ml, 100ml; 4% - 15ml; 5% - 20.0, 50.0, 100.0; 10% - 30.0
Naproxen	Aleve, Anaprox, Antalgin, Feminax Ultra, Flanax, Inaprol, Inza, Midol Extended, Methoxypropriocin, Relief, Nalgesin, Naposin, Naprelan, Naprogesic, Naprosyn, Narocin, Proxen, Pronaxen, Synflex, Sanaprox, Xenobid, Xenar, etc.	Tablets; Peroral suspension in flacons; Rectal suppositories	0.22, 0.25, 0.275, 0.375, 0.5, 0.55; 2.4%, 2.5% - 100 ml; 0.25, 0.5
Etodolac	Elderin	Tablets	0.2, 0.3
Fenoprofen	Nalfon	Tablets	0.2, 0.3
Tolmetin	Tolectin	Tablets; Capsules	0.2, 0.6; 0.4
Ketoprofen	Alreumant, Artrozilen, Asozal, Dexal, Febrofid, Flamax, Flexen, Kefenid, Ketolist retard, Ketoprosil, Meprofen, Niflam, Oruveil, Ostofen, Reumoquin, Synpofen, Orudis, Oruvail, Ketoflam, Ketorin, Keto, Ketomex, Orudis',	Tablets; Tablets retard; Capsules; Capsules retard; Rectal suppositories; Sprey; Powder for parenteral injections (i/m, i/v) in ampoules;	0.05, 0.1; 0.15; 0.05; 0.2; 0.1; 5% - 50 ml; 0.1

Dexketoprofen	Profénid, Bi-Profénid, Ketum, Ketodol, Fastum Gel, Lasonil, Orudis, Oki, Knavon, Ketonal, Arthril, Zon, Orudis, OKI, Gesiket "ATM", Actron, Ketoprofeno, etc.; Dexalgin 25; Dexalgin	Parenteral solution (i/m, i/v) in ampoules; Gel in tubes; Cream in tubes; Tablets; Parenteral solution (i/m, i/v) in ampoules	5% - 2 ml; 2.5% - 30.0, 50.0, 60.0; 5% - 30.0; 25 mg; 25 mg/1 ml - 2 ml
Flurbiprophen	Urbifen, Ansaid, Flurwood, Froben, Raxtan-Sanovel, Strepsils intensive, Flugalin	Tablets; Lingual tablets; Tablets; Capsules retard; Rectal suppositories; Gel	0.1; 8.75 mg; 0.05, 0.1; 0.2; 0.1; 5% - 15.0; 30.0
Pyroxycam	Piroxicam, Doblexan, Piroksan, Roxicam, Zunden, Algitrat, Pirox, Androxicam, Apo-Piroxicam, Brexic-DT, Calmapirol, Calmopirol, Erason, Feldene, Flexase, Gen-Piroxicam, Hotemin, Novo-Piricam, Pirocam, Piroflam, Pirorheum, Piroxiferum, Piroxiflam, Pro-naxen, Remoxicam, Reucam, Sanicam, Toldin, etc.	Tablets; Rectal suppositories; Gel in tubes; Parenteral solution (i/m) in ampoules	0.01, 0.02; 0.01; 0.02; 0.5% - 35.0; 50.0; 2% - 1ml; 2ml
Tenoxycam	Tenicam, Tenoktil, Tilcotil, Tobitil	Capsules; Tablets; Rectal suppositories	0.02; 0.02; 0.02
Meloxycam	Lem, Melox, Meloxam, Mirlox, Movalis.	Tablets; Rectal suppositories	0.0075, 0.015; 0.015
Lornoxycam	Xefocam	Tablets; Powder for parenteral injections (i/m, i/v) in ampoules	0.004, 0.008; 0.008
Amizon	Amizon Max	Capsules;	0.5;

		Tablets; Syrup in flacons	0.25; 10mg/1ml - 100ml
Celecoxib	Celebrex	Capsules	0.1; 0.2
Rofecoxib	Viox	Tablets; Peroral suspension in flacons	0.0125; 0.025; 0.25%, 0.5% - 150 ml
Parecoxib	Dynastat	Lyophilized powder for parenteral injections (i/m, i/v) in flaconis	0.04
Valdecoxib	Bextra	Tablets	0.01, 0.02, 0.04
Etoricoxib	Arcoxia	Tablets	0.06, 0.09, 0.12
Nimesulide	Aponil, Coxtral, Flolid, Mesulid, Nimfast, Nimica, Nimulide, Nize	Tablets; Granules for peroral solution in sachets; Peroral suspension in flacons; Transdermal gel in tubes	0.1, 0.2; 2.0; 1% - 60 ml; 1% - 20.0
Niflumic acid	Donalgin, Acidum niflumicum, Artricid, Dimepon, Dontalgan, Felalgyl, Flaminor, Forenol, Inflaril, Niduran, Niflamol, Nifluran, Niflux, Panreumal, Pefamexan	Capsules; Rectal suppositories; Gel in tubes; Cream in tubes	0.25; 0.4; 0.7; 2.5% - 60.0; 3% - 60.0
Nabumetone	Relafen, Rodanol S	Tablets	0.5, 0.75, 1.0
Tiaprofenic acid	Surgam	Tablets for children; Tablets for adults; Tablets and capsules retard; Rectal suppositories for children; Rectal suppositories for adults; Powder for injections (i/m) in flacons	0.1; 0.15; 0.3; 0.3; 0.15; 0,3; 0.2
Mephenamic acid	Coslan, Lysalgo, Parkemed, Ponstan,	Tablets	0.25, 0.5

	Ponstel, Ponstyl, Pontal, Tanston etc.		
Ketorolac	Adolor, Dolak, Ketanov, Ketorol, Ketorolac Trometamine, Ketrodol, Nato, Toradol, Torolac.	Tablets; Parenteral solution (i/m, i/v) in ampoules	0.01; 3% -1 ml
Diphlunizolum	Adomal, Algobid, Cididol, Di-flonid, Diflunil, Dolisal, Dolobid, Flovacil, Flunidor, Flu-o-donil, Noalodol	Tablets	0.25, 0.5
Nefopam	Oxadol; Akupan-Biocodex	Tablets; Parenteral solution (i/m, i/v) in ampoules; Parenteral solution (i/m, i/v) in ampoules	30 mg; 2% - 1 ml; 2% - 2 ml
Combined analgesics			
Metamizole + Pitofenone + Fenpiverinium	Renalgan	Tablets; Parenteral solution (i/m, i/v) in ampoules	0.5 + 0.005 + 0.0001; 2 ml
Diclofenac + Misoprostol	Artrotec	Tablets	
Paracetamol + Codeine	Prodein	Tablets	0.5 + 0.03
Acetylsalicylic acid + Paracetamol + Caffeine	Citramonum P, Citraparum	Capsules	0.24 + 0.18 + 0.03
Acetylsalicylic acid + Paracetamol + Caffeine + Accorbic acid + Citric acid	Citrapacum	Tablets	0.24 + 0.18 + 0.03 + 0.05 + 0.005
Acetylsalicylic acid + Paracetamol + Caffeine	Ascophenum P	Tablets	0.2 + 0.2 + 0.04
Paracetamol + Caffeine + Chlorphenamine + Vit.C	Gripocide	Capsules	
Paracetamol + Dicyclomine hydrochloride	Cyclopar	Tablets	0.5 + 0.02
Paracetamol + Acetylsalicylic acid + Caffeine + Chlorpheniramine	Grippostad	Capsules	0.2 + 0.15 + 0.025 + 0.0025
Paracetamol + Methamisol sodium + Caffeine + Phenobarbitale + Codeine phosfas	Sedalgin-Neo	Tablets	0.3 + 0.15 + 0.05 + 0.015 + 0.01
Methamisol sodium + Pitofenone + Fenpiverinium	**Baralginum**	Tablets; Parenteral	5ml

bromide		solution (i/m, i/v) in ampoules	
Propiphenason + Phenobarbitale Papaverine hydrochloride + Codeine dihydrophosfas + Ephedrinum chloride + Atropine metabromide	Spasmoveralgin-Neo	Tablets	0.15 + 0.02 + 0.03 + 0.015 + 0.005 + 0.0005
Codeine + Methamisol sodium + Caffeine + Phenobarbitale	Tempalgin	Tablets	0.008 + 0.03 + 0.05 + 0.01
Phenylbutason + Aminophenosonum	Pyrabutol	Tablets	aa 0.125
Phenylbutason + Amydasophenum	Rheopyrin	Dragee; Parenteral solution (i/m, i/v) in ampoules	aa 0.125; 5 ml
Phenylbutazone + dexametazone	Ambene		
Clofexamide + Phenylbutason	Clofezone	Rectal suppositories	0.4
Acetylsalicylic acid + Paracetamol + Caffeine	Thomapyrin	Tablets	0.25 + 0.2 + 0.05
Acetylsalicylic acid + Paracetamol + Vit.C	Thomapyrin C	Tablets	0.25 + 0.2 + 0.2
Acetylsalicylic acid + Citric acid + Sodium bicarbonate	Alka-Seltzer	Tablets	0.324 + 0.965 + 1.625
Acetylsalicylic acid + Glycine + Sodium bicarbonate + Citric acid	Alka-prim	Tablets	0.330 + 0.1 + 1.685 + 0.685
Acetylsalicylic acid + ascorbic acid	Aspirin plus C	Tablets	0.4 + 0.24
Acetylsalicylic acid + ascorbic acid	Aspirin UPSA with Vit.C	Tablets	0.330 + 0.2
Acetylsalicylic acid + ascorbic acid	Aspro with Vit.C	Tablets	0.5 + 0.3
Paracetamol + Caffeine + Phenylephrine + Terpinhydrate + Ascorbic acid	Coldrex	Tablets	0.5 + 0.025 + 0.05 + 0.02 + 0.03
Paracetamol + Caffeine + Codeine	Solpadein	Tablets	0.5 + 0.03 + 0.008
Paracetamol + Caffeine	Panadol extra	Tablets	0.5 + 0.065
Paracetamol + Caffeine + Propyphenazone	Gewadal	Tablets	0.25 + 0.05 + 0.25
Paracetamol + Caffeine + Propyphenazone	Saridon	Tablets	0.25 + 0.05 + 0.15
Paracetamol + Caffeine + Phenylephrine + Chlorphenamine maleate	Coldrin	Tablets	0.3 + 0.003 + 0.01 + 0.002
Paracetamol +	Anacold, Rinzasip	Tablets	0.3 + 0.01 + 0.002

Phenylephrine + Chlorphenamine maleate			
Paracetamol + Ibuprophen	Brustan	Tablets	0.325 + 0.4
Paracetamol + Mefenamic acid	Lanagesic	Tablets	0.5 + 0.25
Paracetamol + Diclophenac	Panoxen	Tablets	0.5 + 0.005
Paracetamol + pyrilamine maleate + pamabrom	Femizol	Tablets	0.5 + 15 mg + 25 mg +
Analgin + Quinine	Analgin-Chinin	Tablets	0.2 + 0.05
Analgin + Bendazol + Papaverine hydrochloride	Andipalum	Tablets	0.25 + 0.02 + 0.02
Analgin + Thiamin + Caffeine	Benalgin	Tablets	0.5 + 38.75 mg + 0.05

Chapter 14. Antipsychotics (Neuroleptics)

Neuroleptics are the drugs, that depress the central nervous system without disturbing consciousness, remove hallucinations, motor and verbal excitation.

Classification of Antipsychotics (neuroleptics)

Typical

Phenothiazine derivatives
Chlorpromazine
Fluphenazine
Perphenazine
Periciazine
Derivative thioxanthenes
Chlorprothixenum
Zuklopentiksol
Derivative butyrophenones
Haloperidol
Droperidolum
Indole derivatives
Dicarbine
Rauwolfia Alkaloid
Reserpine

Atypical

Benzamide
Sulpiride
Tiapride
Derivatives benzodiazepine
Clozapine
Olanzapine

The mechanism of antipsychotic action and adverse effects.

All antipsychotics are known today have a common mechanism of antipsychotic action as reduce the transmission of nerve impulses in the brain systems, where the nerve impulse transmitter is dopamine. There are: *mesolimbic pathway*, *mesocortical pathway*, *nigrostriatal pathway*, *tuberoinfundibular pathway*.

It is believed that a reduction of dopaminergic transmition in *mesolimbic pathway* (antipsychotic action) lead to removal of productive symptoms (delusions, hallucinations, etc.), and the most effective for this are *haloperidol* and *chlorpromazine*, but they cause extrapyramidal disorders.

It is known that a decrease in dopamine level in *mesocortical pathway* causes symptoms such as negative disorders (flattening of affect, apathy, poverty of speech, anhedonia, desocialization, etc.), and cognitive impairment (deficits in attention, working memory, executive functions). Dopamine receptors blockage in mesocortical pathway with prolonged therapy by typical nuroleptics may elicit an enhancement of cognitive dysfunction and violation of higher integrative functions of the brain.

It is obvious that the blockage of dopamine in *nigrostriatal pathway* adducts to typical adverse effects for neuroleptics use, namely extrapyramidal disorders, acathisia, early dyskinesia, trismus, drooling, tardive dyskinesia.

There is evidence that the blockage of dopamine in *tuberoinfundibular pathway* lead to elevation in prolactine level in the blood, and might result in a number of other side effects galactorrhoea, gynecomastia, menstrual disorders, sexual dysfunction, depression, increased risk of osteoporosis, the risk of cancer pathology, infertility, tumors of the pituitary gland.

Acting on the hypothalamus, neuroleptics inhibit the secretion of growth hormone (GH) and corticotropin (CTH). Reduction of nervous impulse transmission in dopamine neurons of trigger zone and the vomiting center provides antiemetic effect.

α1-adrenoceptor blockade with neuroleptics leads to lower blood pressure, orthostatic hypotension, vasodilation, dizziness, drowsiness; *blockade of H1-histamine receptors* causes hypotension, increased demand for carbohydrates and weight gain, sedation. With the *blockade of acetylcholine receptors* are associated anticholinergic side effects of some antipsychotics: the possibility of cognitive impairment, dry mouth, constipation, disturbance of accommodation, increased intraocular pressure, increased heart rate. Blockade of 5-HT1A receptors causes antidepressant and anxiolytic effect of some antipsychotic drugs, and blockade of 5-HT2A lead to prevention of extrapyramidal disorders, and reduction of negative symptoms. The influence of antipsychotics on *lipid metabolism* in high dosage determines a significant risk of cardiovascular disease, the risk of myocardial infarction and stroke, dyslipidemia, and a sharp increase in body weight while taking antipsychotic drugs can trigger the emergence of diabetes mellitus type 2. Particularly high *risk of cardiovascular events* in patients receiving combination therapy with typical and atypical antipsychotics. *Atypical antipsychotics* are more

likely to cause stroke and diabetes mellitus than the typical, and cause more weight gain than haloperidol. There is evidence that in older people antipsychotics cause an *increased risk of pneumonia* by 60%.

Neuroleptic action of Neuroleptics (antipsychotics) is due to α-adrenergic blocking effects and to a lesser degree is due to H1 blocking effects. These effects provide the *peripheral actions* of Neuroleptics also. *Antipsychotic action* of Neuroleptics is ensured by influence on dopaminergic processes, blockage of dopaminergic receptors and impact on serotoninergic processes.

Typical Antipsychotics act due to blockage of dopamine receptors that associate with the risk for extrapyramidal side effects.

Atypical antipsychotic agents there are the newer Antipsychotics. They potently antagonize the 5HT2 receptors, while blocking D2 receptors less potently than older typical antipsychotic agents, resulting in the atypical clinical profile of antipsychotic efficacy with limited extrapyramidal side effects. Also promising are medications that target glutamate and 5HT7 receptors subtypes, receptors for γ-aminobutiric acid (GABA) and acetylcholine (M- and N-) and even peptide hormone receptors *(e.g., oxytocin)*.

Group of *typical antipsychotics* affects mainly on dopamine receptors and blocks typically, 75-80% D2-receptors, in the treatment of psychosis is redundant; *atypical* group affects the metabolism of dopamine to a lesser extent, more - on the metabolism of serotonin and other neurotransmitters; accordingly, they are less likely cause extrapyramidal disorders, and negative symptoms and neurocognitive deficits.

Summing up the above, can be said that adverse effects predicted by monoamine receptor affinities. So, excluding the D2 partial agonist aripiprazole, all antipsychotic agents possess *D2 antagonist properties* that lead to extrapyramidal disorders, akathisia, long-term tardive dyskinesia risk, and hyperprolactinemia. Two side effects such as sedation and weight gain via appetite stimulation are associated with *central antagonism of H1 receptors*. *M1 antagonism* is responsible for central and peripheral anticholinergic effects of antipsychotics. But, most of atypical antipsychotic agents, including risperidone, paliperidone, asenapine, iloperidone, ziprasidone and aripiprazole, have not affinity to muscarinic receptors and do not elicit perceptible anticholinergic effects. Albeit, clozapine and low-potency phenothiazines have considerable anticholinergic adverse effects, quetiapine has moderate muscarinic affinity, but its active metabolite norquetiapine causes anticholinergic side effects. *Adrenergic antagonism* is associated with risk of orthostatic hypotension. In comparison with high-potency typical antipsychotics, low-potency typical agents have much greater affinities for α1 receptors and therefore significantly greater risk for orthostasis.

Typical antipsychotics have all pharmacological effects. Atypical antipsychotics have not neuroleptic effect, do not cause extrapyramidal disorders (Parkinson's syndrome), or cause in lesser degree.

Pharmacological effects of Antipsychotics:

- Antipsychotic
- Neuroleptic
- Sedative
- Antidepressant
- Potentiating
- Antiemetic
- Hypothermic
- Hypotensive
- Adrenolytic
- Cholinolytic (dry mouth, urinary retention, constipation, blurred vision, increased intraocular pressure)
- blockade of serotonin receptors
- blockade of histamine receptors
- Myorelax
- Cataleptic
- Analgesic

Indications for Antipsychotics use:

- Psychosis, schizophrenia, bipolar disorder, mania, treatment-resistant major depression
- Tourette's disorders (tics in patients with Tourette's disorders)
- Huntington's disease
- Autism
- Anesthesia, premedication
- Anacatharsis (uncontrollable vomiting, pernicious vomiting)
- Hypertensive crisis
- Neurodermatosis
- Neuroleptanalgesia
- Hyperthermia, resistant to antipyretics
- Shock
- Migraine, dizziness

Adverse effects of Antipsychotics:

- Extrapyramidal disorders (Parkinson's syndrome)
- Orthostatic (postural) hypotension
- Endocrine disorders: inhibition of pituitary hormone production - CTH, GH and increase secretion of ADH (edema), and prolactin (hyperprolactinemia)
- Antipsychotics, particularly atypicals, appear to cause changes in insulin levels by blocking the muscarinic M3 receptor (which is a key regulator of insulin secretion) expressed on pancreatic β cells and in regions of the brain that regulate glucose homeostasis. Altered insulin levels can lead to diabetes mellitus and fatal diabetic ketoacidosis, especially (in US studies) in African Americans
- Pancreatitis

Overweight (especially atypical antipsychotics – olanzapine and clozapine) due to occupancy of the histamine receptor and changes to neurochemical signaling in regions of the brain that regulate appetite

Clozapine also has a risk of inducing agranulocytosis, a potentially dangerous reduction in the number of white blood cells in the body. Because of this risk, patients prescribed clozapine may need to have regular blood checks to catch the condition early if it does occur, so the patient is in no danger

Tardive dyskinesia. It is believed that there is a greater risk of developing tardive dyskinesia with the older, typical antipsychotic drugs, although the newer antipsychotics are now also known to cause this disorder

A potentially serious side effect of many antipsychotics is that they tend to lower an individual's seizure threshold. Chlorpromazine and clozapine, in particular, have a relatively high seizurogenic potential. Fluphenazine, haloperidol, pimozide and risperidone exhibit a relatively low risk. Caution should be exercised in individuals that have a history of seizurogenic conditions such as epilepsy, or brain damage.

