Clinical Pharmacology

Introduction to Clinical Pharmacology

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Summary

- Definitions
- The aims and goals of Clinical Pharmacology
- History of Clinical Pharmacology
- Clinical trials. IND & NDA
- Methods of Clinical Pharmacology
- Clinical Pharmacology in MOLDOVA
- The concept of Essential medicines and Rational use of drugs
- Selecting your P-drugs

Definitions

- Clinical pharmacology can be defined as the ***study of drugs in humans***.
- Clinical pharmacology is a relatively **new science**.
- It is related to **pharmacotherapy** but is not the same science.
- ***Clinical pharmacology*** has been termed a ***bridging discipline*** because it links **classical pharmacology** with **clinical medicine**.
- **Clinical pharmacology** is a science about **drugs interactions with human body (pathological and health conditions)**.
- It is closley linked to **fundamental pharmacology**.

Aims of Pharmacology (Basic & Clinical)

The fundamental problemes with which **pharmacology** is concerned are following:

- 1). The relationship between **dose** and **biological effect;**
- 2). The localization of the **site of action** of a drug;
- 3). The **mechanism** (s) of action of drug;
- 4). The absorption, distribution, metabolism, and excretion of a drug (**PK**);
- 5). The relationship between **chemical structure** and **biological activity;**

The aims and goals of Clinical Pharmacology

- **Clinical pharmacologists** are concerned both:
- ***I. Optimal use of existing medications;***
- ***II. Scientific study of drugs in humans (PhK & Ph D); AND Therapeutical assessment***

- The ***latter area*** include **both** evaluation of:
- **1).**The ***safety*** and ***efficacy*** of currently available drugs;
- **2).** Development of ***new and improved pharmacotherapy*** ***(this is the main goal of Clinical Pharmacology);***
- The newly available drugs must be **safety** and **efficacy** too.

History

- A few personalities had an significantly influence on clinical pharmacology development:
- **Rudolph Bucheim** (1820-1879) has been credited with establishing pharmacology as a laboratory-based discipline.
- In the United States, **Harry Gold** and **Walter Modell** began in the 1930's to provide the foundation for the ***modern discipline*** of ***clinical pharmacology***.
- They inovated (invention) of ***the double-blind design*** for clinical trials and the use of effect kinetics to measure the absolute bioavailability of **digoxin**.

- Martini described the use of ***placebos, control groups, stratification, rating scales, and the "n of 1" trial design***, and emphasized the need to estimate the adequacy of **sample size** and to establish **baseline** conditions before beginning a trial.
- He also introduced the **term "clinical pharmacology"**.
- More recently, **Sheiner** outlined a number of improvements that continue to be needed in the use of ***statistical methods*** for drug evaluation, and asserted that **clinicians** must **regain** control over **clinical trials;**

Clinical Pharmacology in MOLDOVA

- Clinical Pharmacology is a new discipline in the university curricula in MOLDOVA (it was introduced as a distinct branch of pharmacology in 1999 ORDINUL MS Rmoldova nr 97 Cu privire la aprobare REGULAMENTULUI și includerea specialității medic farmacolog-clinician);
- The NAMMD (National Medicines Agency and Medical Devices) is the MOLDAVIAN competent authority in the field of medicinal products for human use, as regards marketing authorisation, surveillance of the safety of medicinal products in therapeutic use, **authorisation of clinical trials** and issuance of regulations in the medicinal product field, as approved by the Ministry of Health.

- A great challange for the pharmacologists and physicians was ***adverse drug reaction*** (**ADR**) to **thalidomide** – *"an inofensive anxiolytic and antivomiting drug"*;
- Few drugs have focused as much public attention on problem of ADRs as did **thalidomide**, which was first linked in 1961 to catastrophic outbreaks of ***phocomelia*** by Lenz in Germany and McBride in Australia.

- The ***thalidomide tragedy*** provided an major impetus for developing a number of NIH-funded academic centers of excellence of **clinical pharmacology**.
- **NIH = National Institutes of Health**
- **FDA = Food and Drug Administration**
- In 1932, **Paul Martini** published a monograph: Methodology of Therapeutic Investigation, that summarized his experience in **drug evaluation** and probably entitles him to be considered the **"first clinical pharmacologist"**.

