

**ADVERSE DRUG REACTIONS, DRUG SAFETY MONITORING and
PHARMACOVIGILANCE SYSTEM. DRUG-DRUG INTERACTIONS.
COMPLICATIONS from PHARMACOTHERAPY.
CLINICAL PHARMACOLOGY OF POISONING.**

A. Actuality

At the beginning of the 21st century, the medicine has an imposing number of drugs with high potency and the frequency of their use practically doubles every 10 years. The risk of a drug-drug interaction increases with the number of drugs used, sometimes with positive, sometimes with negative consequences. The incidence of complications from pharmacotherapy has increased from 10% to 40% in the last 15 years, according to some bibliographic sources.

Adverse drug reactions can present clinically in many different ways, which requires close collaboration between medical practitioners and pharmacologists, in order to find, register, systematize, prevent and inform healthcare specialists. The aforementioned implies the need for a thorough knowledge of this field of clinical pharmacology.

B. Training aim

Learning the clinical-pharmacological principles of rational drugs administration, taking the drug-drug interaction into account, also the adverse and toxic drugs reactions, with the elaboration of an effective plan to prevent complications from pharmacotherapy.

C. Teaching objectives

The student should be able:

- a) to choose a minimum of complex diagnostic tools, in order to determine the change in the pharmacodynamic properties of drugs, caused by drug-drug interaction;
- b) to analyze and assess the final effects produced by different drug substances, taking into account the possible interactions between them;
- c) to predict the dependence of the adverse reactions on the dosage regimen and the functional state of the organs and systems of the body;
- d) to apply contemporary methods in order to prevent or to manage side effects caused by the drugs;
- e) to elaborate a plan of prophylaxis or/and treatment of drug toxicity and poisoning.

A. Knowledge from previously studied disciplines and related subjects

Clinical disciplines . Particularities of the complex treatment of different diseases and pathological conditions.

Pharmacology. Classification of drug-drug interactions. The notion of drug-drug interaction. Notions of pharmacokinetic and pharmacodynamic drug interactions. Principles of treatment of acute intoxication.

E . Questions for self-training

1. Pharmaceutical drug-drug interactions, incompatibilities of drugs.
2. Pharmacokinetic drug interactions. The main processes of drug kinetics.
3. Drug interactions at the level of absorption. Their impact for the bioavailability of the drugs.
The influencing factors:
 - a) changes of gastrointestinal pH;
 - c) drug-drug interaction in the intestine (formation of poorly absorbable or non-absorbable complexes and their clinical significance);
 - d) drug-drug interaction in the intestine (competition for carrier(s) responsible for absorption, P-glycoprotein exporter);
 - e) intestinal transit changes and bioavailability of drugs.
4. Drug-drug interactions at the distribution level, the factors that can influence them:

- a) regional change of blood flow;
- b) protein displacement, the importance of drug affinity to plasma proteins.
5. Drug-drug interactions at the metabolism level:
 - a) enzymatic induction: the causes and consequences, the main drug inducers;
 - b) enzymatic inhibition: causes and consequences, drugs with inhibitory action on liver microsomal enzymes;
 - c) drugs as: substrates, inhibitors and inducers of cytochrome P450; P-glycoprotein substrates, inhibitors and inducers;
 - d) modification of the hepatic blood flow.
6. Drug-drug interactions at the level of urinary excretion:
 - a) changes in glomerular filtration;
 - b) competition at the tubular secretion;
 - c) competition at the tubular reabsorption . The importance of urinary pH and the pKa of the drug.
7. Pharmacodynamic drug-drug interactions;
 - a) pharmacodynamic interactions at the molecular, cellular level;
 - b) pharmacodynamic interactions at the anatomical-physiological level.
8. Interaction between drugs and food, beverages, herbs.
9. Adverse reactions and drug induced pathological conditions: causes, types and mechanisms. Drug overdose.
10. Drug safety monitoring and pharmacovigilance system, functions and tasks.
11. Drug toxicity, their dependence on the dose or plasma concentration:
 - a) the individual reactivity and the pathological states that modify the pharmacokinetic and pharmacodynamic properties of the drugs;
 - b) the importance of high intrinsic toxicity and narrow therapeutic index;
 - c) drug toxicity induced by drug interactions;
 - d) the dysmorphogenic effects, drug induced mutagenesis and carcinogenesis.
12. Allergic side effects:
 - a) type I allergic reaction (anaphylaxis). Anaphylactoid reactions;
 - b) type II hypersensitivity reactions (cytotoxic);
 - c) type III hypersensitivity reactions (antigen-antibody complexes);
 - d) type IV hypersensitivity reactions (delayed type hypersensitivity).
 Pathogenesis, clinical manifestations, prophylaxis of allergic reactions. Drug desensitization.
13. Idiosyncratic adverse drug reactions. Pharmacogenetic peculiarities responsible for idiosyncratic reactions.
14. Drug-induced pathology:
 - a) of the cardiovascular system;
 - b) of the respiratory system;
 - c) of the gastrointestinal tract;
 - d) of the liver;
 - e) of the blood;
 - f) of the endocrine system;
 - g) of the kidney;
 - h) of the eyes and inner ear;
 - i) of the central and peripheral nervous system.
15. Drug addiction. Clinical manifestations. Prophylaxis and treatment of drug dependence.
16. Phenomena triggered by repeated drug administration (tolerance, dependence, tachyphylaxis, cumulative effect, hypersensitivity, idiosyncrasy, etc.) and associated (synergism, antagonism and their varieties). Phenomena triggered at abrupt discontinuation of treatment.
17. Drug poisoning:
 - a) the general principles of the pharmacological treatment of acute poisoning;
 - b) adsorbents: indications for administration, dosing;

- c) treatment based on chemical interaction;
 - d) chelation therapy - dimercaptol, EDTA, DTPA; mechanism of action; aspects of use;
 - e) immunotherapy for reversal of toxicity due to drug poisoning, antitoxins;
 - f) antidotes: pharmacological, physiological, chemical; classification, mechanisms of action; principles of use.
18. Drug-drug interactions in children. Clinical and pharmacological aspects of adverse reactions in children. Principles of treatment of poisoning in children.
 19. Particularities of drug-drug interactions and adverse drug reaction among elderly. Principles of poisoning among elderly.
 20. Medications that need to be excluded or used with caution in liver disorders.
 21. Medications that need to be excluded or used with caution in renal failure.
 22. Medications that need to be excluded or used with caution during pregnancy.
 23. Medications that need to be excluded or used with caution during breastfeeding.
 24. Complications from pharmacotherapy. Management of complications from pharmacotherapy.
 25. Counterfeit medicines.

Individual work:

1. Short characterization of the main preparations

Vertically. Name of the preparation (in English).

Horizontally. Synonyms, forms of delivery, way of administration, doses (therapeutical, maximal), indications, contraindications, adverse reactions.

Dimercaptol, furosemide, epinephrine hydrochloride, prednisolone, strophanthin, clonidine, insulin, glucose, naloxone, diazepam, magnesium sulphate, sodium bicarbonate, ascorbic acid, atropine, activated charcoal.

2. Indicate the preparations used in (for): poisoning with acids, bronchospasm caused by the anticholinesterase drugs, seizures, intoxication with opioid analgesics, stimulation of the heart, pulmonary and cerebral edema, accelerating the elimination of toxins through the kidneys, psychomotor agitation, acute hypotension, hypertensive crisis, hypoglycemic coma, hyperglycemic coma, cardiac glycoside overdose.

3. Tests on clinical pharmacology (for faculty of medicine) Chişinău 2014, p. 21;

4. Clinical cases in clinical pharmacology, Chişinău-2017, p.115;

5. Virtual situations.