Neuroleptic malignant syndrome (muscle rigidity, fever, autonomic instability, and cognitive changes such as delirium, and is associated with elevated plasma creatine phosphokinase)

Dysphoria (it is a state of feeling unwell or unhappy; a feeling of emotional and mental discomfort as a symptom of discontentment, restlessness, dissatisfaction, malaise, depression or anxiety)

Sexual dysfunction, which may rarely continue after withdrawal, similar to Post-SSRI (selective serotonin reuptake inhibitor) sexual dysfunction.

Both typical and atypical can lead to akathisia

Dystonia, a neurological movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures

Sedation

Local tissue irritation

Pharyngitis

Mental disorders – reduction of intelligence, emotional lability, seizures, and excitation.

Ventricular arrhythmia and sudden cardiac death due to inhibition of K^+ ion channels and elongation of QT interval, especially for thioridazine, mesoridazine, pimozide, i/m injection of droperidole, i/v injection of haloperidol. At the same time the newer atypical antipsychotics have less impact on heart electrophysiology than typical agents. Note that the risk

of sudden cardiac death is dose-dependent for both as the typical and atypical antipsychotic drugs.

Withdrawal symptoms from antipsychotics may emerge during dosage reduction and discontinuation. Withdrawal symptoms can include nausea, emesis, anorexia, diarrhea, rhinorrhea, diaphoresis, myalgia, paresthesia, anxiety, agitation, restlessness, and insomnia.

The side effects are based on potencies of the selected agent to inhibit neurotransmitter receptors. Adverse effects such as extrapyramidal disorders, orthostatic hypotension, sedation, hyperprolactinemia may respond to drug dose reduction, but metabolic anomalies improve only with termination of provocative agent and a transfer to a more metabolically benign medication (table 38,39).

Overdose with typical antipsychotics is of particular concern with low-potency drugs (e.g. chlorpromazine) by reason of the risk of torsades de pointes, sedation, anticholinergic effects, and orthostasis. Along with this the high-potency typical antipsychotics (e.g. haloperidol) and substituted benzamides are at higher risk for extrapyramidal disorders by virtue the high D2 affinity. Overdose with newer atypical antipsychotics much less leads to torsades de pointes ventricular arrhythmias as opposed to older antipsychotic drugs.

Drug-Drug interactions. Antipsychotic agents are not appreciable inhibitors of CYP enzymes (microsomal liver enzymes) with a few exceptions (chlorpromazine, perphenazine, thioridazine).Whereas, antipsychotics are highly protein bound, there is no evidence of significant displacement of other protein bound drugs, thus dosage correction is not needed for agents with narrow therapeutic indices. It is important to consider the influence of smoking, nutraceuticals, grapefruit juice and changes in these behaviors.

Antipsychotics are unsuitable for use during pregnancy and lactation. Some antipsychotics (risperidone, aripiprazole) can be used in pediatric practice for the treatment of autism, bipolar disorder (acute mania), schizophrenia.

Neuroleptics are incompatible with the anticholinesterases, cholinomimetics, adrenomimetics, MAO inhibitors, antihypertensive drugs, and drugs that depress the central nervous system. *Phenothiazine derivatives are incompatible* with the tricyclic antidepressants. *Chlorpromazine is incompatible* with epinephrine, caffeine, morphine, vitamin B12, Cardiac glycosides. *Haloperidol* is *incompatible* with epinephrine, propanidid, reduces the effects of indirect anticoagulants, and potentiates the effect of hypnotics, analgesics.

Reaction	Features	Time of Onset and Risk INFO	Proposed mechanism	Treatment
Acute dystonia	Spasm of muscles of tongue, face, neck, back.	1-5 days; Young, antipsychotic naïve patients at highest risk	Acute dopamine (D) antagonism	Anti-parkinsonian agents are diagnostic and curative (diphenhydromine, or benztropine with the possible re-dosing of these drugs due to long antipsychotic T1/2).
Akathisia	Subjective and objective restlessness; *not* anxiety or ”agitation”.	5-60 days	Unknown	Reduce dose or change drug; clonazepam, propranolol in relatively low doses more effective than anti-parkinsonian agents; β1 selective adrenergic receptor antagonists are less effective; non-lipophilic β adrenergic receptor antagonists have limited CNS penetration and are of no benefit (e.g., atenolol).
Parkinsonism	Bradykinesia, rigidity, variable tremor, mask facies, shuffling gait.	5-30 days Elderly at greatest risk	D antagonism	Dose reduction; change medication; anti-parkinsonian agents (use of amantadine avoids anticholinergic effects of benztropine or diphenhydromine).
Neuroleptic malignant syndrome	Extreme rigidity, fever, unstable BP, myoglobinemia; can be fatal.	weeks-months Can persist for days after	D antagonism	Stop antipsychotic immediately; supportive care; dantrolene and

		stopping antipsychotic		bromocriptine; with persistent antipsychotic affects (e.g., long-action injectable agents), bromocriptine may be tolerated in large doses. Anti-parkinsonian agents are not effective.
Perioral tremor ("rabbit syndrome")	Perioral tremor (may be a late variant of parkinsonism).	months or years of treatment	Unknown	Anti-parkinsonian agents often help (use of amantadine avoids anticholinergic effects of benztropine or diphenhydromine).
Tardive dyskinesia	Orofacial dyskinesia; rarely widespread choreoathetosis or dystonia.	months, years of treatment Elderly at 5-fold greater risk. Risk > potency of D2 blockade	Postsynaptic D-receptor supersensitivity, up-regulation	Prevention crucial; treatment unsatisfactory. May be reversible with early recognition and drug discontinuation

* adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12^{tth} edition. Medical. 2011. – 2084 P.

Table 46*. Potencies of Antipsychotic Agents at Neurotransmitter Receptors** and Metabolic Risk Profile.

Antipsychotic Agents	Dopamine	Serotonine			5HT/D2 Ratio	Dopamine		Muscarinic	Adrenergic		Histamine	Metabolic Risk Profile		
	D2	5HT 1A	5HT 2A	5HT 2C		D1	D4	M1	α1A	α2A	H1	Weight gain	Lipids	Glucose
Typical Agents														
Haloperidol	1.2	2100	57	4500	47	120	5.5	>10,000	12	1130	1700	+/-	-	-
Fluphenazine	0.8	1000	3.2	990	3.9	17	29	1100	6.5	310	14	+/-	-	-
Thiothixene	0.7	410	50	1360	72	51	410	>10,000	12	80	8			
Perphenazine	0.8	420	5.6	130	7.4	37	40	1500	10	810	8.0	+/-	-	-
Loxapine	11	2550	4.4	13	0.4	54	5.1	120	42	150	4.9	+	-	-
Molindone	20	3800	>5000	10,000	>250	>10,000	>20006.4	>10,000	2600	1100	2130	-	-	-
Thioridazine	8.0	140	28	53	3.5	94	12	13	3.2	130	16			
Chlorpromazine	3.6	2120	3.6	16	1	76		32	0.3	250	3.1	+++	+++	++
Atypical Agents														
Asenapine***	1.4	2.7	0.1	0.03	0.05	1.4	1.1	>10,000	1.2	1.2	1.0	+/-	-	-
Ziprasidone	6.8	12	0.6	13	0.1	30	39	>10,000	18	160	63	+/-	-	-
Sertindole***	2.7	280	0.4	0.90	0.2	12	13	>5000	1.8	640	130	+/-	-	-
Zotepine***	8.0	470	2.7	3.2	0.3	71	39	330	6.0	210	3.2			
Risperidone	3.2	420	0.2	50	0.05	240	7.3	>10,000	5.0	16	20	+	+/-	+/-
Paliperidone	4.2	20	0.7	48	0.2	41	54	>10,000	2.5	4.7	19	+	+/-	+/-
Iloperidone	6.3	90	5.6	43	0.9	130	25	4900	0.3	160	12	+	+/-	+/-
Aripiprazole	1.6	6.0	8.7	22	5.0	1200	510	6800	26	74	28	+/-	-	-
Sulpiride***	6.4	>10,000	>10,000	>10,000	>1000	>10,000	54	>10,000	>10,000	>5000	>10,000			
Olanzapine	31	2300	3.7	10	0.1	70	18	2.5	110	310	2.2			
Quetiapine	380	390	640	1840	2.0	990	2020	37	22	2900	6.9	+	+	+/-
Clozapine	160	120	5.4	9.4	0.03	270	24	6.2	1.6	90	1.1	++++	+++	+++

* - adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12th edition. Medical. 2011. – 2084 P.

- Data are averaged Ki values (nM) from published sources determined by competition with radioligands for bonding to the indicated cloned human receptors. Data derived from receptor binding to human or rat brain tissue is used when cloned human receptor data is lacking.

- Not available in the US.

The classification and peculiarities of some antipsychotics, and other agents with antipsychotic activity

Commonly used antipsychotic medications are listed below by drug group Trade names appear in parentheses.

First generation antipsychotics

Main article: Typical antipsychotics:

- **Butyrophenones**
  - Haloperidol (Haldol, Serenace)
  - Droperidol (Droleptan, Inapsine)
- **Phenothiazines**
  - Chlorpromazine (Thorazine, Largactil)
  - Fluphenazine (Prolixin) - Available in decanoate (long-acting) form
  - Perphenazine (Trilafon)
  - Prochlorperazine (Compazine)
  - Thioridazine (Mellaril)
  - Trifluoperazine (Stelazine)
  - Mesoridazine (Serentil)
  - Periciazine
  - Promazine
  - Triflupromazine (Vesprin)
  - Levomepromazine (Nozinan)
  - Promethazine (Phenergan)
  - Pimozide (Orap)
  - Cyamemazine (Tercian)
- **Thioxanthenes**
  - Chlorprothixene (Cloxan, Taractan, Truxal)
  - Clopenthixol (Sordinol)
  - Flupenthixol (Depixol, Fluanxol)
  - Thiothixene (Navane)
  - Zuclopenthixol (Cisordinol, Clopixol, Acuphase)

Second generation antipsychotics

Main article: Atypical antipsychotics:

- Clozapine (Clozaril) – Requires weekly to biweekly complete blood count due to risk of agranulocytosis
- Olanzapine (Zyprexa) – Used to treat psychotic disorders including schizophrenia, acute manic episodes, and maintenance of bipolar disorder
- Risperidone (Risperdal) – Divided dosing is recommended until initial titration is completed, at which time the drug can be administered once daily. Used off-label to treat Tourette syndrome and anxiety disorder.
- Quetiapine (Seroquel) – Used primarily to treat bipolar disorder and schizophrenia, and "off-label" to treat chronic insomnia; it is a powerful sedative.

Ziprasidone (Geodon) – Approved in 2004 to treat bipolar disorder. Side-effects include a prolonged QT interval in the heart, which can be dangerous for patients with heart disease or those taking other drugs that prolong the QT interval.

Amisulpride (Solian) – Selective dopamine antagonist. Higher doses (greater than 400 mg) act upon post-synaptic dopamine receptors resulting in a reduction in the positive symptoms of schizophrenia, such as psychosis. Lower doses, however, act upon dopamine autoreceptors, resulting in increased dopamine transmission, improving the negative symptoms of schizophrenia. Lower doses of amisulpride have also been shown to have antidepressant and anxiolytic effects in non-schizophrenic patients, leading to its use in dysthymia and social phobias. Amisulpride has not been approved for use by the Food and Drug Administration in the United States.

Asenapine (Saphris) is a 5-HT2A- and D2-receptor antagonist under development for the treatment of schizophrenia and acute mania associated with bipolar disorder.

Paliperidone (Invega) – Derivative of risperidone that was approved in 2006, it offers a controlled release once-daily dose, or a once-monthly depot injection.

Iloperidone (Fanapt, Fanapta, and previously known as Zomaril) – Approved by the FDA in 2009, it is fairly well tolerated, although hypotension, dizziness, and somnolence were very common side effects.

Zotepine (Nipolept, Losizopilon, Lodopin, Setous) – An atypical antipsychotic indicated for acute and chronic schizophrenia. It was approved in Japan circa 1982 and Germany in 1990.

Sertindole (Serdolect, and Serlect in Mexico). Sertindole was developed by the Danish pharmaceutical company H. Lundbeck. Like the other atypical antipsychotics, it is believed to have antagonist activity at dopamine and serotonin receptors in the brain.

Lurasidone (Latuda), recently approved by the FDA for schizophrenia and pending approval for bipolar disorder. Given once daily, it has shown mixed Phase III efficacy results but has a relatively well-tolerated side effect profile.

Third generation antipsychotics

Aripiprazole (Abilify) – Mechanism of action is thought to reduce susceptibility to metabolic symptoms seen in some other atypical antipsychotics. The extent to which these effects differ from other atypical antipsychotics is debated.

Partial agonists of dopamine receptors.

Other options

Cannabidiol is one of the main components of *Cannabis sativa*. Cannabidiol differs from the active drug in cannabis, tetrahydrocannabinol, in that cannabidiol lacks the typical mind altering and recreational effects. One study has suggested that cannabidiol may be as effective as atypical

antipsychotics in treating schizophrenia. Some further research has supported these results, and found fewer side effects with cannabidiol than with amisulpride.

Tetrabenazine is similar in function to antipsychotic drugs, though is not, in general, considered an antipsychotic itself. Its main usefulness is the treatment of hyperkinetic movement disorders such as Huntington's disease and Tourette syndrome, rather than for conditions such as schizophrenia. Also, rather than having the potential to cause tardive dyskinesia, which most antipsychotics have, tetrabenazine can be an effective treatment for the condition.

Metabotropic glutamate receptor 2 agonism has been seen as a promising strategy in the development of novel antipsychotics. When tested in patients, the research substance *LY2140023* yielded promising results and had few side effects. The active metabolite of this prodrug targets the brain glutamate receptors mGluR2/3 rather than dopamine receptors.

Glycine transporter 1 inhibition. RG1678 has been shown in phase 2 clinical trials to be selectively effective for the negative symptoms of schizophrenia.

A placebo-controlled trial has suggested that adding L-theanine, an amino acid found in green tea and available as supplement, to ongoing antipsychotic medication may be helpful in reducing some symptoms of schizophrenia.

Table 47. Medicinal forms of Antipsychotics (Neuroleptics)

INN	**Trade names**	**Medicinal forms**	
Chlorpromazine	Aminazinum, Ampliactil, Amplictil, Chlorazin, Chlorpromanyl, Chlorpromazine, Contomin, Fenactil, Hibanil, Hibernal, Kloproman, Largactil, Megaphen, Plegomazin, Promactil, Propaphenin, Thorazine, etc.	Tablets; Dragee; Parenteral solution (i/m, i/v) in ampoules	0.01; 0.025; 0.05; 0.1; 0.25; 2.5% - 1ml, 2ml, 5ml, 10ml
Fluphenazine	Phthorphenazinum, Moditen, Anatensol, Dapotum, Elinol, Flumazine, Flumezin, Lyogen, Lyorodin, Mirenil, Pacinol, Pacinone, Permitil, Prolixin, Sevinal, Sevinol, Sevinon, Siqualine, Siqualone, Tensofin, Teviral, Trancin, Vespazin, etc.	Tablets; Dragee; Parenteral solution (i/m) in ampoules	0.001; 0.0025; 0.005; 0.00025; 0.001; 0.0025; 0.005; 0.25% - 1ml

Perphenazine h/chl.	Aethaperazinum, Chlorpiprazin, Chlorpiprozine, Decentan, Fentazin, Neuropax, Perphenan, Perphenazine, Trilafon, Trilifan, etc.	Tablets	0.004; 0.006; 0.01
Periciazine	Neuleptile, Aolept, Apamin, Nemactil, Neulactil, Pericyazine, Propericiazine	Capsules; Peroral solution in flacons	0.01; 4% - 30ml, 125ml
Chlorprothixene	Truxal, Chlothixen, Minithixen, Tactaran, Taractan, Tarasan, Trictal, Truxil, Vetacalm, etc.	Tablets; Parenteral solution (i/m) in ampoules	0.005; 0.015; 0.025; 0.05; 2.5% - 1ml
Zuclopentixol	Clopixol, Clopixol-accuphase	Tablets; Parenteral oil solution (i/m) in ampoules	0.002; 0.01; 0.025; 5% - 1ml, 2ml
Haloperidol	Halopidol, Halophen, Haloper, Aloperidin, Apo-Haloperidol, Haldol, Halopidol, Senorm, Seranase, Serenace, Trancodol, etc.	Tablets; Tablets forte; Peroral solution in flacons; Parenteral solution (i/m, i/v) in ampoules; Parenteral oil solution (i/m) in ampoules	0.0005; 0.001; 0.0015; 0.002; 0.005; 0.01; 0.005; 0.2% - 10ml; 0.5% - 1ml; 5% - 1ml
Droperidol	DehydrobenzperidolDridol, Droleptan, Droperidol, Inapsin, Sintodril, etc	Parenteral solution (s/c, i/m, i/v) in ampoules	0.25% - 2ml, 5ml, 10ml
Dicarbine	Carbidinum	Tablets; Parenteral solution (i/m) in ampoules	0.025; 1.25% - 2ml
Reserpine	see page 150-151, 154		
Sulpiride	Abilit, Betamax, Depral, Digton, Dobren, Dogmalid, Dogmatil, Eglonyl, Eusulpid, Lisopiride, Megotyl, Miradon, Mirbanil, Nivelan, Norestran, Omperan, Prosulpin, Sulpiril	Capsules; Tablets forte; Peroral solution in flacons; Parenteral solution (i/m) in ampoules	0.05; 0.1; 0.2; 0.2; 0.5% - 100ml; 5% - 2ml

Clozapine	Azaleptin, Alemoxan, Clazaril, Iprox, Lapenax, Lepotex, Leponex, Alemoxan.	Tablets; Granules for peroral solution in sachets; Parenteral solution (i/m) in ampoules; Tablets	0.025; 0.1; 0.5; 1.0; 2.5% - 2ml; 0.05
Olanzapine	Ziprexa	Tablets	0.005, 0.0075, 0.01
Asenapine	Saphris	Sublingual tablets	5mg
Ziprasidone	Zipsila, Zeldox	Capsules; Powder for parenteral solution (i/m) in ampoules	40mg, 80mg; 30mg
Sertindole	Serdolect	Tablets	4mg, 12mg, 16mg, 20mg
Zotepine	Nipolept, Zoleptil, Lodopin	Tablets; Dragee; Granules for peroral solution	25mg, 50mg, 100mg; 25mg, 50mg, 100mg; 10%, 50%
Risperidone	Risperdal, Ridal, Sizodon, Riscalin, Risdone, Riswel, Rispolept, Zepidone, Riperidone, Rispen Risperidona, Apexidone, Rissar, Torendo Q, Belivon,	Tablets	1mg, 2mg, 4mg
Paliperidone	Invega Sustenna, Xeplion	Tablets; Suspension for i/m introduction in the syringes	3mg, 6mg, 9mg, 12mg; 25mg/0.25ml; 50mg/0.5ml; 75mg/0.75ml; 100mg/1ml; 150mg/1.5ml
Iloperidone	Fanapt, Fanapta, Zomaril	Tablets	1mg, 2mg, 4mg, 6mg, 8mg, 10mg, 12mg
Aripiprazole	Zilaxera, Abilify, Aripiprex, Amdoal	Tablets	5mg, 10mg, 15mg, 30mg
Quetiapine	Seroquel, Xeroquel, Ketipinor, Quepin, Syquel, Nantarid, Ketilept, Victoel, Seroquel prolong, Kventiax, Lakvel, Gedonin	Tablets	25mg, 100mg, 150mg, 200mg, 300mg, 400mg

Chapter 15. Anxiolytics (Tranquilizers)

Anxiolytics are psychotropic drugs that remove the fear, anxiety, irritability, aggressiveness. They are also called ataractics (ataraxia – equanimity, indifference), antifears (phobos – fear). Anxiolytics depress CNS. Unlike antipsychotics anxiolytics have no antipsychotic activity, practically no influence on the autonomic nervous system (except benactyzine); they do not provide extrapyramidal disorders.