Thalidomide disaster

- ***Contemporary drug development*** is a **complex process** that is conventionally divided into **preclinical research** and a number of **clinical development** phases;

- A following figure illustrate these two main steps:
- **I.Preclinical Development**
- **II.Clinical Development**

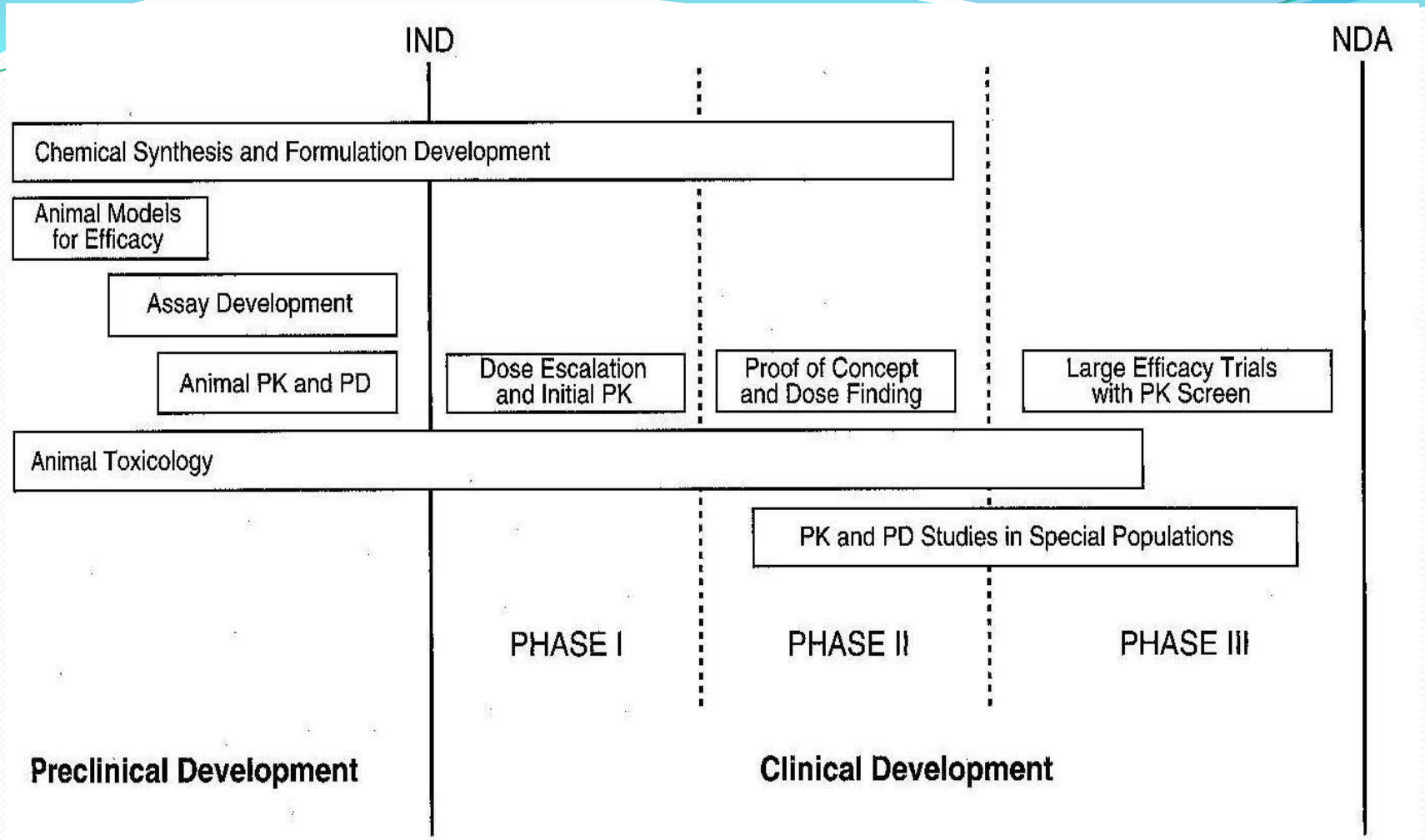


FIGURE 1.1 The process of new drug development in the United States. (PK indicates pharmacokinetic studies; PD indicates studies of drug effect or pharmacodynamics). Further explanation is provided in the text. (Modified from Peck CC *et al.* Clin Pharmacol Ther 1992;51:465–73.)