Classification of Anxiolytics according the chemical structure

Benzodiazepines derivatives **(benzodiazepine receptor agonists)**

Chlordiazepoxide
Diazepam
Bromdihydrochlorphenylbenzodiazepine (Phenazepam)
Oxazepam
Lorazepam
Medazepam
Hydrazinecarbonylmethylbromphenyldihydrobenzadiazepine
(Gidazepam) Alprazolam

Carbamic (butyl) esters of substituted propanediol

Meprobamate

Diphenylmethane derivatives

Benactyzine
Hydroxyzine

Different chemical groups

Benzoclidine
Tetramethyltetraazocycloocyandione
(Mebicar) Buspirone

DAILY Anxiolytics

Medazepam
Gidazepam
Mebikar
Benzoclidine

In clinical practice, anxiolytics are divided into ***typical*** and ***atypical***. Benzodiazepines belong to the *typical anxiolytics*, whereas derivatives of other chemical groups of anxiolytics belong to the *atypical agents*. Moreover a significant number of drugs possess anxiolytic activity. There are some antidepressants, neuroleptics, nootrops, central myorelaxants, drugs pro narcosis, opioids, central α2 adrenergic agonists, β adrenergic blockers, calcium channels blockers, et al.

From a clinical point of view anxiolytics are divided into: sedative agents that have expressed sedative and hypnotic effects (benzodiazepines); daily anxiolytics that have anxiolytic effect and a low sedative, hypnotic, anticonvulsive and antispasmodic activity. They can be used in out-patients because the daily anxiolytics have a little effect on the rate of physical and mental reactions.

The mechanism of action of Anxiolytics. The mechanism of anxiolytic action of anxiolytics is insufficiently studied. It is believed that anxiolytics reduce the excitability of the limbic system, pituitary and hypothalamus, i.e. those brain structures that are responsible for emotional state. In addition, they inhibit the process interaction of these structures with the cerebral cortex of the brain, and oppress the polysynaptic spinal reflexes.

Benzodiazepine anxiolytics are the agonists of benzodiazepine receptors that are closely related to the γ-aminobutyric acid (GABA) receptors, and affect GABA-ergic system, activating the specific GABA receptors. In other words, activation of benzodiazepine receptors leads to activation of GABA receptors that promotes disclosing of chloride channels, increasing the flow of chloride ions into the neuron, and inhibition of neurons of the CNS, especially in the limbic system, cortex, hypothalamus, thalamus, reticular formation, spinal cord. This process causes a membrane hyperpolarization and suppressed neuronal activity in CNS and it is called the GABA-benzodiazepine chloride complex (complex Costa). Today there are several subtypes of benzodiazepine receptors: BZ1, BZ2, BZ3, or w1, w2, w3. Endogenous ligands for these are many of the physiologically active compounds: peptides, purines, nicotinamide hypoxanthine, β-carbolines, etc.

Anxiolytics have little effect on noradrenergic, dopaminergic, serotoninergic systems; moderately inhibit the synthesis of norepinephrine and dopamine (Benzodiazepine derivatives). Also it was found that benzodiazepine derivatives inhibit the release of excitatory amino acids (glutamine, asparagine) of axon terminals, and some of them reduce inactivation of adenosine, and block Ca^{+} and Na^{+} channels.

Several subtypes of benzodiazepine receptors have been allocated on the membrane of the neurons of the brain structures that regulate the emotional state (the limbic system, hypothalamus, nucleus of the thalamus, the spinal cord). Therefore, benzodiazepines have multifaceted activity: anxiolytic, sedative, hypnotic, anticonvulsive and antispasmodic.

Diphenylmethane derivatives inhibit the cholinergic system in the brain, as a result they are called central cholinolytics. Their use nowadays is restricted due to the adverse effects.

The mechanism of action of carbamic esters of substituted propanediol today remains unsolved, although the representative of this group Meprobamate – is a founder of tranquilizers and was synthesized in finding central muscle relaxants. It is known that drugs of this group have no expressed action on benzodiazepine and cholinergic receptors.

In accordance with the different mechanisms of action, all anxiolytics were separated into: agonists of benzodiazepine receptors; agonists of serotonine receptors; and other mechanisms of action.

Pharmacological effects of Anxiolytics:

Anxiolytic
Sedative
Hypnotic
Amnesic
Antispasmodic (they decrease the smooth muscle tone)
Anticonvulsive
Stabilization of vegetative nervous system and endocrine system
All pharmacological effects of benzodiazepines are dose-dependent.

Indications for the Anxiolytics use:

Neurosis
Light psychosis
Neurogenic diseases (hypertension, angina pectoris, peptic ulcer and dvenadtsatipaloy intestine, etc.)
Premedication
Spastic states
Sleep disturbances associated with negative emotions
Depression
Withdrawal syndrome in alcoholism and narcotic drug addiction
Neurodermatitis
Parkinson disease
Climacteric neuroses
Epileptic status

In general, the therapeutic uses of the benzodiazepines depend on its $T_{1/2}$. Anti-axyety benzodiazepines should have a long $T_{1/2}$ despite the drawback of the risk of neuropsychological deficits caused by drug accumulation.

Adverse effects of Anxiolytics:

Drowsiness, fatigue, dizziness, weakening of memory, impaired concentration of attention, headache, nervousness, discoordination movement, addiction, increased reaction time, motor incoordination, anterograde amnesia *(benzodiazepine derivatives)*
Withdrawal syndrome, addictive/habitation, addiction *(especially meprobamate)*, euphoria *(benactyzine, meprobamate)*
Dry mouth, hypotension, tachycardia, mydriasis, constipation, nausea, allergic reactions
Overdose of tranquilizers leads to motor and mental excitement, anger, sleep disorders, vision disorders, convulsions *(especially benactyzine, hydroxyzine)*

The specific antagonist of benzodiazepine receptors is *flumazenil*. It is a competitive antagonist of the benzodiazepines, and is used in case of

benzodiazepine tranquilizer overdoses to reduce their central effects (except anticonvulsive).

Anxiolytics can not be used during the work, which requires more attention, rapid mental and motor reaction.

Undesirable is the use of anxiolytics with MAO inhibitors (reinforce their effects), antipsychotic agents, alcohol, etc., that depress the CNS functions (summation of the inhibitory effect on the CNS).

Undesirable is the use of anxiolytics with peripheral muscle relaxants (increased peripheral myorelax effect).

The solution of diazepam is not compatible in the same syringe with any drugs (to prevent formation of precipitate).

Characteristics of certain groups of Anxiolytics

Benzodiazepines are the weak bases and have a good absorption in duodenum. Maximal their concentration in plasma is in 1-2 hours. The binding of the benzodiazepines with plasma proteins is from 60% to 95%. Benzodiazepines penetrate biological barriers; form a high concentration especially in cortex, cerebellum, midbrain and spinal cord. Besides, benzodiazepines have a high affinity to fat tissue. Benzodiazepines are metabolized in the liver: most of them by microsomal enzimes with the formation of active metabolites that prolong the action of the agent. In order to reduce the duration of tranquilizers in clinic are used their active metabolites (e.g., a metabolite of diazepam – oxazepam). They are named as prodrugs. $T_{1/2}$ depends on age of patients: from 31 hours in newborns to 100 hours in older people; and depends on function of internal organs (e.g., in patients with liver cirrhosis $T_{1/2}$ is doubled. Based on the characteristics of pharmacokinetics, benzodiazepines can be divided into the following groups: the average duration of activity ($T_{1/2}$ 6-24 hours) – *oxazepam, lorazepam*; long-action ($T_{1/2}$ more than 24 hours) - *diazepam, Phenazepam*.

Due to the intensity and the ratio of the pharmacological effects and therefore in clinical use the benzodiazepines are divided into the following groups: agents with expressed *anxiolytic action* (e.g., *diazepam, lorazepam*), agents with moderate anxiolytic action (e.g., *chlordiazepoxide, oxazepam, Gidazepam*); agents with expressed *sedative and hypnotic action* (e.g., *Phenazepam, diazepam, lorazepam, chlordiazepoxide, oxazepam*); agents with expressed *anticonvulsive action* (e.g., *chlonazepam, diazepam, Phenazepam, lorazepam*); agents with expressed *antispasmodic action* (they decrease the smooth muscle tone) (e.g., *diazepam, chlordiazepoxide, lorazepam*).

The *sequence of manifestations of the tranquilizer central effects* is: anticonvulsive, anxiolitic, light sedation, reduce attention, intelligence, amnestic effect, deep sedation, relaxation, sleep.

Table 48. Medicinal forms of Anxiolytics

INN	Trade names	Medicinal forms	
Chlordiazepoxide	Ansiacal, Apo-Benzodiapin, Chlordiazepoxide, Decadil, Droxol, Elenium, Equinbral, Labiton, Librium, Lixin, Napoton, Novosed, Radepur, Sonimen, Timosin, Viansin, Chlozepidum, Angirex, Klopoxid, Librax , Libritabs, Mesural, Multum, Novapam, Risolid, Silibrin, Tropium	Tablets; Dragee; Capsules	0.005, 0.01; 0.025
Diazepam	Valium, Antenex, Anstolin, Apaurin, Apo-Diazepam, Apozepam, Bensedin, Calmpose, Diapam, Diazepam, Diazepex, Diazex, Dicam, Dizep, Eridan, Faustan, Lembrol, Novo-Dipam, Pacitrian, Quetinil, Relanium, Relium, Saromet, Seduxen, Sibazonum, Serenamin, Serensin, Sonacon, Stesolin, Ushamir, Valitran, Vatran, Vival, etc.	Tablets; Parenteral solution (i/m, i/v) in ampoules	0.001; 0.002; 0.005; 0.01; 0.5% - 2ml
Oxazepam	Adumbran, Oxazepam, Praxiten, Psicopax, Rondar, Serax, Serenal, Tazepam, Alepam, Medopam, Murelax, Noripam, Nozepam, Opamox, Ox-Pam, Purata, Serepax, Vaben, Sobril, Oxascand, Zaxpam etc.	Tablets	0.01; 0.015; 0.03
Bromdihydrochlorphenylbenzodiazepine	Phenazepam	Tablets; Parenteral solution (i/m, i/v) in ampoules	0.0005; 0.001; 0.0025; 0.1%, 0.3% - 1ml
Lorazepam	Ansilor, Apo-Lorazepam, Ativan, Kalmalin, Lorafen, Loram, Lorenin, Lorsedal, Lorsilan, Sidenar, Tavor, Temesta, Trapex, Lorax, Lorivan, Merlit, Trapax, etc.	Tablets; Dragee	0.0005, 0.001, 0.002, 0.0025; 0.001, 0.0025
Medazepam	Mezapamum, Rudotel, Ansilan, Anxitol, Benson, Emopan, Enobrin, Imazepam, Medaurin, Medazepol, Megasedan, Nivelton,	Tablets; Granules for peroral suspension in banks	0.01; 150ml

	Nobritem, Nobrium, Pazital, Stratium, etc.		
Hydrazinecarbonylmethylbromphenyldihydrobenzadiazepine	Gidazepam	Tablets	0.02; 0.05
Alprazolam	Alprox, Alzolam, Cassadan, Chelex, Frontin, Lamoz, Neurol, Prinax, Restil, Solanax, Tafil, Trankimazin, Tricca, Xanor, Zoldac, Zotran, Xanax	Tablets; Tablets retard	0.00025, 0.0005, 0.001, 0.002 0.0005, 0.001, 0.002, 0.003
Meprobamate	Andaxin, Aneural, Apo-Meprobamate, Biobamat, Equanil, Gadexyl, Harmonin, Mepavlon, Meprotanum, Meproban, Meprospan, Miltown, Nephentine, Pankalma, Pertranquile, Procalmadiol, Quanil, Restenil, Sedanyl, Sedazil, Sedral, Tensonal, Tranquil, Tranquilan, Tranquiline, Tranquisan, etc.	Tablets	0.2
Benactyzine	Amisylum, Actozine, Amitakon, Benactina, Benactyzine, Cafron, Cevanol, Lucidil, Nervatil, Neurobenzile, Parasan, Phobex, Procalm, Suavitil, Tranquilline, etc.	Tablets	0.001, 0.002
Hydroxyzine	Alamon, Arcanax, Atarax, Atara, Aterax, Atazin, Clorixin, Disron, Durrax, Quiess, Forticalman, Tranquizine, Hyzine, Iremoxin, Multipax, Neocalma, Neurolax, Orgatrax, Placidol, Quiess, Ucerax, Vistaril, Equipose, Masmoran, Paxistil. (Vistaril, Equipose, Masmoran, Paxistil are preparations of the pamoate salt, while Atarax, Alamon, Aterax, Durrax, Tran-Q,	Tablets; Syrup in flacons; Parenteral solution (i/m) in ampoules	0.01, 0.025; 0.2% - 200ml; 5% - 2ml

	Orgatrax, Quiess, and Tranquizine are of the hydrochloride salt		
Benzoclidine	Oxylidinum	Tablets; Parenteral solution (s/c, i/m) in ampoules	0.02, 0.05; 2%, 5% - 1ml
Tetramethyltetraazabicyclooctandione	Mebicar, Adaptol, Mebix	Tablets	0.3, 0.5
Buspirone	Bespar, Buspar, Spitomin	Tablets	0.005, 0.01
Flumazenil	Anexate, Romazicon	Parenteral solution (i/v) in ampoules	0.01% -5ml, 10ml

Chapter 15. Hypnotic drugs

Hypnotics can depress the function of CNS and elicit calming and drowsiness (sedation). They inhibit the CNS in dose-dependent fashion: from mild sedation to coma and death. Hypnotics promote the onset of sleep and support a sleep which is similar to the physiological sleep in it electroencephalographic characteristics and from which the patient can be awakened easily.

Classification of Hypnotics

I. Barbiturates:

Phenobarbital
Cyclobarbital
Reladorm (Cyclobarbital + Diazepam)

Benzodiazepines:

Triazolam
Midazolam
Brotizolam*
Temazepam
Nitrazepam*
Flurazepam
Flunitrazepam

*- not available for clinical use in the U.S.

III. Different chemical groups:

Methaqualone
Doxylamine
Bromizoval

"Z compounds":

Zopiclone
Eszopiclone (Lunesta)
Zolpidem (Ambien)
Zalepton (Sonata)

Mechanisms of action of different classification groups of Hypnotics. All *benzodiazepines* (table 37) are the agonists of benzodiazepine receptors, and as a result they also are agonists GABA receptors which exist as multi-subunit, ligand-gated chlorine channels, thereby enhancing the GABA-induced ionic flow through these channels. Heterogeneity among sites of binding and action of benzodiazepines, GABA-gated chlorine channels expressed in different neurons allowed developing the new hypnotic drugs, so called "Z compounds". There are zolpidem (Ambien), an imidazopyridine, the pyrazolopyrimidines zalepton (Sonata) and the cyclopyrrolones zopiclone and eszopiclone (Lunesta). They evidently invoke sedative-hypnotic effects due to interaction with a subset of benzodiazepine binding sites.

Pharmacological effects of Benzodiazepine Hypnotics:

central effects:

Sedative
Hypnotic
Muscle-relaxant
Anxiolytic
Anticonvulsive
Anterograde amnesia

peripheral effects:

Coronary vasodilatation (after i/v administration of therapeutic doses)
Decrease BP and increase heart rate
Neuromuscular blockade (only after administration of a very high doses).

All benzodiazepines have similar pharmacological profiles, but drugs differ in selectivity, and clinical use of the individual benzodiazepines varies considerably. If the benzodiazepine dose is increased, sedation progresses to hypnosis and then to stupor. Benzodiazepines do not cause general anesthesia due to the fact that consciousness usually persists, however, "preanesthetic" doses induce *amnesia* for events subsequent to administration of the drug. In "preanesthetic" doses (e.g., for endoscopy) benzodiazepines *slightly depress alveolar ventilation* and cause *rerspiratory acidosis*, can cause *apnea* during anesthesia or when given with opioids. Hypnotic doses of benzodiazepines may worsen *sleep-related brething disorders*, may cause *hypoventilation* and *hypoxemia*. In patients with obstructive sleep apnea, hypnotic doses of benzodiazepines may increase *alveolar hypoxia* , *pulmonary hypertension*, and *cardiac ventricular load*. Diazepam decreases *noctural gastric secretion* in humans.

All benzodiazepines have high lipid-water distribution coefficients in the non-ionized form. *According to the duration of action the benzodiazepines are divided in 4 groups:* ultra-short-acting benzodiazepines; short-action agents ($T_{1/2}$ < 6 hours), including triazolam, midazolam, zolpidem, eszopiclone; intermediate-acting agents ($T_{1/2}$ 6-24 hours), including estazolam, temazepam; long-acting agents ($T_{1/2}$ < 24 hours), including flurazepam, diazepam and quazepam.

The *ideal hypnotic* agent would have a rapid onset of action, cause stable sleep throughout the night, and no residual action till the following morning.

Indications for Benzodiazepines use:

Insomnia
Anxiety disorders
Preanesthetic medication
Status epilepticus
Convulsions
Management of alcohol withdrawal syndrome
Adjunctive treatment in acute mania and certain movement disorders
Mostly benzodiazepines can be used interchangeability. In general, the therapeutic use of the benzodiazepines depends on its $T_{1/2}$. A short elimination $T_{1/2}$ is desirable for hypnotics, although it carries the drawback of increased abuse liability and severity of withdrawal syndrome after drug discontinuation.

Adverse effects of Benzodiazepines:

Withdrawal syndrome: dysphoria, irritability, sweating, unpleasant dreams, tremors, anorexia, and faintness or dizziness
Lassitude
Increased reaction time
Motor incoordination
Impairment of mental and motor functions
Confusion
Anterograde amnesia
Euphoria
Dependence and abuse
Restlessness
Hallucinations
Sleep-walking
Sleep-talking
Hypomanic behavior
Residual effects
Weakness
Headache
Blurred vision
Nausea, vomiting
Epigastric distress, diarrhea
Joint pains
Chest pains
Incontinence
Paradoxical effects: increase the frequency of seizures in patients with epilepsy; garrulousness, anxiety, irritability, tachycardia, sweating
Hepatotoxic effect
Allergic reaction

Hematologic reaction

Hypothermia, hypotonia, and mild respiratory depression may be in the neonate in case of use benzodiazepines before or during labor

When the drugs are given at the intended time of sleep, the persistence of these effects during the waking hours is adverse. The residual effects and degree of impairment may be underestimated**.**

Drug-Drug interactions. Ethanol increases both the rate of absorption of benzodiazepines and the associated CNS depression. Valproates and benzodiazepines in case of combination may cause psychotic episodes.

Original benzodiazepine receptor agonists ("Z compounds"). Z compounds (*zolpidem*, *zaleplon*, *zopiclone*, *eszopiclone*) are not structurally related to each other and to benzodiazepines; however they have hypnotic effect due to the agonist effects on the benzodiazepine site of the GABA receptor. In comparison to benzodiazepines, Z compounds are less effective as anticonvulsants or muscle relaxants. Lately Z compounds replace benzodiazepines in the treatment of insomnia by virtue its less potential for dependence and abuse than traditional benzodiazepines. And nevertheless, long-term use of Z compounds, especially in high doses leads to tolerance and physical dependence. Overdose with Z compounds is similar to that of benzodiazepine overdose and can be treated with the benzodiazepine antagonist *flumazenil*.

Melatonine congeners. In US *ramelteon (Rozerem)* is used for treatment of insomnia, especially sleep onset difficulties. Ramelteon is an analog of melatonine. It is known that melatonin plays a critical role in the regulation of the circadian rhythms of several biological functions including sleep – awake. Mechanism of action of ramelteon is to bind to specific melatonin receptors in the suprachiasmatic nucleus – M1 and M2. Ramelteon binds these receptors with high affinity. Ramelteon is not known to bind to any other types of receptors, such as benzodiazepine-binding site on GABA receptors, opiate, dopamine, acethylcholine, neuropeptide receptors.

Barbiturates. The barbiturates were once used widely as sedative-hypnotic drugs, but they are now replaced with safer benzodiazepines, except for a few uses (table 43). The barbiturates reversibly inhibit the activity of all excitable tissues, however direct its effects on peripheral excitable tissues are weak. Together with that, the acute barbiturate intoxication causes serious malfunctions in cardiovascular system and respiratory system.

Barbiturates act throughout the CNS; they depress polysynaptic responses primarily at synapses where neurotransmission is mediated by GABA acting at GABA receptors. The site of inhibition is postsynaptic in cortical and cerebellar pyramidal cells, in the cuneate nucleus, substantia nigra, thalamic neurons, or presynaptic in spinal cord. Hypnotic doses of barbiturates increase the total sleep time and alter the stages of sleep in dose-dependent manner. The barbiturates are the inductors of the liver microsomal enzymes which control the biotransformation of barbiturates. That's why the repeated introduction of barbiturates leads to the tolerance to the effects on sleep which occurs within a few days, and the effect on

total sleep time may be reduced by as much as 50% after 2 weeks of use. Tolerance to the effects on mood, sedation, hypnosis develops more rapidly and is more significant than tolerance to the anticonvulsive and lethal effects. Pharmacodynamic tolerance to barbiturates gives cross-tolerance to all CNS depressants, including ethanol.

Pharmacological effects that limit the use of barbiturates as hypnotics now:

Barbiturates alter the physiological structure of sleep

They cause dreaming, nightmares, fitful sleep

Barbiturates provoke aftereffect: violation of motor coordination, drowsiness, muscle weakness

Barbiturates induce abuse, drug addiction, and require greater and greater doses to the soporific effect and large doses of them are toxic to the humans

In some persons, barbiturates may cause paradoxical effect: excitement, insomnia, inebriation, restlessness, delirium, an increase the patient's perception of pain

Hypersensitivity

As the inductors of the liver microsomal enzymes, barbiturates alter the pharmacokinetics and pharmacodynamics of drugs that are metabolized by microsomal liver enzymes

Action of barbiturates on peripheral nervous system. The barbiturates selectively suppress neurotransmission in autonomic ganglia and decrease nicotinic excitation by choline esters. This mechanism has a value in the fall of BP in case of intravenous introduction of barbiturates. Barbiturates enchance the blocking effects of both depolarizing and nondepolarizing neuromuscular blocking agents during barbiturate anesthesia. Barbiturates depress *respiratory system in* doses more than hypnotic; in case of i/v administration, barbiturates may increase the risk of *ventricular arrhythmias*, especially when epinephrine or halothane is also present. Besides, anesthetic concentration of barbiturates has direct electrophysiological effects on the heart, change the function of Na^+ and K^+ channels. But, direct depression of *cardiac contractility* occurs only when acute barbiturate poisoning. Barbiturates elicit dose-dependent decrease of *GIT* tone and contractility. In the *liver* barbiturates induce the microsomal enzymes. Severe oliguria or anuria may occur in acute barbiturate poisoning.

Contraindications for Barbiturates use:

Kidney and liver disease

Pregnancy, lactation

Arterial hypotension

Atherosclerosis

Chronic alcoholism

Barbiturates are *absolutely contraindicated* in patients with porphyria, because these agents enchance porphyrin synthesis.

Barbiturate poisoning is a significant clinical problem, problem of suicide, and accidental poisonings in children or drug abusers. The treatment of barbiturate poisoning is based on symptomatic therapy. CNS stimulators are contraindicated

because they increase the mortality rate. In severe cases of barbiturate poisoning, the hemodialysis or hemoperfusion is necessary.

Table 49*. Trade names, Routs of administration, and Therapeutic Uses of Benzodiazepines

Compound	**Routs of administration**	**$T_{1/2}$[b] hours**	**Therapeutic Uses[a]**	**Comments**
Alprazolam	Oral	12±2	Anxiety disoders, agoraphobia	Withdrawal symptoms may be especially severe
Chlordiazepoxide	Oral, i/m, i/v	10±3.4	Anxiety disoders, management of alcohol withdrawal, anesthetic premedication	Long-acting and self-tapering because of active metabolites
Clonazepam	Oral	23±5	Seizure disoders, adjunctive treatment in acute mania and certain movement disoders	Tolerance develops to anticonvulsant effects
Clorazepate	Oral	2.0±0.9	Anxiety disoders, seizure disorders	Prodrug; activity due to formation of nordazepam during absorption
Diazepam	Oral, i/m, i/v, rectal	43±13	Anxiety disoders, status epilepticus, skeletal muscle relaxation, anesthetic premedication	Prototypical benzodiazepine
Estazolam	Oral	10-24	Insomnia	Contains triazoloring; adverse effects may be similar to those of triazolam
Flurazepam	Oral	74±24	Insomnia	Active metabolites accumulate with chronic use
Lorazepam	Oral, i/m, i/v	14±5	Anxiety disoders, preanesthetic medication	Metabolites solely by conjugation
Midazolam	i/m, i/v	1.9±0.6	Preanesthetic and intraoperative medication	Rapidly inactivated
Oxazepam	Oral	8.0±2.4	Anxiety disorders	Metabolites solely by conjugation
Quazepam	Oral	39	Insomnia	Active metabolites accumulate with

				chronic use
Temazepam	Oral	11±6	Insomnia	Metabolized mainly by conjugation
Triazolam	Oral	2.9±1.0	Insomnia	Rapidly inactivated; may cause disturbing daytime side effects

* - adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12th edition. Medical. 2011. – 2084 P.

a - The therapeutic uses are identified as examples to emphasize that most benzodiazepines can be used interchangeability.

b - Half-life of active metabolite may differ.

Table 50*. Trade names, Routs of administration, and Therapeutic Uses of Barbiturates

Compound (Trade names)	**Routs of administration**	**$T_{1/2}$ hours**	**Therapeutic Uses**	**Comments**
Amobarbital (Amytal)	i/m, i/v	10-40	Insomnia, preoperative sedation, emergency management of seizures	Only Na^+ salt administered parenterally
Butabarbital (Butisol, others)	Oral	35-50	Insomnia, preoperative sedation	Redistribution shortens duration of action of single dose to 8 hours
Mephobarbital (Mebaral)	Oral	10-70	Seizures disorders, daytime sedation	Second-line anticonvulsant
Methohexital (Brevital)	i/v	3-5**	Induction and maintenance of anesthesia	Only Na^+ salt available; single dose provides 5-7 min of anesthesia**
Pentobarbital (Nembutal)	Oral, i/m, i/v, rectal	15-50	Insomnia, preoperative sedation, emergency management of seizures	Only Na^+ salt administered parenterally
Phenobarbital (Luminal, others)	Oral, i/m, i/v	80-120	Seizures disorders, status epilepticus, daytime sedation	First-line anticonvulsant, only Na^+ salt administered parenterally
Secobarbital (Seconal)	Oral	15-40	Insomnia, preoperative sedation	Only Na^+ salt available
Thiopental (Pentothal)	i/v	8-10**	Induction/maintenance of anesthesia, preoperative sedation, emergency management of seizures	Only Na^+ salt available; single dose provides brief of anesthesia**

* - adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12th edition. Medical. 2011. – 2084 P.

** - value represents terminal $T_{1/2}$ due to metabolism by the liver; redistribution following parenteral administration produces effects lasting only a few minutes.

Table 51. Medicinal forms of Hypnotics

INN	Trade names	Medicinal forms	
Phenobarbital	Barbiphen, Dormiral, Epanal, Fenemal, Gardenal, Hypnotal, Lepinal, Luminal, Mephabarbital, Neurobarb, Nirvonal, Phenobarbitone, Sedonal, Sevenal, etc.	Powder; Tablets; Peroral solution in flacons	0.005; 0.05; 0.1; 0.2% - 100ml
Cyclobarbital	Aethylhexabital, Cavonyl, Cyclobarbitone, Cyclohexal, Cyclonal, Cyclosedal, Dormiphan, Dormiphene, Fanodorm, Hexemal, Hypnoval, Normanox, Palinum1, Panodorm, Phanoctal, Phanodorm, Phriodorm, Prodorm, Somnokalan, etc.	Powder	Cyclobarbital is excluded from the nomenclature of medicines
Cyclobarbital + Diazepam	Reladorm	Tablets	0.1 + 0.01
Triazolam	Apo-Triazo, Apo-Triolam, Clorazolam, Halcion, Insomnium, Novidorm, Nuctan, Somneton, Songar, etc.	Tablets	0.00025
Midazolam	Dormicum, Dormonid, Flormidal, Fulsed, Versed	Tablets; Parenteral solution (i/m, i/v) in flacons; ampoules	0.0075; 0.015; 0.1% - 5ml, 10ml; 0.5% - 1ml, 3ml
Brotizolam	Lendormin	Tablets	0.00025
Temazepam	Signopam	Tablets	0.01
Nitrazepam	Apodorm, Benzalin, Berladorm, Calsmin, Dumolid, Epibenzalin, Epinelbon, Eunoctin, Hipnax, Hipsal, Insomin, Livetan, Magadon, Mitidin, Mogadan, Mogadon,	Tablets	0.005; 0.01

	Nelbon, Neozepam, Nitram, Nitrazepam, Nitrenpax, Nitrodiazepam, Nitrosam, Pacidrim, Pacisyn, Radedorm, Serenex, Somitran, Sonipam, Sonnolin, etc.		
Flurazepam	Apo-Flurazepam	Capsules	0.015; 0.03
Flunitrazepam	Hypnodorm, Hypnosedon, Narcozep, Primum, Rohypnol, Sedex, Somnubene, Valsera, etc.	Tablets; Parenteral solution (i/m, i/v) in ampoules	0.001; 0.002; 0.2% - 1ml
Zopiclone	Imovan, Zimovane	Tablets	0.0075
Eszopiclone (is the *S(+)* enantiomer of zopiclone)	Lunesta	Tablets	1mg, 2mg, 3mg
Zolpidem	Ivadal, Sanval, Ambien	Tablets	0.005; 0.01
Zalepton	Sonata	Capsules	0.005
Methaqualone	Aqualon, Bendor, Citexal, Dormigen, Dormilone, Dormised, Dormotil, Dorsedine, Holodorm, Ipnolan, Ipnosed, Mandrax, Mekvalon, Melsomin, Mequalon, Mezulon, Motolon, Mynal, Nobadorm, Noctilene, Normorest, Optinoxan, Orthonal, Quaalude, Revonal, Ronqualone, Somberol, Somnidon, Somnomed, Somnotropon, Tolinon, Toquilone, Toraflon, Torinal, etc.	Tablets	0.2
Doxylamine	Donormil	Tablets	0.015
Bromisoval	Abroval, Albroman, Alluval, Alural, Bromodorm, Bromuralum, Bromuresan, Dormigene, Isobromyl, Isoneurin, Isoval, Leunerval, Sedural, Somnibrom, Somnurol, Valurea, etc.		
Ramelteon	Rozerem	Tablets	8mg

Chapter 17. **Antiepileptic drugs** and **Antiparkinsonian drugs**

Antiepileptic drugs and **Antiparkinsonian** drugs belong to group of anticonvulsant drugs.

Antiepileptic drugs

More than 40 separate forms of epilepsy have been identified. The defective synaptic function might lead to convulsions. Namely, improving of excitatory synaptic activity or oppression of inhibitory synaptic activity may evoke a convulsion. In this way, the drugs for therapy of epilepsy should oppress the activating amino acids (glutamate, aspartate), or increase the activity of GABA. More over, antagonists of the $GABA_A$ receptor or agonists of glutamat receptors elicit seizures in experimental animals, and vice versa. The drugs described as antiepileptic guarantee the symptomatic therapy and not effective as anti-epileptogenic agents. So, therapy of epilepsy is symptomatic in that available drugs inhibit seizures. A major problem of this therapy is the length of its duration, and as a result, the unfavorable effects are possible. The ideal anticonvulsant drug would depress all convulsions without causing adverse effects. Unfortunately, the drugs that are used currently provoke undesirable effects from minimal impairment of CNS to death from aplastic anemia or hepatic failure. Anti-seizure drugs interact with oral contraceptives and lead to teratogenic effects, and effects on vitamin K metabolism in pregnant women. Anti-seizure drugs have been associated with vitamin K deficiency in newborns, which can result in a coagulopaty and intracerebral hemorrhage. And that is why treatment with vitamin K, 10mg/day during the last month of gestation, has been recommended for prophylaxis.

Classification of Antiepileptic drugs according the mechanism of action

Barbiturates: Phenobarbital *(see above in table 44)*
Benzobarbital
Primidone

Stimulators of GABA: Valproic acid
Vigabatrin
Tiagabine
Valpromide

Inhibitors of neuromediator acids – aspartate & glutamate: Lamotrigine
Topiramate

Drugs of "hybrid" neuromediator action: Carbamazepine
Oxcarbazepine
Phenytoin
Felbamate

Benzodiazepines: Clonazepam
Diazepam

Different drugs: Ethosuximide
Beclamide
Gabapentine
Puphemide
Pregabalin
Lacozamide

Table 52*. Proposed Mechanisms of Action of Anti-Seizure Drugs

Molecular Target and Activity	**Drug**	**Consequences of Action**
NA^+ channels modulatos that: *enhance fast inactivation* *enhance slow inactivation*	phenitoin, carbamazepine, lamotrigine, felbamate, oxcarbazepine, topiramate, valproic acid lacozamide	· block action potential propagation · stabilize neuronal membranes · reduce neurotransmitter release, focal firing, and seizure spread; · increases spike frequency adaptation · reduces action potential bursts, focal firing, and seizure spread · stabilizes neuronal membranes
Ca^{2+} channel blockers	ethosuximide, valproic acid, lamotrigine	· reduce neurotransmitter release · reduce slow-depolarization and spike-wave discharges
α2δ ligands	gabapentin, pregabalin	· modulate neurotransmitter release
$GABA_A$ receptor allosteric modulators	benzodiazepines, phenobarbital, felbamate, topiramate, carbamazepine, oxcarbazepine	· increase membrane hyperpolarization and seizure threshold · reduce focal firing benzodiazepines - attenuate spike-wave discharges phenobarbital, carbamazepine, oxcarbazepine - aggravate spike-wave discharges
GABA uptake inhibitors/ GABA-transaminase inhibitors	tiagabine, vigabatrin	· increase GABA level and membrane hyperpolarization · reduce focal firing · aggravate spike-wave discharges
***N*-Methyl-D-aspartate (NMDA) receptor antagonists**	felbamate	· reduces slow excitatory neurotransmission · reduces excitatory amino acid neurotoxicity · delays epileptogenesis

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptor antagonists	phenobarbital, topiramate	· reduce fast excitatory neurotransmission and focal firing
Enhancers of Hyperpolarization-activated cyclic nucleotide-gated (HCN) channel activity	lamotrigine	· buffers large hyperpolarizing and depolarizing inputs · suppresses action potential initiation by dendritic inputs
Synaptic vesicle glycoprotein 2A (SV2A) protein ligand	levetiracetam	· unknown; may decrease transmitter release
Inhibitors of brain carbonic anhydrase	acetazolamide, topiramate, zonisamide	· increase HCN-mediated currents · reduce NMDA-mediated currents · increase GABA-mediated inhibition

* - adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12th edition. Medical. 2011. – 2084 P.

Table 53*. Classification of Epileptic Seizures and Indications for Anti-Seizure Drugs

Seizure Type	Features	Conventional Anti-Seizure Drugs	Recently Developed Anti-Seizure Drugs
Partial Seizures			
Simple partial	Diverse manifistations determined by the region of cortex activated by the seizure *(e.g., if motor cortex representing left thumb, clonic jerking of left thumb results; if somatosensory cortex representing left thumb, paresthesia of left thumb results)*, lasting approximating 20-60 seconds. *Key feature is represervation of consciousness.*	carbamazepine, phenytoin, valproate	gabapentin, lacosamide, lamotrigine, levetiracetam, rufinamide, tiagabine, topiramate, zonisamide
Complex partial	Impaired consciousness lasting 30 seconds to 2 minutes, often associated with purposeless movements such as lip smacking or hand wringing.		
Partial with secondary generalized	Simple or complex partial seizure evolves into a tonic-clonic seizure with loss of consciousness and	carbamazepine, phenobarbital,	

tonic-clonic seizure	sustained contractions (tonic) of muscles throughout the body followed by periods of muscles contraction alternating with period of relaxation (clonic), typically lasting 1-2 minutes.	phenytoin, primidone, valproate	
Generalised Seizures			
Absence seizure	Abrupt onset of impaired consciousness associated with staring and cessation of ongoing activities typically lasting less than 30 seconds.	ethosuximide, valproate, clonazepam	lamotrigine
Myoclonic seizure	A brief (perhaps a second), shocklike contraction of muscles that may be restricted to part of one extremity or may be generalized.	valproate, clonazepam	levetiracetam
Tonic-clonic seizure	As described earlier in table for partial with secondarily generalized tonic-clonic seizures except that it is not preceded by partial seizure.	carbamazepine, phenobarbital, phenytoin, primidone, valproate	lamotrigine, levetiracetam, topiramate

* - adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12th edition. Medical. 2011. – 2084 P.