- Less than 1/3 of the drugs tested in clinical research – in the marketplace;
- A good clinical trial requires multidisciplinary perssonel:
- **1). Basic scientists**
- **2). Clinical pharmacologists**
- **3). Clinician specialists**
- **4). Statisticians**

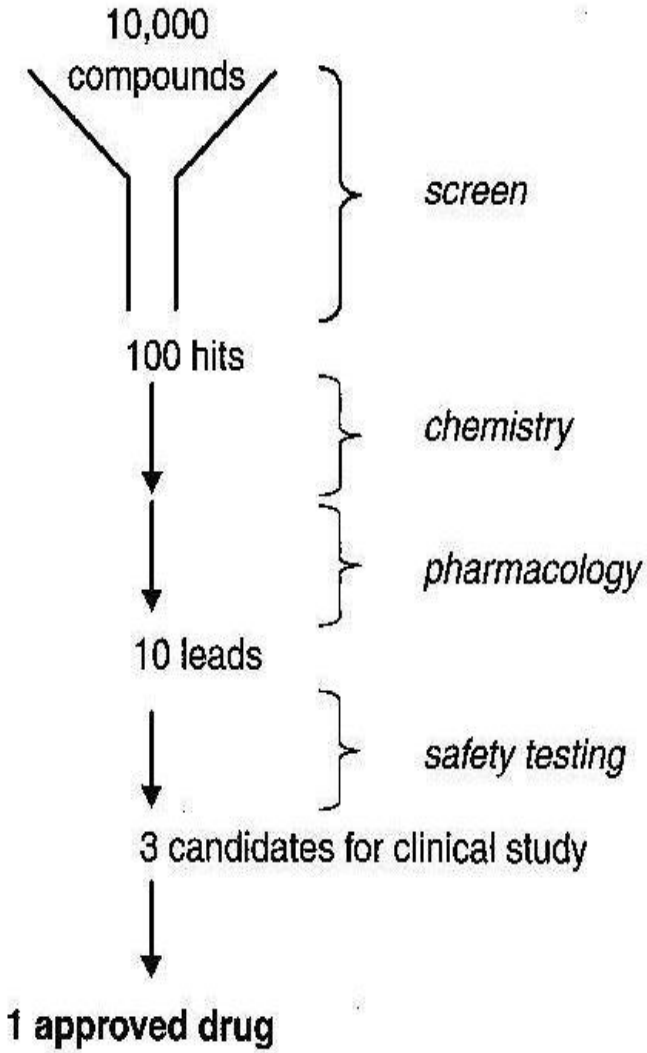


FIGURE 28.1 The screening funnel. Loss of compounds is to be expected as candidates proceed through the preclinical process.

Methods of Clinical Pharmacology

- To avoid **some errors** in clinical trials some methods are used:
- **1). Crossover design** – alternating of **test drug** with **placebo** and **standard drug;**
- **Placebo** response; In clinical trials **placebo** = an **inert** form with the same properties of the tested drug (odor, consistency);
- To eliminate this phenomen (placebo response) we can use:
- **2). Single-blind design or**
- **3). Double –blind design**
- In the **last design** – only a third person know about testing drug (with the special code);

Clinical trials IND & NDA

- Once a drug is judget ready to be studied in humans, a Notice of Claimed Investigational Exemption for a New Drug (IND) must be filed with the Regulatory Authority (RA) in Drug Domain (ex: FDA-USA, EMA-EU, NMA-RMoldova);
- The IND includes:
- **1). Information on the composition and source of the drug;**
- **2). Manufacturing information;**
- **3). All data from animal studies;**
- **4). Clinical plans and protocols;**
- **5). The names and credentials of physicians who will conduct the clinical trials.**