Table 54. Medicinal forms of Antiepileptic drugs

INN	Trade names	Medicinal forms	
Benzobarbital	Benzonal	Tablets	0.05; 0.1
Primidone	Hexamidinum, Desoxyphenobarbitone, Lepimidin, Lespiral, Liskantin, Mylepsin, Mysoline, Prilepsin, Primaclone, Primidone, etc.	Tablets	0.125; 0.25
Phenobarbital	Luminalum	Tablets	0.1; 0.05; 0.005
Valproic acid	Apilepsin, Acediprol, Convulex, Depakene, Depakin, Depakote, Deprakine, Diplexin, Divalproex, Encorate, Encorate Chrono, Epikine, Epilim, Everiden, Lepeilan, Orfilept, Orfiril, Propymal, Valpakine,	Tablets; Syrup	0.3; 5% - 100ml

	Valparine XR, Valporin, Valprin, Valproate sodium, Valpron, etc.		
Vigabatrin	Sabril	Tablets; Powder	500 mg; 500 mg/ sachet
Valpromide	Depamide	Tablets	0.3
Tiagabine	Gabitril	Tablets	5mg, 10mg, 15mg
Lamotrigine	Lamictal, Lamitor	Tablets; Chewable tablets	0.025, 0.05, 0.1; 0.005, 0.025, 0.1
Topiramate	Topamax	Tablets; Capsules	25 mg, 50 mg, 100 mg, 200 mg; 15 mg, 25 mg, 50 mg
Carbamazepine	Actinerval, Apo-Carbamazepin, Carbadac, Carbapin, Carbasan, Carbatol, Epial, Gen-Carbasan, Gen-Carpaz, Mazepine, Novo-Carbamaz, Stazepin, Storilat, Tegretol, Timonil, Zagretol, Zeptol, Finlepsin, etc.	Tablets; Tablets retard	0.1, 0.2; 0.2, 0.4
Oxcarbazepine - is keto analog of carbamazepine	Trileptal, Trexapin, etc.	Tablets; Peroral suspension	0.15, 0.3, 0.6; 0.3/5 ml
Phenytoin	Alepsin, Dihydantoin, Diphenin, Dilantin sodium, Diphantoine, Diphedan, Epanutin, Eptoin, Hydantal, Hydantoinal, Phenytek, Sodanton, Solantoin, etc.	Tablets; Parenteral solution (i/v) in ampoules; Capsules; Peroral suspension; Coated tablets; Chewable tablets	0.117 Phenytoin + 0.032 Sodium hydrocarbonate; 250 mg – 5 ml; 25 mg, 50 mg, 100 mg; 30 mg – 5 ml; 100 mg; 50 mg
Felbamate	Felbatol	Tablets; Peroral suspension	0.4, 0.6; 60%
Clonazepam	Antelepsin, Clonotril, Iktoril, Iktorivil, Ravatril, Ravotril, Rivatril, Rivotril, others	Tablets; Peroral solution; Parenteral solution (i/v) in	0.00025, 0.0005, 0.001, 0.002; 0.25%; 0.05% -2 ml

		ampoules	
Ethosuximide	Aethosuximid, Asamid, Ethymal, Etomal, Pemalin, Petinimid, Pyknolepsin, Ronton, Succimal, Suxilep, Zarontin, others	Capsules	0.25
Beclamide	Chloracon, Benzchlorpropamide, Hibicon, Nydrane, Posidrine	Tablets	0.25
Gabapentin	Neurontin, Convalis, Gabagamma, Gapentek, Lepsitin, Tebantin	Capsules; Tablets	0.1, 0.3, 0.4; 0.6, 0.8
Pregabalin	Lyrica	Capsules; Oral solution	25 mg, 50 mg, 100 mg, 200 mg, 300 mg; 20mg/1ml - 473ml
Levitiracetam	Keppra, others	Tablets; Oral solution	250 mg, 500 mg; 100 mg/1 ml - 300 ml
Zonosamide	Zonegran	Capsules	25 mg, 50 mg, 100 mg
Puphemide		Tablets	0.25
Lacozamide	Vimpat	Tablets; Syrup; Parenteral solution (i/v) in ampoules	50 mg, 100mg, 150 mg, 200 mg; 100 mg/1 ml - 200 ml; 10 mg/ 1ml
Rufinamide	Banzel, Inovelon	Tablets; Peroral suspension	100 mg, 200 mg, 400 mg; 40 mg/1 ml - 460 ml

Drugs for treatment Parkinson disease

Parkinson disease is characterized by several features:

Bradykinesia
Muscular rigidity
Resting tremor
An impairment of postural balance leading to disturbances of gait and falling.

Patogenic base of PD is insufficiency of dopaminergic nervous transmission. The distinctive feature of PD is loss of pigmented, dopaminergic neurons of substantia nigra pars compacta, with the appearance of intracellular inclusions known as *Lewy bodies*. Loss of 70%-80% of dopaminergic neurons causes

symptoms of PD that are progressed over 5-10 years to a rigid, akinetic state and inability to care for themselves. Causes of death are immobility, aspiration pneumonia or pulmonary embolism. Loss of dopaminergic neurons affects other areas of the brain, namely, brainstem, hippocampus, and cerebral cortex that is likely responsible for "non-motor" peculiarities of PD, such as sleep disorders, depression, and memory impairment. In addition to idiopathic Parkinson's disease and Parkinson's syndrome exists, which may be the cause of neurodegenerative disoders, stroke, intoxication with dopanin receptor antagonists, the use of antipsychotics, like haloperidol and thorazine, anti-emetics such as prochloperazine and metoclopramide.

The treatment of Parkinson disease is based on the drugs that may increase the dopaminergic nervous transmission. In other words, these drugs should enhance dopamine levels in dopaminergic neurons; or inhibit Mono-amino oxydase (MAO) and Catecol-O-Methyltransferase (COMT), because after release, dopamine is transported back into dopaminergic terminals by the presynaptic uptake mechanism or metabolized by the actions of MAO and COMT; or activate dopamine receptors. There are following medications: dopamine precursors, MAO inhibitors, COMT inhibitors, dopamine receptor agonists.

Dopamine precursors are the short-acting drugs. They cause "Wearing off" symptoms. 'Wearing off' is a common phrase used in PD. It describes the period of time between the end of the effect of one dose of medication, and the beginning of the next one. That is, the beneficial effects of the previous dose appear to be 'wearing off'. There is no definite explanation for what causes wearing off. Levodopa works by supplying dopamine to the nerve cells of people with PD. However, as PD progresses, it is possible that the levodopa medication is less able to compensate for the increasing loss of dopamine-producing nerve cells. Another possibility is based on the theory that, in early PD, the extra dopamine supplied by each levodopa dose is stored and then released when needed. In more advanced PD, the dopamine can no longer be stored and so it is released all at once, beginning by working well (ON time), progressing to working too well (ON with dyskinesias), returning to working well again (ON time), and then wearing off (OFF time). These variations are examples of motor fluctuations. The symptoms of wearing off vary from person to person, and may not occur after every dose of levodopa. Wearing off tends to produce a mild and gradual increase in symptoms, with some people noticing an increase in tremor or slowness. In contrast, other types of motor fluctuations associated with more advanced PD, such as those known as ON–OFF fluctuations, have more rapid and sometimes unpredictable switches between periods of good function and periods of poor function. People may experience a return of symptoms including tremor, stiffness, anxiety, depression, and pain.

Dopamine receptor agonists have direct action on striatal dopamine receptors; they do not depend on the functional abilities of the nigrostriatal neurons. Dopamine receptor agonists have duration of action longer than that of levodopa. They are used for prevention and treatment of motor disorders in

Parkinson's disease. Dopamine receptor agonists reduce a need for exogenous levodopa.

COMT inhibitors block peripheral conversation of levodopa to 3-*O*-methyl DOPA, increasing both the plasma $T_{1/2}$ of levodopa as well as the fraction of each dose that reaches the CNS. They reduce the "Wearing off" symptoms in patients with levodopa/carbidopa.

MAO inhibitors act on both isoemzymes MAO-A and MAO-B that are present in the periphery, and inactivate monoamines of intestinal origin. Two selective inhibitors MAO-B are used fot treatment of PD: *seleginine* and *rasagiline*. They inhibit breakdown of dopamine in the striatum, but do not inhibit peripheral metabolism of catecholamines and can be taken safely with levodopa in contrast to non-selective MAO inhibitors. They do not provide "cheese effect": when tyramine-rich foods (such as mature cheese, yeast extracts and fermented soya bean products, wine, pickled herring, broad bean pods) are ingested in conjunction with a monoamine oxidase inhibitor, tyramine is responsible for the so-called "cheese effect (syndrome)". The "cheese effect" is associated with the selective inhibition of MAO-A, the enzyme responsible for intraneuronal oxidation of noradrenaline, and may cause a dangerous rise in blood pressure. An early warning symptom may be a throbbing headache. A consequence of action of MAO-B inhibitors in the brain is a reduction in overal metabolism of dopamine, and as a result, a reduction in formation of toxic free radicals.

Table 55*. Drugs for Treatment of Parkinson Disease

Agent	Features of Pharmacokinetics	Adverse effects	Comments
Levodopa Formulations			
Carbidopa/levodopa; Carbidopa/levodopa sustained release; Carbidopa/levodopa orally disintegrating tablets	Peak of plasma concentration 0.5-2 hours; $T_{1/2}$ 1-3 hours; The duration of action 6-8 hours; Rate and extent of absorption depends on the rate of gastric emptying, the pH of gastric juice, the length of time the drug is exposed to the degradative enzymes of gastric and intestinal mucosa, competitors like dietary amino acids. More over levodopa and aromatic amino acids	Dyspeptic symptoms (nausea, vomiting, loss of appetite), orthostatic hypotension, arrhythmia, chronic and choreoathetoid hyperkinesis, psychotic and paranoid reactions, headache, blurred vision, and leukopenia, agranulocytosis, allergic reactions; "Wearing off" symptoms.	Levodopa is administered in combination with peripherally acting inhibitor of aromatic L-amino acid decarboxylase, such as carbidopa or benserazide, drugs that do not penetrate well into the CNS, to prevent decarboxylation by enzymes in the intestinal mucosa and in other peripheral sites. Inhibition of peripheral decarboxylase noticeably increases the fraction of levodopa that

	have the same membrane transporter to overcome the BBB for entry into the CNS. In the brain levodopa is converted to dopamine by decarboxylation first of all within the presynaptic terminals of dopaminergic neurons in the stratium.		remains unmetabolized and available to cross the BBB. In addition, dopamine release into the circulation by peripheral conversation of levodopa creates adverse effects, especially nausea and hypotension.
COMT Inhibitors			
Entacapone; Stalevo (combination entacapone with levodopa/carbidopa)	It has short action, and inhibits peripheral COMT.	Nausea, orthostatic hypotension, vivid dreams, confusion, and hallucinations	
Tolcapone	It has duration action, and inhibits both central and peripheral COMT.	Nausea, orthostatic hypotension, vivid dreams, confusion, and hallucinations; May be hepatotoxic.	Use only in patients not responding satisfactorily to other treatments. Requires monitoring of liver function.
Carbidopa/levodopa/ entacapone			
Dopamine Agonists			
Apomorphine	It penetrates the blood-brain barrier, as a result it has a central dopaminergic action.	May cause collaps, loss of consciousness (in case of the concomitant use with ondansetron), hallucinations, neurological disorders, allergic reactions, QT prolongation, injection-site reactions, dyskinesia, and abnormal behavior.	It has high affinity for D4 receptors, moderate affinity for D2, D3, D5 and adrenergic α_{1D}, α_{2B}, and α_{2C} receptors, and low affinity for D1 receptors. Apomorphine do not use for treatment PD due to nausea, vomiting, toxic effect on kidney. Trimethobenzamide (Tebamide, Tigan) is an antiemetic used to prevent nausea and vomiting. Apomorphine is FDA-approved as a “rescue

			therapy". Use only in patients not responding satisfactorily to other treatments.
Bromocriptine			Older agent.
Pergolide			Older agent. It was withdrawn from U.S. market in 2007 due to cardiac valve fibrosis.
Pramipexole Ropinirole	These are the newest agents. The duration of action 8-24 hours.	They cause hallucination, confusion, nausea, orthostatic hypotension, fatigue and somnolence, attacks of irresistible sleepiness.	They have selective activity at D2 class site (specifically at D2 and D3 receptors). Both are well absorbed orally and have similar therapeutic action.
Ropinirole sustained release			It is in a once-daily sustained release formulation, is more convenient and may reduce adverse effects related to intermittent dosing.
MAO Inhibitors			
Rasagiline	It is well absorbed from the GIT. Fat food slows the absorption of its.	*Often* - headaches, depression, dizziness, anorexia, convulsions, arthralgia, arthritis, pain in the neck, the vesicles bullous rash, contact dermatitis, stenocardia, flu-like symptoms, fever, leukopenia, rhinitis, weakness, conjunctivitis, acute disorders of the urinary system, allergic reactions; *rarely* - insufficiency of the cerebral circulation, skin carcinoma,	It reduces levodopa-related 'Wearing off' symptoms. It has a neuroprotective effect. Rasagiline at therapeutic doses does not block the metabolism of dietary biogenic amines (including tyramine) and therefore causes no tyramine-mediated hypertensive syndrome. It does not cause "tyramine syndrome", which allows patients to be used without restriction in the diet foodstuffs containing significant amounts of tyramine (including

		myocardial infarction; dyspeptic symptoms (nausea, vomiting, loss of appetite).	cheese, chocolate).
Selegiline	Metabolites of selegiline include amphetamine and methamphetamine, which may cause adverse effects.	Anxiety, insomnia due to metabolites; May be stupor, rigidity, agitation, and hypertermia when selegiline administered with the analgesic meperidine.	Orally disintegrating tablets (Zelapar), transdermal patch (Emsam) allow reducing hepatic first-pass metabolism and in this way limiting the formation of amphetamine metabolites. Selegiline may have antidepressant effects, especially at daily doses 20mg, and is under investigation for administration by transdermal patch.
Other Medications			
Trihexyphenidyl HCl (antimuscarinic agent: central M-, N-cholinolytic and peripheral M-cholinolytic)	Effect of the drug occurs within 1 hour after oral administration, and the maximum effect lasts for 2-3 hours, and the total duration of effect is 6-12 hours. After i/m injection it is absorbed within a few minutes, the effect develops after 5-10 minutes and lasts up to 12 hours.	Headache, irritability, delusions, hallucinations, mental disorientation (predominantly in patients with atherosclerosis); Effects due to the anticholinergic activity: dry mucous membranes of the mouth, visual impairment, increased intraocular pressure, constipation, difficulty urinating, and tachycardia.	Prescribe the drug with caution in patients older than 60 years because of increased sensitivity to the drug, the possibility of deterioration in memory and thinking. You should regularly monitor the intraocular pressure. Perhaps the development of drug dependence. During the period of treatment must be careful when driving and occupation of other potentially hazardous activities that require high concentration of attention and speed of psychomotor reactions.

	from the GIT. It passes through the BBB, placenta, into breast milk. T1/2 - is about 15 hours. It is excreted primarily by the kidneys unchanged.	Dizziness, insomnia, anxiety, irritability, blurred vision, agitation, tremor, seizures, visual hallucinations; heart failure, tachycardia, orthostatic hypotension; anorexia, nausea, dry mouth, dyspepsia; urinary retention in patients with benign prostatic hyperplasia, polyuria, nocturia, peripheral edema, dermatitis, the appearance of a bluish color of the skin of upper and lower limbs.	It is antiviral agent for prophylaxis and treatment of ingluenza A, but has antiparkinsonian activity.

* - adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12th edition. Medical. 2011. – 2084 P.

Table 56. Medicinal forms of the drugs for treatment Parkinson disease

INN	Trade names	Medicinal forms	
Levodopa	Avodopa, Bendopa, Bio-dopa, Brocadopa, Caldopa, Cicandopa, Dalutrin, Deadopa, Dopacin, Dopaflex, Dopal, Doparkin, Dopastral, Doprin, Eldopar, Eurodopa, Larodopa, L-Dopa, Levopa, Le-vopar, Madopan, Medidopa, Oridopa, Pardopa, Parkidopa, Parmidin, Speciadopa, Tonodopa, Veldopa, others	Tablets; Capsules	0.25; 0.5
Carbidopa/levodopa	Parcopa	Tablets	25/100 mg, 10/100 mg, 25/125 mg
Entacapone	Comtan, Comtess	Tablets	0.2
Entacapone with levodopa/carbidopa: levodopa/carbidopa/ entacapone	Stalevo	Tablets	50/12.5/200 mg, 75/18.75/200 mg, 100/25/200 mg,

			125/31.5/200 mg, 150/37.5/200 mg, 175/43.75/200 mg, 200/50/200 mg
Tolcapone	Tasmar	Tablets	0.1
Apomorphine	Apokyn, Ixense, Spontane, Uprima	Powder Parenteral solution (s/c) in aqmpouls Powder in gelatine capsules	 1% - 1 ml; 0.01, 0.02, 0.03, 0.04, 0.06
Bromocriptine	Aberginum, Bromergon, Bromocriptinum mesilat, Lactodel, Parlodel, Pravidel, Serocriptine	Tablets Capsules	0.0025, 0.004, 0.01; 0.005, 0.01
Pergolide	Permax	Tablets as mesilate	50, 250 micrograms, 0.001
Pramipexole	Mirapexin, Mirapex, Mirapexin prolonged release		180, 350, 700 micrograms; 260, 520 micrograms, 1.05 mg, 1.57 mg, 2.1 mg, 2.62 mg, 3.15 mg
Ropinirole Ropinirole sustained release	Requip, Adartrel, Requip XL	Tablets as hydrochloride	0.25, 0.5, 0.001, 0.002, 0.005, 0.002, 0.004, 0.008
Selegiline hydrochloride	Eldepryl, Emsam, Zelapar	Tablets	0.005, 0.01
Rasagiline	Azilect	Tablets as mesilate	0.001
Trihexyphenidyl HCl	Artane, Apo-Trihex, Parkin, Pacitane, Benzhexol, Anti-Spas, Antitrem, Aparkan, Benzhexol hydrochoride, Pacitane, Parkan, Parkinsan, Parkopan, Peragit, Pipanol, Romparkin, Tremin, Trihetphenidili hydrochloridum, Trihexyphenidyl hydrochloride, Triphenidyl, Trixyl, Cyclodolum, etc.	Tablets	0.001, 0.002, 0.005
Amantadine	Symmetrel, Midantan, PK-Merz	Film-coated tablets	0.1, 0.2

Chapter 18. Sedative drugs

Sedative drugs – are those that have a mild sedative effect by strengthening the processes of inhibition in the CNS in dose-dependent fashion. In comparison with the antipsychotics and tranquilizers they do not cause muscle relaxation, ataxia, decreased muscle activity, drowsiness, drug dependence and are widely used in clinical practice. Sedatives reduce activity, excitation of medium and mild degree, and cause calm of patients.

Classification of Sedative drugs

I. Plant origin medications: preparations of *Valeriana L.*, preparations of *Leonurus L.*, preparations of *Polemonium coeruleum L.* , preparations of *Paeonia L., and combined drugs:* Valocordin, Valoserdin, Novo-passit, Corvalol, Corvaldin, etc.

II. Bromides: sodium bromide, potassium bromide, bromcamphora.

Bromine is an antagonist of chlorine in human body. It has good absorption from GIT mucosa and is distributed primarily in body fluids including blood plasma**.** Bromine quantity in the cells of the body is small. Bromine excretion is through kidney, sweat glands and GIT. $T_{1/2}$ is about 2 weeks.

Pharmacological effects of Bromides:

sedative
increase the threshold of brain excitement
restoration of of reflex activity in cases of its violation

Indications for Bromides use:

neurosis
convulsion in patients with epilepsy, chorea, laryngism and other pathological spasmodic states

The treatment begins from little doses with a gradual increase and reduction of the salt intake.

Contraindications for Bromides use:

idiosyncrasy
heart insufficiency
kidney diseases
expressed atherosclerosis
anemia
eczematous, bullous skin rash

Adverse effects of Bromides use:

bromism
Acne-form dermatitis and other forms of skin disease may also be seen, as well as mucous hypersecretion in the lungs. Asthma and rhinitis may worsen. Rarely, tongue disorder, bad breath and obstipation occur. ***Bromism.*** Symptomes: running nose, cough, conjunctivitis, weakness, ataxia, reducing memory, acne bromica, depression, lethargy, somnolence, loss of appetite and cachexia, exicosis, loss of reflexes or pathologic reflexes, clonic seizures, tremor, loss of neural sensitivity, paresis, cerebral edema with associated

headache and papilledema of the eyes, delirium: confusion, abnormal speech, loss of concentration and memory, aggressiveness and psychosis.

Antidote of Bromides – NaCl.

Table 57. Medicinal forms of Sedative drugs

INN	Trade names	Medicinal forms	
Sodium bromide	Natrium bromatum, Natrii bromidum	Powder; Tablets; Peroral solution cum sirupo fructuario in flacons; Parenteral solution (i/v) in ampoules	0.15; 0.5; 1%, 2%, 3% - 100ml; 5%, 10%, 20% - 5ml, 10ml
Potassium bromide	Kalii bromidum	Powder; Tablets; Peroral solution cum sirupo fructuario in flacons	0.05; 0.1; 1% - 100ml
Bromcamphora	Camphora monobromata	Tablets	0.15; 0.25
Rhizoma cum radicibus Valerianae		Species	
Valerian		Tinctura in flacons	25ml, 30ml, 40ml
Leonurus		Tinctura in flacons	25ml
Menthae piperitae oleum + Phenobarbital + Humuli lupuli cones oleum + Ethylbromizovalerionate	Valocordin	Peroral solution in flacons	25ml
Origani herba + Menthae piperitae oleum + Phenobarbital + Ethylbromizovalerionate	Valoserdin	Peroral solution in flacons	25ml
Guaifenesin and extracts of hawthorn, hops, St. John's wort, lemon balm, passionflower, valerian and elderberry	Novo-passit	Tablets; Peroral solution in flacons	100ml
Menthae piperitae oleum + Phenobarbital + Ethylbromisovalerinate	Corvalol	Peroral solution in flacons	25ml
Ethylbromisovalerinate + Phenobarbital + Menthae piperitae oleum + Humuli lupuli oleum	Corvaldin	Peroral solution in flacons	25ml

Chapter 19. Antidepressants

Antidepressant drugs – are used for trearment depression. In accordance with the **mechanism of action**, all antidepressants are divided into first and second generation. The most widely used modern drugs are *second-generation antidepressants*, namely: selective serotonine reuptake inhibitors (SSRIs), serotonine-norepinephrine reuptake inhibitors (SNRIs), selective norepinephrine reuptake inhibitors (SNRIs). Reuptake of transmitter in monoamine system is the main mechanism of action by which neurotransmission is interrupted, thus inhibition of this reuptake can promote neurotransmission, apparently by deceleration clearance of the transmitter from the synapse and prolonging the dwell-time of the transmitter in the synapse. Besides, reuptake inhibitors hamper either Se, the neuronal Se transporter - 5-HT; NE, the neuronal NE transporter or both. In a like manner, the *first generation antidepressants* include monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). They also promote neurotransmission by inhibiting monoamine metabolism and thereby facilitating neurotransmitter storage in secretory granules, TCAs by inhibiting 5-HT and NE reuptake. These first generation agents manifest adverse effects and drugs and food interactions that limit their use in the current treatment.

In general, antidepressants enhance serotoninergic and noradrenergic transmission; they evoke adaptive or regulatory mechanisms to improve the effectiveness of therapy; increase density or sensitivity of adrenergic or serotoninergic receptors, receptor-G-protein coupling and cyclic nucleotide signaling; cause induction of neurotrophic factors, and contribute neurogenesis in the hippocampus.

Unfortunately, neither earlier theories of the mechanisms of antidepressant action nor current theories have yet led to new antidepressant treatments. Nevertheless, the potential targets for elaboration of the new antidepressants may be glutamate, neurokinin, corticotropin releasing hormone receptors, cyclic nucleotide pohosphodiesterases.

All antidepressants have “therapeutic lag” lasting 3-4 weeks before therapeutic response. But, if given antidepressant is not effective after 8-week trial in an adequate dose it should be switched to another antidepressant with different mechanism of action.

The metabolism of most antidepressants is mediated by hepatic CYPs.

Classification of antidepressants

I. Monoamine oxidase inhibitors (MAOIs):

Nonselective inhibitors of MAO-A and MAO-B (Irreversible action):

Nialamide

Selective inhibitors of MAO-A (Reversible action):

Pyrazidol

Tetrindole (Hexahydrocyclohexilpyrazynocarbazol)

Metralindol
Moclobemide
Befol
Feprosidnin

II. Monoamine reuptake inhibitors:

Nonselective monoamine reuptake inhibitors (tricyclic antidepressants):

Tertiary amine tricyclic antidepressants:

Imipramine
Clomipramine
Amitriptyline
Trimipramine
Doxepine

Secondary amine tricyclic antidepressants:

Maprotiline
Amoxapine
Nortriptyline
Protriptyline
Desipramine

Particular tricyclic antidepressants:

Pipofezine
Fluacizine

Selective norepinephrine reuptake inhibitors (NRIs):

Reboxetine
Viloxazine
Atomoxetine

Selective serotonine reuptake inhibitors (SSRIs):

Fluoxetine
Fluvoxamine
Sertraline
Paroxetine
Citalopram

Serotonine-norepinephrine reuptake inhibitors (SNRIs):

Milnacipran
Venlafaxine
Duloxetine

III. Selective serotonin reuptake enhancer (SSRE):

Tianeptine

IV. Atypical antidepressants:

Trazodone
Nefazodone
Mirtazapine

Mianserin
Atomoxetine
Bupropion
Duloxetine

V. Miscellaneous preparations:

Hyperici perforati herbae extract (Negrustin, Deprim)

The main pharmacological effects:

Antidepressive
Anticholinergic
Antihistaminic
Antidiuretic
Sedative/stimulanting
Anxiolytic
Analgesic

Indications: Antidepressants are drugs used for the treatment of depression. Despite their name, they are often used to treat a wide range of other conditions, *on-* or *off-label*, such as:

Anxiety disorders
Obsessive compulsive disorder
Eating disorders
Chronic pain, neuropathic pain
Some hormone-mediated disorders such as dysmenorrhea
Snoring
Migraines
Attention-deficit hyperactivity disorder
Substance abuse
Occasionally even insomnia or other sleep disorders

Antidepressants can be used both alone or in combination with other medications.

Features of Antidepressant Adverse effects:

"Therapeutic lag" phenomenon –is a delay of therapeutic response to antidepressant treatment

"Switch" phenomenon – is the transition from a depressed episode to a manic or hypomanic episode in patients receiving antidepressants and emergence of bipolar illness; SSRIs, Nialamide and Bupropion may be somewhat less likely to induce "switch" phenomenon that other antidepressants

Antidepressants are considered as indirect risk factor of suicidal ideation or suicide attempts and self-injurious behavior; FDA has a issued "black box" caution especially about the use of SSRIs, and some other antidepressants in children and adolescents

"Cheese" syndrome (tyramine, or serotonin syndrome): to avoid the development of "cheese" syndrome during treatment by *Nonselective*

monoamine reuptake inhibitors (tricyclic antidepressants) should be excluded from the diet the food containing tyramine, including cheese, cream, coffee, beer, wine, smoked food

Nonselective monoamine reuptake inhibitors (tricyclic antidepressants) may have antihistamine effects, sedative, analgesic, and antiparkinsonian effects, weight gain, quinidine-like effects on cardiac conduction, hepatotoxicity

Tricyclic antidepressants may cause headache, nausea, dizziness, sweating, tachycardia, cognitive dulling, blurred vision, dry mouth, constipation, difficulty urinating (adverse effects mediated by antagonism of muscarinic acetylcholine receptors); antagonism of α1 adrenergic receptors contributes to ortostatic hypotension and sedation

Anticholinergic effects: *disturbance* of accommodation, dry mouth, urinary retention, confusion, etc.

Tolerance

Withdrawal syndrome; dizziness, headache, nervousness, nausea, insomnia

Addiction to medication

Antidepressants lower the seizure threshold

SNRIs *venlafaxine* in high doses can induce sustained diastolic hypertension

SSRIs may cause dyspepsia, diarrhea, anorexia, emesis – as a result of stimulation of CNS and peripheral 5-HT3 receptors; sweating, headache, insomnia, anxiety, irritability, tremor, impotention, decreased libido, sexual dysfunction (erectile dysfunction, anorgasmia, ejaculatory delay) – due to excessive stimulation of brain 5-HT2 receptors; in case of continued treatment may be dullness of intellectual abilities and concentration

Using neuronal serotonin reuptake inhibitors with tricyclic antidepressants may develop a "serotonin syndrome"

Serotonin Receptor Antagonists (Atypical Antidepressants) mirtazapine may elicit somnolence, increased appetite, weight gain, and rarely – agranulocytosis; *trazodone* use is associated with priapism; nefazodone may cause liver failure; *bupropion* in high doses may cause seizures

MAOI use is associated with hypertensive crisis resulting from food or drug interactions

It is difficult to distinguish the adverse effects of antidepressants from symptoms of depression

Contraindications:

Glaucoma

Prostate hypertrophy

Atherosclerosis

Infection diseases

Tuberculosis in active phase

Liver, kidney and heart insufficiency

Diseases of hematopoietic system

Pregnancy

Cerebral blood circulation insufficiency

Arterial hypotension
Idiosyncrasy
Convulsive syndrome, epilepsy

Peculiar properties of SSRIs:

SSRIs treatment causes stimulation of 5-HT1A and 5-HT7 autoreceptors on cell bodies in the raphe nucleus and 5-HT1D autoreceptors on serotoninergic terminals, and this reduces serotonin synthesis and release toward pre-drug levels.

With repeated treatment with SSRIs, there is a gradual down-regulation and desensitization of these autoreceptor mechanisms

Down-regulation of postsynaptic 5-HT2A receptors may contribute to antidepressant efficacy directly or by influencing the function of noradrenergic and other neurons via serotoninergic heteroreceptors

Other postsynaptic 5-HT receptors remain responsive to increased synaptic concentration of 5-HT and contribute to the therapeutic effects of the SSRIs

SSRIs do not block histamine receptors

FDA has approved *fluvoxamine* for treatment of obsessive-compulsive disorder and social anxiety disorder, but not depression

citalopram is labeled for the use in premenstrual dysphoric disorder

SSRIs are used for preventing vasovagal symptoms in post-menopausal women

SSRIs are more effective and safer in overdose than TCAs

SSRIs have affected a broad range of psychiatric, behavioral, and medical conditions, for which they are used, on and off label

they are effective in treating major depression

SSRIs demonstrate the effectiveness in the treatment of generalized anxiety, panic, social anxiety and obsessive-compulsive disorder

Setraline and *paroxetine* nave been approved for treatment of posttraumatic strees disorder

There is no strong relationship between SSRI serum concentration and therapeutic efficacy

CYP2D6 is involved in the metabolism of most SSRIs and the SSRIs are at least moderately potent inhibitors of this isoenzyme. This is very important for drug interactions.

Peculiar properties of SNRIs:

SNRIs with non-tricyclic structure have been approved for treatment of depression, anxiety disorders and pain: *venlafaxine* and its demethylated metabolite, *desvenlafaxine*; *duloxetine*; and *milnacipran*

Duloxetine – off-label uses include stress urinary incontinence, autism, binge eating disoders, hot flashes, pain syndromes (fibromyalgia and neuropathic pain associated with peripheral neuropathy), premenstrual dysphoric disorders; it is used in the treatment of depression and anxiety,

Venlafaxine is most effective drug for preventing vasovagal symptoms in postmenopausal women, and is used in posttraumatic stress disorders

SNRIs are eliminated by hepatic metabolism and by renal excretion.

Serotonin Receptor Antagonists of 5-HT2 family of receptors (Atypical Antidepressants): *trazodone, nefazodone, mirtazapine, mianserin are* effective antidepressants.

Trazodone blocks 5-HT2 and α1 adrenergic receptors, and also inhibits the serotonin transporter

Trazodone have been used widely both alone and concurrently with SSRIs or SNRIs to treat insomnia, depression

Mianserin and mirtazapine potently block histamine H1 receptors, and also have some affinity for α2 adrenergic receptors, 5-HT2A, 5-HT2C, 5-HT3 receptors

Mianserin and mirtazapine are used as sedating and for treatment of the depressed patients with insomnia.

Clearance of Serotonin Receptor Antagonists is decreased in the elderly and in patients with renal or hepatic impairment.

Others Atypical Antidepressants: *bupropion* acts via multiple mechanisms. It is reuptake inhibitor of both NE and D which leads to enhancement of noradrenergic and dopaminergic neurotransmission. *Bupropion* is indicated for the treatment of depression, prevention of seasonal depressive disorder, and as a smoking cessation treatment. Bupropion has effects on sleep EEG. *Bupropion* may improve symptoms of attention deficit hyperactivity and has been used off-label for neuropathic pain and weight loss. This drug is widely used in combination with SSRIs to reach a greater antidepressant response. The elimination of *bupropion* involves both hepatic and renal routes.

TCAs cause serious side effects, but have established value for treatment of major depression. Tertiary amine TCAs have been used for treating insomnia and a variety of pain conditions. Majority of TCAs also block H1, 5-HT2, α1, and muscarinic receptors. One TCA, *amoxapine*, also is dopaminergic receptor antagonist and may elicit extrapyramidal side effect such as tardive dyskinesia. TCAs are largely eliminated by hepatic CYPs. About 76% of patients metabolize TCAs slowly due to variant CYP2D6 isoenzyme.

MAOIs are rarely used because of their toxicity and major drug and food interactions. MAOIs are metabolized by acetylation. A significant part of population is “slow acetylators”. Foods containing tyramine are a contributing factor. MAO-A within the intestinal wall and MAO-A and MAO-B in the liver degrade dietary tyramine. In case of inhibition of MAO-A the ingestion of cheeses, red wines, sauerkraut, fava beans, and other tyramine-containing foods leads to accumulation of tyramine in adrenergic nerve endings and neurotransmitter vesicles and induces NE and Ep release. The released catecholamines stimulate postsynaptic receptors in the periphery, increasing blood pressure. Thereby, the transdermal patch is better tolerated end safer.

Table 58*. Antidepressants: INN, Amine effects, adverse effects

INN	Amine effects	Adverse effects								
		Agitation	***Seizures***	***Sedation***	***Hypo-tension***	***Anti-cholinergic effects***	***GI effects***	***Weith gain***	***Sexual effects***	***Cardiac effects***
Monoamine oxidase inhibitors (MAOIs):										
Nonselective monoamine oxidase (MAO-A and MAO-B) inhibitors										
Nialamide		3+	0	0	2+	3+	2+	3+	2+	2+
Selective monoamine oxidase (MAO-A) inhibitors										
Pyrazidol		+/-	0	+/-	0	0	2+	0	0	+
Tetrindole	inhibitor of deamination of Se and NE	3+				0		0		
Metralindol	NE-, Se-ergic activator	3+	0	0	0/+	0	2+	0	0	+
Moclobemide** Befol	inhibits the destruction of NE and Se, a lesser degree, D	3+ 3+	0 0	0 0	hyper-tension	0 0	2+ 0	0 0	0 0	0 0
	concentration of monoamine neurotransmitters in the CNS									
Feprosidnin	enhances NE and Ep action	3+	0	paradoxical sedative effect	hyper-tension	2+	2+	0	0	+

Monoamine reuptake inhibitors:										
Nonselective monoamine reuptake inhibitors (tricyclic antidepressants):										
Tertiary amine tricyclic antidepressants:										
Imipramine	NE, Se	0/+	2+	2+	2+	2+	0/+	2+	2+	3+
Clomipramine	NE, Se	0	3+	2+	2+	3+	+	2+	3+	3+
Amitriptyline	NE, Se	0	2+	3+	3+	3+	0/+	2+	2+	3+
Trimipramine	NE, Se	0	2+	3+	2+	3+	0/+	2+	2+	3+
Doxepine	NE, Se	0	2+	3+	2+	2+	0/+	2+	2+	3+
Secondary amine tricyclic antidepressants:										
Maprotiline	NE	0/+	3+	2+	2+	2+	0/+	+	2+	2+
Amoxapine	NE, D	0	2+	+	2+	+	0/+	+	2+	2+
Nortriptyline	NE	0	+	+	+	+	0/+	+	2+	2+
Protriptyline	NE	2+	2+	0/+	+	2+	0/+	+	2+	3+
Desipramine	NE	+	+	0/+	+	+	0/+	+	2+	2+
Particular tricyclic antidepressants:										
Pipofezine	inhibits the NE and Se reuptake	0	0	2+	0	0	0	0	0	0
Fluacizine		0	0	2+	2+	3+	+	0	0	0
Selective norepinephrine reuptake inhibitors (NRIs):										
Reboxetine	NE	2+	2+	0	2+	+	0	0	2+	2+
Viloxazine	NE	+	+	0	hyper-tension	+	0	0	0	2+
Atomoxetine	NE	0	0	3+	hyper-tension	2+	2+	weight loss	2+	+
Selective serotonine reuptake inhibitors (SSRIs):										
Fluoxetine	Se	+	0/+	0/+	0	0	3+	0/+	3+	0/+
Fluvoxamine	Se	0	0	0/+	0	0	3+	0	3+	0
Sertraline	Se	+	0	0/+	0	0	3+	0	3+	0

Paroxetine	Se	+	0	0/+	0	0/+	3+	0	3+	0
Citalopram	Se	0/+	0	0/+	0	0	3+	0	3+	0
Escitalopram	Se	0/+	0	0/+	0	0	3+	0	3+	0
Serotonine-norepinephrine reuptake inhibitors (SNRIs):										
Milnacipran	NE, Se	2+	2+	0	hyper-tension	2+	0	0	0	2+
Venlafaxine	Se, NE	0/+	0	0	0	0	3+	0	3+	0/+
Duloxetine	Se, NE, D	0/+	0	0	2+	2+	2+	weight loss	2+	2+
Selective serotonin reuptake enhancer (SSRE):										
Tianeptine	Se	0	0	0/+	0/+	0/+	0/+	0	0	0/+
Atypical antidepressants:										
Trazodone	Se	0	0	3+	0	0	2+	+	+	0/+
Nefazodone	Se	0	0	3+	0	0	2+	0/+	0/+	0/+
Mirtazapine	Se, NE	0	0	4+	0/+	0	0/+	0/+	0	0
Mianserin		0	0	2+	2+	0	0	0	0	0
Atomoxetine	NE	0	0	0	0	0	0/+	0	0	0
Bupropion	D, NE	3+	4+	0	0	0	2+	0	0	0
Duloxetine	NE, Se	+	0	0/+	0/+	0	0/+	0/+	0/+	0/+
Miscellaneous preparations:										
Hyperici perforati herbae extract	Se, D, NE, GABA, glutaminic acid	0	0	2+	0	+	+	0	0	0

* - adopted from Goodman & Gilman's The Pharmacological Bases of THERAPEUTICS. 12 edition. Medical. 2011. – 2084 P. with autor's changes and additions

** - it is not approved for use in U.S.

0 negligible; 0/+ minimal; + mild; 2+ moderate; 3+ moderately severe; 4+ severe; +/- agitation (activating effect) in patients with apathetic, anergic depression and sedation in patients with agitated states