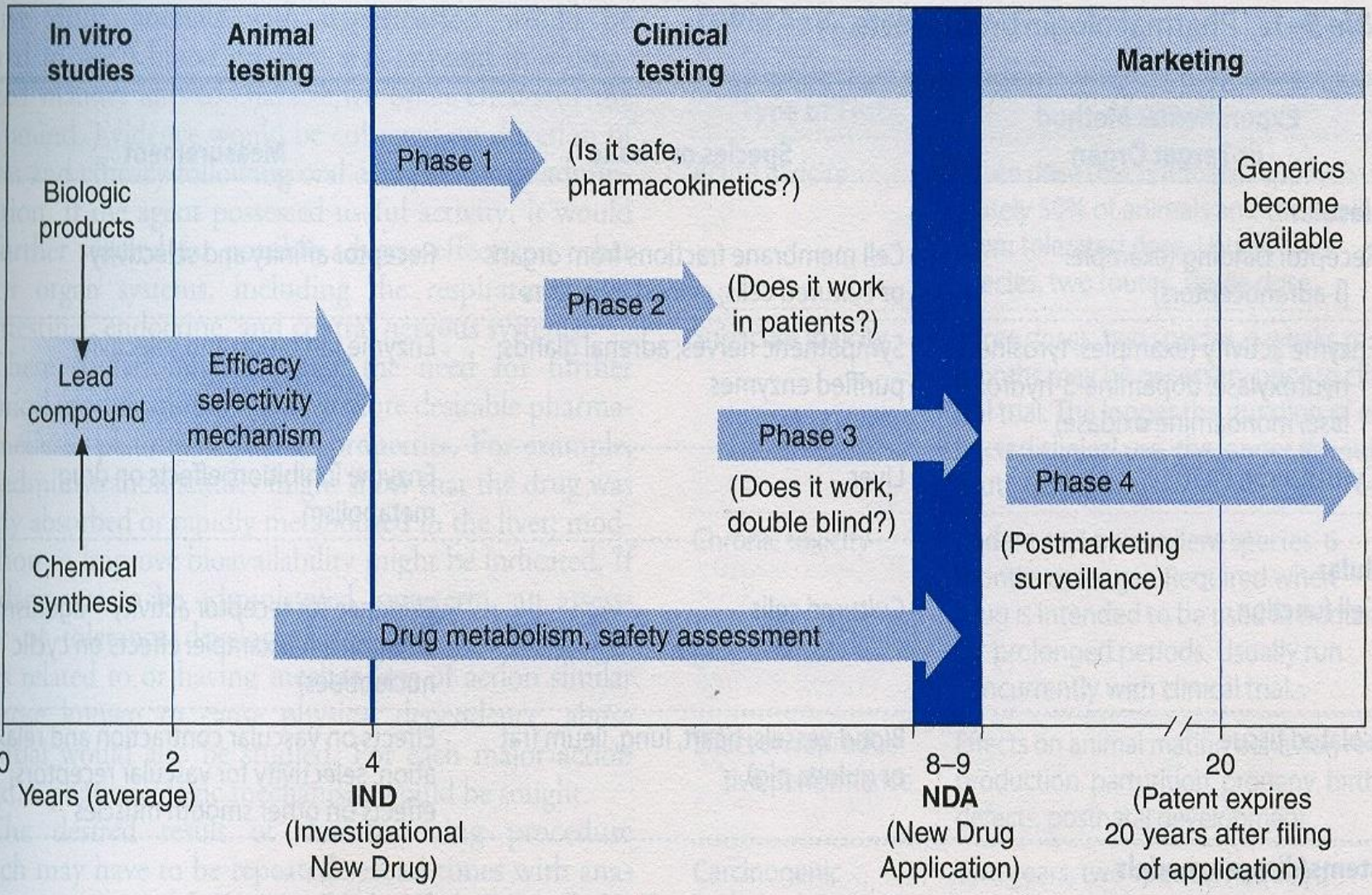


Figure 5–1. The development and testing process required to bring a drug to market in the USA. Some of the requirements may be different for drugs used in life-threatening diseases.

- Its often requires 4-6 years of clinical testing;
- The volunteers or patients must be informed;
- **Phase 1**
- The drug is studied in 20-80 healthy volunteers;
- In this phase the trial is **open** – investigators and subjects know what is being given;
- Its evaluated toxicity, PK profile of the drug;
- Phase 1 studies its performed by the **clinical pharmacologists** – in research centres;

- **Phase 2**
- In this phase testing drug is evaluated in **patients;**
- **The goal** – to determine **efficacy** of the drug;
- A small number (100-200) of patients – is evaluated in great detail;
- A **single-blind design** is used with ***placebo*** and an ***older active drug*** (to compare);
- The ADRs (***drug toxicity***) might also detected in this phase;
- Phase 2 of trials are done in **clinical centres (university hospitals);**

- **Phase 3**
- The drug is evaluated in much larger numbers of patients (**thousands**) to further establish **safety** and **efficacy;**
- Using information gathered in phases 1 and 2, phase 3 trials are designed to minimize errors caused by placebo effects, variable course of disease, etc.;
- Therefore, **double-blind** and **crossover** techniques are frequently used;
- Phase 3 studies can be difficult to design and execute;

- Are usually **expensive** because a large numbers of patients involved and the masses of data that must be collected and analyzed;
- The investigators are usually **specialists in the disease** being treated;
- Certain toxic effects (caused by immunologic processes) may be first become apparent in phase 3;
- If phase 3 results meet expectations, application will be made for permission to market the new agent.

- The process of applying for marketing approval requires submission of a New Drug Application (NDA) to the RA;
- The RA review this material and a decision on approval may take **3 years** or **longer;**
- In cases where an urgent need is percieved (eg, cancer chemotherapy), the process of preclinical and clinical testing and RA review may be greatly accelerated;
- **For serious diseases**, the RA may permit extensive but controlled marketing of a new drug before phase 3 studies are completed;

Drug Names and Categories

- Chemical; generic; official; trade or brand name
- Several trade names: Use generic name to avoid confusion
- After drug approval RA assigns categories:
  - Prescription
  - Nonprescription
  - Controlled substance

Drug Classes and Categories

- Drugs are classified by the chemical type of the active ingredient or by the way it is used to treat a particular condition
- PRESCRIPTION DRUGS
  - The prescription contains the name of the drug
  - the dosage
  - the method and times of administration
  - Signature of the licensed health care provider

NONPRESCRIPTION DRUGS-OTC

- Acetylsalicylic Acid (ASA) as any NSAID may cause GI bleeding and salicylism
- Labeling provides the consumer with info regarding the drug, dosage, contraindications, precautions and advers reactions
- Consumers are urged to read the directions carefully prior to taking any OTC drugs

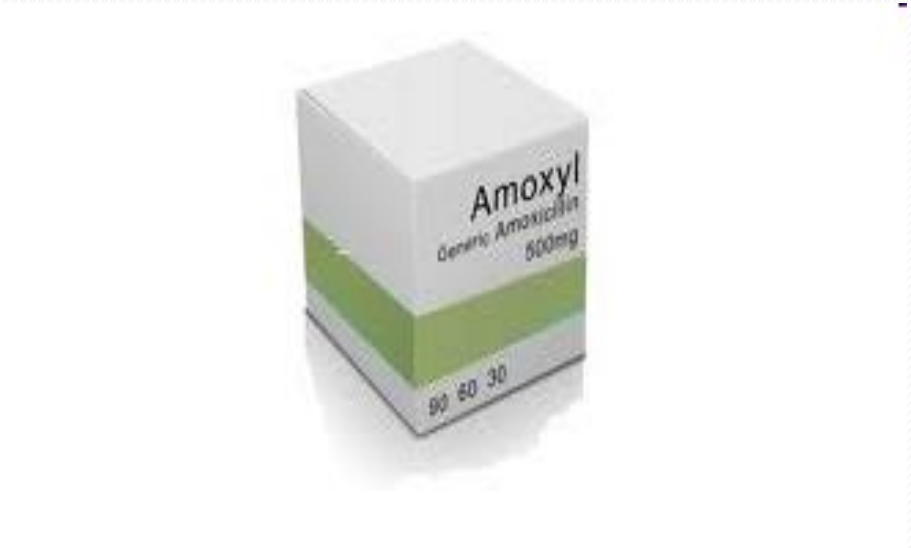
Controlled Substances

- The Controlled Substances Act of 1970 established a schedule or classification system for drugs with abuse potential- USA.
- Act regulates the manufacture, distribution and dispensing of these drugs

DRUG NAMES

Individual drugs may have several different names, but the two most commonly used are the generic name and the trade name (also called the brand or proprietary name). The *generic name* (eg, amoxicillin) is related to the chemical or official name and is independent of the manufacturer. *The generic name often indicates the drug group (eg, drugs with generic names ending in "cillin" are penicillins).* The *trade name* is designated and patented by the manufacturer. For example, amoxicillin is manufactured by several pharmaceutical companies, some of which assign a specific trade name (eg, Amoxil, Trimox) and several of which use only the generic name. In drug literature, trade names are capitalized and generic names are lowercase unless in a list or at the beginning of a sentence. Drugs may be prescribed and dispensed by generic or trade name.