Table 59. Medicinal forms of Antidepressants

INN	Trade names	Medicinal forms	
Nialamide	Espril, Nialamide, Niamid, Niaquitil, Nuredal, Nyazin, Psicodisten, etc.	Tablets	0.025
Pirlindole	Lifril, Pyrazidol	Tablets	0.025 0.05
Hexahydrocycloh exilpyrazynocarb azol	Tetrindole	Tablets	0.025 0.05
Metralindol	Inkazan	Tablets; Parenteral solution in ampules (i/m, i/v)	0.025; 1.25% - 2 ml, 10 ml
Moclobemide	Amira, Aurorix, Clobemix, Depnil, Manerix, Clorix	Tablets	0.15, 0.3
Befol		Tablets; Parenteral solution in ampules (i/v)	0.01, 0.025; 0,25% - 2 ml
Feprosidnin	Sydnophen	Tablets	0.005
Imipramine	Tofranil, Melipramine, Antideprin, Depranil, Deprimin, Deprinol, Depsonil, Dynaprin, Eupramin, Imipramil, Impramine, Impril, Irmin, Melipramin, Norfanil, Novopramine, Pryleugan, Surplix, Tofranil, etc.	Tablets; Parenteral solution in ampules (i/m)	0.01, 0.025, 0.05, 0.075; 1.25% - 2 ml
Clomipramine	Anafranil, Chlorimipramine, Clofranil, Clominal, Hydiphen, Klomipramin, Monochlorimipramine, Neoprex	Tablets; Tablets retard; Dragee; Parenteral solution in ampules (i/m, i/v)	0.01, 0.025; 0.075; 0.025; 1.25% - 2 ml
Opipramol	Dinsidon, Insidon, Opramol, Oprimol, Pramolan	Dragee	0.05
Amitriptyline	Elavil, Damileni maleinas, Adepril, Amineurin, Amiprin, Amirol, Amizol, Apo-Amitriptylin, Atryptal, Daprimen, Elatral, Elavil, Elivel, Enovil, Lantron, Laroxal, Laroxyl, Lentizol, Proheptadien, Redomex, Saroten, Sarotex, Teperin, Triptizol, Triptopol, Triptyl, Tryptanol, Tryptizol, etc.	Tablets; Capsules retard; Parenteral solution in ampules (i/m, i/v); Capsules	0.01, 0.025, 0.05, 0.075; 0.025, 0.05; 1%-2 ml; 0.05
Pipofezine	Aza-xazin, Dizaphenum	Tablets	0.025
Fluacizine	Phthoracizinum	Tablets; Parenteral solution in ampules (i/m)	0.01, 0,025; 1.25% - 1 ml

Maprotiline	Ladiomil, Ludiomil, Ludionil, Maprotibene	Dragee; Parenteral solution in ampules (i/m, i/v)	0.01, 0.025, 0.05, 0.075; 0.5% - 5 ml
Doxepine	Sinequan	Capsules	0.01, 0.025
Reboxetine	Edronax	Tablets	0.002, 0.004
Fluoxetine	Deprenon, Deprex, Floxet, Fludac, Flunat, Fluval, Fluxonil, Framex, Oxedep, Portal, Prodel, Prodep, Prozac	Capsules; Tablets	0.01, 0.02; 0.01, 0.02
Fluvoxamine	Avoxin, Fevarin, Floxyfral, Myroxim	Tablets	0.05, 0.1
Sertraline	Zoloft, Lustral	Tablets	0.05, 0.1
Paroxetine	Paxil, Rexetin	Tablets	0.02
Citalopram	Cipral, Cipramil, Lupram, Sepram	Tablets	0.02, 0.04
Trazodone	Azona, Beneficat, Bi-maran, Desyrel, Geripax, Menegan, Molipaxin, Pragmarel, Pragmazine, Sideril, Thombran, Tramensan, Trazolan, Trazone, Tresin, Trittico	Capsules; Tablets retard; Parenteral solution in ampules (i/m, i/v)	0.025, 0.05, 0.1; 0.075, 0.15; 1% - 5 ml
Milnacipran	Ixel, Savella, Dalcipran, Toledomin	Capsules	0.025, 0.05
Venlafaxine	Efevelon, Velafax, Velaxin, Velaxor, Effexor	Tablets; Capsules	0.025, 0.0375, 0.05, 0.075; 0.075, 0.15
Duloxetine	Cymbalta, Yentreve	Capsules	0.06, 0.12
Mirtazapine	Mirzaten, Remeron	Tablets	0.015, 0.03, 0.045
Tianeptine	Stablon, Coaxil, Tatinol	Tablets	0.0125
Mianserin	Bolvidon, Lerivon, Miansan, Norial, Tolvin, Tolvon	Tablets	0.01, 0.03
Herba Hyperici	Negrustin, Helarium Hypericum, Doppelherz® Nervotonik	Capsules	0.425
Hyperici perforate herbae extract	Deprim	Tablets	0.06

Chapter 20. Psychomotor stimulants

Psychomotor stimulants stimulate CNS, cause excitement and euphoria, decrease feeling of fatigue, and increase motor activity.

Classification of Psychomotor stimulants accordingly chemical structure

Methylxanthines:
Caffeine
Caffeine end sodium benzoate
Phenylalkylamines derivatives:
Amphetamine, α-methylphenethylamine
Sydnonimine derivatives:
Mesocarb
Piperidine derivatives:
Methylphenidate

Mechanism of action of Psychomotor stimulants.

There are several mechanisms of action of ***Methylxanthine*** **–** *caffeine*, including translocation of extracellular calcium, increase in cyclic adenosine monophosphate and cyclic guanosine monophosphate caused by the inhibition of phosphodiesterase and blockade of adenosine receptors.

The effects of ***Phenylalkylamines derivative*** **–** *amphetamine* on CNC and peripheral nervous system are indirect, and both depend upon an elevation of the level of catecholamine neurotransmitters in synaptic spaces. Amphetamine achieves this effect by releasing intracellular stores of catecholamines, and also inhibits MAO that leads to high level of catecholamines that are readily released into synaptic spaces. Amphetamine has stronger effect on dopaminergic brain structures than noradrenergic.

Sydnonimine derivative **–** *mesocarb* has stronger effect on noradrenergic brain structures than dopaminergic, facilitating the release of norepinephrine from stable depot, and also inhibits MAO, but it does not have peripheral adrenomimetic effects.

Piperidine derivative **–** *methylphenidate* has CNS stimulant properties similar to those of *amphetamine* and may also lead to abuse, although its addictive potential is controversial. Methylphenidate is a more potent dopamine transport inhibitor thus making more dopamine available.

Pharmacological effects:

Stimulant effect on CNS
Hypertensive *(caffeine, amphetamine)*
Thymoleptic (*mesocarb*)
Weakening of the action of drugs that depress CNS (hypnotics, sedatives, tranquilizers, alcohol, etc.)

Analeptic
Cardiostimulant
Decreasing of stomach secretion
Increasing of diuresis
Improving of glycogenolysis, lipolysis *(caffeine)*
Anorexia

Indications:

For the increasing of mental and physical performance
Migraine *(caffeine)*
Nocturnal enuresis, or nighttime urinary incontinence *(caffeine, mesocarb)*
Narcolepsy, or hypersomnia *(caffeine, amphetamine)*
As a subsidiary drugs for treatment of apnea in children
For improvement of the effect of electroconvulsive therapy

Adverse effects:

Caffeine in moderate doses may cause insomnia, anxiety, and agitation; in high doses it may cause nausea, vomiting, and convulsions; the lethal doses (about 10 g – about 100 cups of coffee daily) induce cardiac arrhythmia, tachycardia; the consumption of 600 mg of caffeine (about six cups of coffee daily) may produce lethargy, irritability, and headache.

Amphetamine causes addiction, leading to psychological and physiological dependence, drug-seeking behavior; may develop tolerance to euphoric and anorectic (due to amphetamine action on lateral hypothalamic feeding center) effects in cause of its chronic use; amphetamine abusers often administer the drugs by i/v injection and by smoking; the euphoria caused by amphetamine lasts 4-6 hours. *Central effects:* insomnia, irritability, weakness, dizziness, tremor, hyperactive reflexes, confusion, delirium, panic states, suicidal tendencies. *Chronic amphetamine use* induces "amphetamine psychosis" – psychotic episodes associated with schizophrenia. *Cardiovascular effects:* palpitation, cardiac arrhythmias, hypertension, anginal pain, circulatory collapse; may be headache, chills, excessive sweating. *GIT effects:* anorexia, nausea, vomiting, abdominal cramps, diarrhea.

Mesocarb use may be associated with neuro-psychiatric disorders; it may cause headache, irritability, restlessness, insomnia, loss of appetite, anorexia, increased blood pressure, allergic reactions. In patients with pre-existing psychopathology mesocarb may induce aggravation of delusions and hallucinations.

Methylphenidate may cause abdominal pain and nausea; anorexia, insomnia, nervousness, and fever.

In case of a long-term using and/or a using in high doses of *Psychomotor stimulants* may be developed cardiomyopathy, arterial hypertension, psychotic reactions, impotence, weigh loss, confusion, increasing of tactile and pain sensitivity, tremor, tinnitus, convulsions.

Contraindications:

Increased excitement
Insomnia
Arterial hypertension and atherosclerosis
Organic diseases of cardiac and vessel system
Advanced age
Glaucoma
Phobia
Liver diseases
Alcoholism
Thyrotoxicosis
Epilepsy
Idiosyncrasy

Features of psychomotor stimulants

Caffeine act on *CNS*: stimulates cortex and other areas of the brain that leads to decline in fatigue, increases the mental activity. This effect of *caffeine* is manifested in case of the use of two cups of coffee (100-200 mg daily). Consumption of 1.5 g of *caffeine* (12-15 cups of coffee daily) induces anxiety and tremors. Very high dose of *caffeine* (2-5 g daily) causes stimulation of spinal cord. The stimulating effects of *caffeine* are inherent in the rapid development of tolerance, and withdrawal syndrome is accompanied by fatigue and sedation. Acting on the *cardiovascular system*, *caffeine* causes positive inotropic and chronotropic effects, that may be dangerous to the patients with IHD and may result in premature ventricular contractions. Caffeine has diuretic action due to increase urinary output of sodium, chloride, and potassium. Caffeine stimulates secretion of hydrocholic acid from gastric mucosa. This drug and its derivatives relax the smooth muscles of the bronchioles. Caffeine crosses BBB, PB and is secreted into the mother's milk, it is metabolized in the liver by CYPA2 pathway, and it is excreted in the urine.

Amphetamine is a noncatecholaminergic sympathetic amine. This drug has D and NE release-enhancing properties. *Amphetamine* stimulates the entire cerebrospinal axis, cortex, brainstem, and medulla oblongata, this leads to elevate alertness, decreased fatigue, depressed appetite, and insomnia. *Amphetamine* acts on adrenergic system: indirectly stimulates adrenergic receptors through NE release. The side effects of this drug limit the use of it. *Amphetamine* is absorbed from GIT, metabolized by the liver, and excreted in the urine. *Chlorpromazine* or *haloperidol* relieves the CNS symptoms of amphetamine overdoses as well as the hypertension through of their α-blocking effects. Administration of *sodium bicarbonate* will increase the reabsorption of *dextroamphetamine* from the renal tubules into the bloodstream.

Mesocarb stimulates noradrenergic and in less degree – dopaminergic transmission. Its action is developed gradually, not accompanied by severe euphoria and motor excitation. Mesocarb is well absorbed from GIT. Mesocarb is used for

treatment of asthenic conditions accompanied by lethargy, apathy, decreased performance, increased sleepiness, but also caused by antipsychotics and anxiolytics; hypochondria, stupor and stupor like conditions; asthenic-neurotic syndrome after undergoing intoxication, infection, trauma, physical and mental fatigue; sluggish schizophrenia, artificial exacerbation of schizophrenia (in order to overcome resistance to therapy psychotropic drugs), correction of side effects (muscle relaxation, drowsiness) caused an benzodiazepine anxiolytics; withdrawal syndrome in chronic alcoholism, adynamic depression; fatigue in mentally healthy people; mental retardation in children with adynamia, aspontaneity in organic diseases of CNS. Mesocarb cannot be used in patients with atherosclerosis, arterial hypertension, together with MAO-inhibitors and with TCAs, in pregnant women, and in case of idiosyncrasy.

Methylphenidate has stimulant effects similar to those of amphetamine and may induce abuse. This drug is widely used in children with attention deficit, hyperactivity disorder, and for the treatment of narcolepsy. *Methylphenidate* is absorbed from GIT and is excreted with urine. This drug increases the seizure frequency, especially in patients who take antidepressants. *Methylphenidate* is contraindicated in patients with glaucoma.

Table 60. Medicinal forms of Psychomotor stimulants

INN	Trade names	Medicinal forms	
Caffeine	Guaranin, Theinum	Powder for internal use	0.1
Caffeine sodium benzoate		Tablets for children; Tablets for adults; Solution for injection in ampules; Solution for injection in syrette (s/c)	0.075; 0.1, 0.2; 10% , 20% - 1 ml, 2 ml; 10%, 20% - 1ml
Amphetamine	Aktedrin, Alentol, Amfetamine, Amphamine, Amphedrine, Benzedrine sulfate, Benzopropamin, Euphodyn, Isoamin, Ortedrine, Psychedrinum, Psychoton, Racephen, Raphetamin, Sympamin, Sympatedrine, Phenaminum, etc.	Tablets	0.01
Mesocarb	Sidnocarb, Sydnocarb	Tablets	0.005, 0.01, 0.025
Methylphenidate	Centedrin, Rilatine	Tablets	0.01

Chapter 21. Analeptics

Analeptics – there are the drugs that at therapeutic doses restore weakened function of the vital centers of the medulla oblongata, ie respiratory and vasomotor.

Classification of Analeptics

I. By action type:

Analeptics of direct action:

Bemegride
Caffeine
Methylamide ethylilamidazolecarbonate

Analeptics of reflex action:

Lobeline
Cytisine
Almitrine
Solutio Ammonii caustici 10%

Analeptics of mixed action:

Niketamide
Sulfocamphoric acid + procaine (Sulfacamfocainum)
Pentylenetetrazol
Camphor

II. predominant action on certain areas CNS:

Cortex (caffeine)
Medulla oblongata (methylamide ethylilamidazolecarbonate, niketamide, Sulfacamfocainum, bemegride)
Spinal cord (strychnine)

Mechanism of action of Analeptics

Analeptics of direct action activate centers of medulla oblongata, especially respiratory center and vasomotor center through depression of GABA-A receptors.

Analeptics of reflex action stimulate chemoreceptors of carotid sinus, activate medulla oblongata centers.

Analeptics of mixed action have direct action on CNS and reflex action due to stimulation of chemoreceptors of carotid sinus and activation of medulla oblongata centers. Thus, *niketamide* directly activates vasomotor center of medulla oblongata, and by reflex it activates respiratory center of medulla oblongata as a result of stimulation of chemoreceptors of carotid sinus. *Sulfacamfocainum* directly excites the CNS, and especially the vital centers of the medulla oblongata: vasomotor and respiratory, and this drug acts also indirectly through carotid sinus. *Sulfacamfocainum* intensifies the exchange in the heart muscle; it increases sensitivity of the heart muscle to sympathetic influence resulting in its cardiotonic effect. Sulfacamfocainum has direct vasospastic effect in abdominal cavity that

lead to redistribution of blood, increasing of the veins tonus and a blood flow to the heart, intensification of blood circulation in heart, lungs and brain. Pentylenetetrazol arouses vasomotor and respiratory centers of medulla oblongata, stimulates respiration, and elevates BP, blood circulation, especially in the case of depression of the vital centers of the medulla oblongata. Pentylenetetrazol has not direct action on the heart and the vessels. In high doses this drug causes an excitement of the brain and spinal cord, it demonstrates "awaking" action in event of acute poisoning by hypnotics and narcotics, and pentylenetetrazol in high doses may elicit convulsions in virtue of its impact on motor zones of the brain and partially – due to its influence on spinal cord.

Pharmacological effects of Analeptics:

Incitation of vasomotor and respiratory centers of medulla oblongata *(all analeptics)*

Elevation of BP *(bemegride, niketamide, Sulfacamfocainum, pentylenetetrazol)*

Enhancement of myocardial contractility *(niketamide, caffeine, Sulfacamfocainum, pentylenetetrazol)*

Stimulation of CNS, antagonism with hypnotics *(bemegride, pentylenetetrazol),* opioid analgesics, alcohol and drugs for general anestesia *(bemegride, methylamide ethylilamidazolecarbonate, pentylenetetrazol)*

Antiphlogistic, antiallergic actions by the activation of pituitary functions *(methylamide ethylilamidazolecarbonate)*

stimulation of reflex function of spinal cord, increase of skeletal muscle tonus and smooth muscle tonus, improvement in visual acuity, taste, smelling, hearing, tactile sensitivity (strychnine)

The ability to cause seizures *(all analeptics)*

Indications for Analeptics:

Acute poisoning by hypnotics and narcotics *(bemegride, methylamide ethylilamidazolecarbonate, caffeine, pentylenetetrazol, niketamide)*

Acute and chronic violations of blood circulation (niketamide, caffeine, Sulfacamfocainum, pentylenetetrazol, cytisine)

Shock, collapse, asphyxia *(niketamide, cytisine, Sulfacamfocainum, methylamide ethylilamidazolecarbonate, pentylenetetrazol)*

Acute and chronic heart failure (Sulfacamfocainum, caffeine, pentylenetetrazol)

Respiratory insufficiency *(camphor, niketamide)*

Fetal asphyxia, newborn asphyxia (methylamide ethylilamidazolecarbonate, pentylenetetrazol)

Functional vision insufficiency, violation of vision, hearing, smelling; paralysis, paresis, gastrointestinal atony *(strychnine)*

Adverse effects of Analeptics:

Symptoms of CNS excitement, arterial hypertension, tremor, hyperventilation, arrhythmia, convulsion; in case of long-term action – tolerance, dyspepsia *(bemegride, methylamide ethylilamidazolecarbonate)*

Reduction of BP by procaine action *(Sulfacamfocainum)*

Vomiting, hyperemia of the face, clonic seizures, cardiac arrhythmia, local pain in place of injection *(niketamide)*

Increase of muscle tonus and difficulties of breathing and swallowing *(strychnine)*

In case of rapidly direction of *pentylenetetrazol* may be convulsions

Contraindications for Analeptics:

Sulfacamfocainum can not be used in patients with idiosyncrasy to procaine

Bemegride can not be used in patients with psychosis, psychomotor excitement, and epilepsy

Niketamide can not be used in patients with tendency to seizures

Pentylenetetrazol can not be used in patients with acute endocarditis, aortic aneurysm, and active tuberculosis

Methylamide ethylilamidazolecarbonate can not be used in patients with hypersensitivity to this drug, expressed CNS depression, motor and psychic excitement, poisonings with convulsive remedies, arterial hypertension, glaucoma, expressed atherosclerosis, circulatory and heart decompensation, in elderly people

Strychnine can not be used in patients with arterial hypertension, bronchial asthma, IHD, acute and chronic nephritis, hepatitis, tendency to seizures, thyrotoxicosis, in pregnant women

Cytisine can not be used in patients with acute ulcer disease of duodenum or/and stomach, organic diseases of heart and blood circulation

Table 61. Medicinal forms of Analeptics

INN	Trade names	Medicinal forms	
Camphor		Oil solution for injections (s/c)	20% - 1ml, 2 ml, 10 мл
Sulfocamphoric acid + procaine	Sulfacamfocainum	Solution for injections (i/v, i/m, s/c) in ampoules	10% - 2 ml
Niketamide	Anacardone, Cardiamidum, Coraethamidum, Coramin, Cormed, Corvitol, Corvoton, Nicethamidum, Nicorine, Nikethamide, Nikorin, Tonocard, etc.	Solution for injections (i/v, i/m, s/c) in ampules; Solution for injections (i/v, i/m, s/c) in syrette; Solution for peroral use in flacons	25% - 1 ml, 2 ml; 25% - 1 ml 25% - 15 ml, 30 ml
Bemegride	Ahypnon, Etimid, Eukraton, Glutamisol, Malysol, Megibal, Megimide, Methertharmide, Mikedimide, Zentraleptin	Solution for injections (i/v) in ampoules	0.5% - 10 ml
Almitrine	Armanor	Tablets	0.05
Caffeine	Guaranin, Theinum	Powder for peroral use	0.1
Caffeine		Powder, Tablets	0.1, 0.2; 0.075 - for

sodium benzoate		Solution for injections (s/c) in ampoules	children; 10%, 20% - 1 ml, 2 ml
Lobeline	Lobeton, Lobesilum	Solution for injections (i/v, i/m) in ampules and in syrette; Tablets	1% - 1 ml 0.002
Cytisine	Baptitoxine, Sophorine, Tabex	Solution for injections (i/v, i/m) in ampules; Tablets	0.15% - 1 ml; 1.5 mg
Solutio Ammonii caustici 10%	Нашатирний спирт	Solution in flacons; Solution in ampules for inhalation, for peroral use, for external use	10% - 10 ml, 40 ml, 100 ml, 10% - 1 ml
Methylamide ethylilamidazolecarbonate	Aethimizolum	Powder, Tablets; Solution for injections (i/v, i/m, s/c) in ampoules	0.1; 1% , 1.5% - 3 ml, 5 ml
Pentylenetetrazol	Cardiazol, Angiazol, Centrazol, Deumacar, Diovascol, Leptazol, Metrazol, Pentamethazolum, Pentazol, Pentetrazolum, Pentrazol, Phrenazole, Tetracor, etc.	Tablets; Solution for injections (i/v, i/m, s/c) in ampules	0.1; 10% - 1 ml
Strychnine	Strychninum nitricum	Solution for injections (s/c) in ampules; Peroral solution	0.1% - 1 ml

Currently, in the clinic, analeptics of reflex action *lobeline and cytisine* are applied as tablets for treatment of the patients with nicotine smoking addiction. They are **Lobesilum** and **Tabex.** They are N-cholinimimetics of reflex action and stimulate N-cholinergic receptors of vegetative ganglia and adrenal gland, and stimulate respiration and Ep excretion from adrenal medulla. Lobeline and cytisine have the mechanism of action similar as nicotine. *Adverse effects* may occur at the beginning of treatment. There are changes in taste and appetite, dry mouth, headache, dizziness, tremor, insomnia, increased irritability, myalgia, chest pain, abdominal pain, nausea, dyspepsia, tachycardia, a slight increase in BP, lower body weight, sweating. *Contraindications:* hypersensitivity to the drugs, IHD, cardiac arrhythmias, atherosclerosis, gastric and duodenal ulcer, pregnancy and lactation. *Overdose* of lobeline and cytisine has the symptoms of nicotine intoxication: nausea, vomiting, mydriasis (dilated pupils), weakness, tachycardia, clonic convulsions, and respiratory paralysis. Tabex and Lobesilum can greatly impair driving and other psychomotor skills.

Chapter 22. Nootropics (Cognitive enhancers)

Nootropics – the drugs that activate higher integrative brain function, improve intellection, memory, learning ability. Positive effect on higher nervous activity only occurs during prolonged applications (2-5 months). Nootropics are also referred to as smart drugs, memory enhancers, neuroenhancers, cognitive enhancers, and intelligence enhancers.

Mechanism of action of Nootropics connects with stimulation of GABA-A receptors and glutamate receptors, and with the increase of ATP synthesis, glucose utilization, improving of synaptic mediator processes, synthesis of RNA, proteins, membrane phospholipids. Nootropics are thought to work by altering the availability of the brain's supply of neurochemicals (neurotransmitters, enzymes, and hormones).

Classification of Nootropics

Pirolidone derivatives:
Piracetam
Etiracetam
Dupracetam
Aniracetam

GABA derivatives:
Acidum gamma-aminobutyricum Gamma-amino-beta-phenilbutirate hydrochloride (Phenybutum) Hopantenic acid
Nicotinoyl gamma-aminobutiric acid (Picamilonum)

Pirodoxine derivatives:
Pyritinol
Pyridoxine + Trionin (Biotredin)

Dimethylaminoethanol derivatives (predecessors of Ach):
Deanol aceglumate
Meclofenoxate

Cerebrovascular drugs:
Ginkgo Biloba

6. Neuropeptides and their analogs:
Metionil-glutamil-gistidil-fenilalanil-prolil-glicil-prolin (Semax)

Amino acids and substances that influence on the system of excitatory amino acids:
Aminoacetic acid (Glycine)

2-mercantobenzimidazole:
Ethylthiobenzymidazol hydrobromide (Bemithylum)

Vitamin-like substances:
Idebenone

Polypeptides:
Cerebrolysin

Substances of other pharmacological groups with nootropic component :
Correctors of brain blood circulation insufficiency:
Nicergoline
Vinpocetine
Xantinol nicotinate
Vincamine
Cinnarizine
Restorative substances and adaptogens :
Ginseng
Melatonin
Lecithin
Psychostimulators:
Sulbutiamine
Antihypoxants and antioxidants:
Ethylmethylhydroxypyridine succinate (Mexidolum)
Drugs of other groups:
Oxydate sodium

Pharmacological effects:

Nootropic: improvement of thinking, attention, language
Mnemotropny: enhancement of memory, learning
Raising the level of consciousness, mental clarity (impact on the oppressed consciousness and clouding of consciousness)
Adaptogenic: influence on tolerance to a variety of exogenous factors, including drugs, increasing overall resistance to the action of extreme factors
Antiasthenic: the impact of weakness, lethargy, exhaustion, mental and physical phenomena of fatigue
Psychogogic
Antidepressive
Sedative
Vegetative
Antikinetic
Antiparkinsonian
Antiepileptic
Hypoglycemic
Energetic action due to enhancing of glucose consumption by cells of the body
Increase of somatotropic hormone release
Anabolic
Lipolytic
Antitoxic
Immunostimulatory

At the core of the ***therapeutic action of nootropics*** are several mechanisms: improvement of the energy state of neurons (increased synthesis of ATP, anti-hypoxic and anti-oxidant effects); activation of the plastic processes in the CNS

due to increased synthesis of RNA and proteins; strengthening of the processes of synaptic transmission in the CNS; improvement of the glucose utilization; membrane-stabilizing action.

Indications:

Traumatic brain injury, stroke, chronic cerebral vascular disorders
Hypertension and atherosclerotic encephalopathy
Mental retardation in children, poor memory
Depression
Senile dementia
Abstinence
Alcohol poisoning
Hypoxic conditions
Open-angle glaucoma
Migraine
Stuttering, tics in children
Meniere's disease
Asthenia
Neuroses
Epilepsy
Parkinson disease

Adverse effects:

dizziness
tremor
nervousness
irritability
feeling of anxiety
sleep disorders
nausea
vomiting
dyspepsia
increased body temperature
fluctuations in blood pressure
allergic reaction

Contraindications:

the sharp increase in intracranial pressure
epileptic syndrome
hemorrhagic stroke
individual adverse reaction
pregnancy

Besides, some of the Nootropics have specific adverse reactions: *piracetam* is contraindicated in acute venous insufficiency in children with diabetes, it is not recommended for children under 1 year and acute renal failure. *Sodium oxybate* improper for hypokalemia, myasthenia gravis. Due to the sedative effect it should not be given during daylight hours to the patients whose work requires quick

physical and mental reactions. Hopantenic acid is contraindicated in severe acute kidney disease. Phenybutum is contraindicated in hepatic impairment. Pyritinol no need to appoint in case of psychomotor agitation, epilepsy, and increased convulsive readiness. Picamilonum is contraindicated in acute and chronic kidney disease.

Table 62. Medicinal forms of Nootropics

INN	Trade names	Medicinal forms	
Acidum gamma-aminobutyricum	Aminalonum, Apogamma, Encefalon, GABA, Gaballon, Gamarex, Gammalon, Gammaneuron, Gammar, Gammasol, Mielogen, Mielomade, etc.	Tablets	0.25
Piracetam	Braintop, Breinox, Cerebril, Cerebropan, Ceretran, Ciclo-cetam, Cintilan, Dinacel, Dinagen, Encefalux, Eumental, Euvifor, Fortineural, Gabacet, Gericetam, Lucetam, Memotropil, Mera-piran, Neutrofin, Noocebril, Noocefal, Nootropil, Normar-brain, Norotrop, Norzetam, Oikamid, Pirabene, Piracetam, Piramem, Piratam, Piratropil, Pirroxil, Pyramem, Stamin, Stimocartex, Stimubral, etc.	Capsules; Tablets for children; Tablets; Granules for syrup for children in jars; in packages; Peroral solution in flacons; Elixir for children in flacons; Parenteral solution for infusions in flacons; Parenteral solution (i/m, i/v) in ampoules, in flacons	0.4; 0.2; 0.4; 0.5, 0.8, 1.2; 56.0 (2.0); 2.8 (0.1); 20%, 33%-125 ml; 3.2%-118 ml; 4.8%-125 ml; 250 ml, 500 ml, 1000 ml; 20%-5 ml, 15 ml; 20%-60 ml
Oxydate sodium	Oxybate sodium, Sodium gamma-hydroxybutyrate	Parenteral solution (i/m, i/v) in ampoules; Syrup in flacons	20%-5 ml, 10 ml; 5%-400 ml
Gamma-amino-beta-phenilbutirate hydrochloride	Phenibutum	Tablets	0.25
Hopantenic acid	Calcium homopantothenat, Hopaten, Pantogamum	Tablets; Syrup in flacons	0.25, 0.5; 10%-50 ml, 100 ml
Nicotinoyl gamma-aminobutiric acid	Picamilonum	Tablets; Parenteral solution (i/m, i/v) in ampoules	0.01, 0.02 , 0.05; 5%, 10%-2 ml
Pyritinol	Biocephalin, Cefalogen, Cerebol, Cervitalin, Cogitan, Dipiridol, Enbol, Encefabol, Encefort, Encephabol, Encerebrovit,	Tablets; Dragee; Syrup in flacons	0.05, 0.1, 0.2; 0.1; 2%-200 ml

	Enerbol, Estisol, Neurotin, Neuroxin, Piritinol, Psicobolin, Pyrithioxin, Pyritinol, Tonobrain, etc.		
Meclofenoxate	Analux, Centrophenoxine, Cerutil, Claretil, Clofenoxine, Lucidril, Meclofenoxate, Meclon, Mexazine, Nisantol, Pro-seryl, Ropoxyl, etc.	Tablets	0.1
Deanol aceglumate	Clirigil, Dardanin, Deanol Aceglumate, Nooclerin, Otrun, Risatarim, etc.	Peroral solution in flacons	20%-50 ml, 100 ml, 200 ml
Memoplant	Ginos	Tablets	0.04
Aminoacetic acid	Aciport, Amitone, Glicocol, Glicosil, Glycine, Glycolixir, Glycosthene, etc.	Sub-lingual tablets	0.1
Metionil-glutamil-gistidil-fenilalanil-prolil-glicil-prolin	Semaxum, Minicem	Solution for nasal use	0.1%, 1%-3 ml
Idebenone	Noben	Capsules; Film-coated tablets	0.03
Cerebrolysin	Cerebrolysinum	Parenteral solution (i/m, i/v) in ampoules	21.5%-1 ml, 5 ml, 10ml
Nicergoline	Sermionum, Dasovas, Dospan, Ergotop, Fisilax, Nargoline, Nicotergoline, Nimergoline, Sinscleron, Varsan, etc.	Tablets; Powder for injections in ampoules (i/v, i/m)	0.005, 0.01; 0.004
Vinpocetine	Inex, Telectol, Vinpocetine	Tablets; Parenteral solution (i/v) in ampoules	0,005; 0.5%-2 ml
Xantinol nicotinate	Angioamin, Complamex, Complamin, Contamex, Mehemin, Sadamin, Teonicol, Vedrin, Xantinol nicotinate, Xavin, etc.	Tablets; Tablets retard; Parenteral solution (i/v) in ampoules	0.15; 0.5; 15%-2 ml
Vincamine	Vincanorum, Vincapan, Vincamin	Tablets	0.02
Cinnarizine	Cinnarizine, Cinarin, Cinazin, Cinedil, Cinnaron, Cinnasan, Cinniprine, Cirizin, Dimitronal, Disiron, Glamil, Labyril, Marisan, Midronal, Mitronal, Stugeron, Stutgeron, Vertizin, etc.	Tablets, Capsules; Tablets, Capsules forte Peroral suspension	0.025; 0,075; 7.5%-20 ml
Melatonin	Eucalin, Melapur, Melatonum, Melaxen, etc.	Tablets	0.003

Sulbutiamine	Enerion	Tablets	0.2
Ethylmethylhydroxypyridine succinate	Mexidolum	Tablets; Parenteral solution (i/m, i/v) in ampoules	0.125; 5%-2 i 5 ml
Ethylthiobenzymidazol hydrobromid	Bemithylum	Tablets	0.125, 0.25, 0.5
Ginseng	Tincture of Ginseng, Ginsana	Tincture in flacons; Capsules	50 ml; 0.1

Chapter 23. Adaptogens, Actoprotectors

Adaptogens – pharmacological group of drugs of natural (plant or animal) or synthetic origin that can enhance non-specific resistance to a wide range of harmful effects of physical, chemical and biological nature.

Mechanism of action of Adaptogens connects with:

activation of the RNA and protein synthesis resulting in an restorative processes are observed

antioxidant action

reduction of biochemical abnormalities in stress reactions

normalization of the functions of pituitary-adrenal and immune systems.

Classification of Adaptogens

I. Adaptogens of plant origin:

Tincture of Ginseng root

Extract of Ginseng (Ginsana)

Alcoholic tincture of Ginseng

Extract of Eleutherococcus senticosus (Siberian Ginseng) Tincture of Schisandra chinensis

Rhodiolae extract fluid – Extractum Rhodiolae fluidum (Rhodiolae roseae – rhizomata et radices)

Tincture of Echinopanacis rhizomata

Tincture of radices Araliae mandshuricae – tincture Araliae

Tincture of Sterculia plantanifolia – tincture Sterculiae

Extract of Rhaponticum carthamoides (Maral root or Rhaponticum), (Extractum Leuzeae fluidum)

Ecdistenum (Rhaponticum carthamoides) – a natural compound of steroid structure, separated from the roots and rhizomes of Leuzea carthamoides

Saparalum – sum of glycosides from the roots of Aralia

II. Adaptogens of animal origin:

Pantocrinum – extract from not ossified horns (antlers), Maral, Manchurian deer and spotted deer

Rantarinum – extract from male reindeer antlers

Pharmacological effects of Adaptogens:

Improvement of physical and mental performance, reducing of fatigue, eating disorders, recovery of the diurnal cycle of body functions

Increase of endurance of the body to the influence of the harmful effects of high air temperature, cooling, toxic industrial poisons, ionizing radiation, etc.

Improvement of specific and nonspecific immunity

Improvement of blood circulation, respiration, vision, hearing

Cardioprotective effect

Hepatoprotective effect

Stimulation of hematopoiesis.

Indications:

Physical overloads

Physical and mental overfatigue

Asthenic syndrome

Condition after infectious and somatic diseases

Radiation exposure, radiation disease

In stomatology in the form of applications for the treatment of infectious processes

Adverse effects:

Excessive CNS and cardiovascular system stimulation

Arterial hypertension

Hyperglycemia

Contraindications:

The drugs are not recommended in the evening

Atherosclerosis

Organic diseases of heart

IHD, stenocardia (angina pectoris)

Hypercoagulability

Severe forms of glomerulonephritis

Diarrhea

Table 63. Medicinal forms of Adaptogens

INN	Trade names	Medicinal forms	
Ginseng, Tincture of Ginseng	Tincture "Bioginseng", Ginsana	Tincture 1:10 in 70% ethyl alcohol for peroral use in flacons; Capsules	25 ml, 50 ml; 0.1
Extract of Eleutherococcus fluidum, Acanthopanax senticosus		Extract 1:1 in 70% ethyl alcohol for peroral use in flacons	50 ml

Tincture of Schisandra		Tincture 1:5 in 95% ethyl alcohol for peroral use in flacons	50 ml
Extract of Rhodiola fluidum		Extract 1:1 in 40% ethyl alcohol for peroral use in flacons	30 ml, 50 ml
Tincture of Echinopanax	Oplopanax elatus	Tincture 1:5 in 70% ethyl alcohol for peroral use in flacons	50 ml
Tincture of Aralia Aralia mandshurica, Aralia manshuricae radices	Saparalum	Tincture 1:5 in 70% ethyl alcohol for peroral use in flacons; Tablets	50, 100 ml; 0.05
Tincture of Sterculia platanifolia		Tincture for peroral use in flacons	25 ml
Extract of Leuzea fluidum	Rhaponticus carthamoides, Leuzea carthamoides D.C.	Extract 1:1 in 70% ethyl alcohol for peroral use in flacons	40 ml
Ecdistenum 20-beta-hydroxyecdysterone	Ecdysterone, Ectysterone, Turkesterone, Ponasterone, Ecdysone, Ecdystene	Tablets	0.005
Pantocrinum Antlers of the extract	Pantocrinum Rantarinum	Aqueous alcoholic extract for peroral use in flacons; Tablets; Parenteral solution (i/m, s/c) in ampoules; Tablets	30, 50, 100 ml; 0.075, 0,15; 1 ml, 2 ml; 0.25

Actoprotectors – not have the expressed stimulating effect on CNS, but improve mental and physical activity, increase capacity for work, reduce fatigability. Actoprotectors increase the body's resistance to hypoxia, to high and low ambient temperatures.

Mechanism of action: actoprotectors belong to the metabolic drugs of inexhaustible type of action. They have an antihypoxic activity too. Actoprotectors directly stimulate RNA and protein synthesis in different cells including enzymatic synthesis, structural and proteins synthesis related to the immune system; activate synthesis of the enzymes of gluconeogenesis which provides the utilization of lactate – the factor limiting performance and re-synthesis of carbohydrates – the most important sources of energy under extreme stresses, leading to an increase in physical performance. Enhancing formation of mitochondrial enzymes and structural proteins of mitochondria provides increased energy production and maintenance of a high degree of coupling of oxidation with phosphorylation. Maintaining a high level of ATP synthesis in case of oxygen deficiency contributes

to severe antihypoxic and antiischemic activity of actoprotectors. Actoprotectors increase the synthesis of antioxidant enzymes and have expressed antioxidant activity.

This group includes: *Ethylthiobenzymidazol hydrobromide (Bemithylum)*, vitamins and biogenic stimulants. But, Bemithylum is standard drug for the group of Actoprotectors.

Pharmacological effects:

psychogogic
antihypoxic
increase in work capacity
immunostimulating

Indications:

asthenic conditions,
neurosis
after injuries
in complex therapy of infectious diseases
in sports medicine to restore muscle activity after intense exercises

Adverse effects:

dyspepsia
headache
flushing of the face

Contraindications:

idiosyncrasy
hypoglycemia

Table 64. Medicinal forms of Actoprotectors.

INN	Trade names	Medicinal forms	
Ethylthiobenzymidazol hydrobromide	Bemithylum	Tablets	0.125, 0.25, 0.5

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