Amoxicillin



Ranitidin


Ranitidin 150 mg


Ranitic® 150 mg akut
Filmtabletten
Wirkstoff: Ranitidin
Zur Verminderung der Magensäureproduktion
150 mg
10 Filmtabletten N1
HEXAL


Ranitidin 150 mg
20 comprimate
PENTRU ADMINISTRARE ORALĂ
fabiol
FABIOL S.A.
București
b-dul Timișoara nr. 50


Ranisan® 150 mg
30 obalených tabliet

Metronidazole

ORPHAN DRUG

- A drug used to treat, prevent, or diagnose an orphan disease. An orphan disease is a rare disease or condition that affects fewer than 200,000 people in the United States. Orphan diseases are often serious or life threatening. In 1983, the U.S. government passed a law, called the Orphan Drug Act, to give drug companies certain financial benefits for developing orphan drugs that are safe and effective.
-

- An **orphan drug** is a pharmaceutical agent developed to treat medical conditions which, because they are so rare, would not be profitable to produce without government assistance. The conditions are referred to as orphan diseases.
- The assignment of **orphan status** to a disease and to drugs developed to treat it is a matter of public policy in many countries and has yielded medical breakthroughs that might not otherwise have been achieved, due to the economics of drug research and development.[1]
- In the U.S. and the EU, it is easier to gain marketing approval for an orphan drug. There may be other financial incentives, such as an extended period of exclusivity, during which the producer has sole rights to market the drug. All are intended to encourage development of drugs which would otherwise lack sufficient profit motive to attract corporate research budgets and personnel

Medicamente “orfane”

- Conform Regulamentului European nr 141/2000, numai medicamentele pentru uz uman pot fi desemnate ca “medicamente orfane”, această terminologie neaplicându-se la suplimentele nutriționale și produsele dietetic, la dispozitivele medicale și medicamente veterinare.
- Medicamentele desemnate ca orfane sunt incluse în Registrul Comunitar pentru produse medicinale orfane.
- În 2001 a fost înființat Comitetul pentru medicamente orfane însărcinat cu examinarea cererilor de denumire depuse de către persoanele sau firmele care intenționează să conceapă medicamente pentru boli rare.

Maladie rara Angioedem eriditar AEE

- Angioedemul ereditar – sau deficitul de inhibitor de C1-esterază – este o boală genetică rară, caracterizată prin episoade recurente de angioedem izolat, care au, cel mai frecvent, răsunet asupra tegumentului sau asupra tractului respirator superior și gastrointestinal.
- Prevalența AEE este relativ scăzută cuprinsă între **1 : 10 000 și 1: 50 000** de persoane.
- Într-o analiză a pacienților care nu au antecedente de AEE în familia lor, dar care au un nivel relativ scăzut de C1-INH mutant și manifestă un angioedem recurent, 25% dintre pacienții noi cu AEE au avut modificări C1-INH care nu prezintă semne de moștenire[7)8)].
- Există trei tipuri de AAE după deficiența de inhibitor C1 (C1-INH)[9)].
- **AEE de tip I este în primul rând cauzată de o deficiență a proteinelor din sânge (inhibitori ai esterazei C1) care în mod normal suprimă activarea sistemului complement. Stimularea excesivă a acestui sistem conduce la producerea de anafilatoxine inflamatorii, care afectează fluxul fluidelor corporale dintre sistemul vascular și țesuturile corpului.**
- **Această deficiență este responsabilă pentru aproximativ 80-85% din cazuri.**

Conestat alfa is the recombinant analogue of the human C1 esterase inhibitor (rhC1INH) produced by recombinant DNA technology in the milk of transgenic rabbits.

- Pharming Reports Positive Results from Compassionate Use of Ruconest in COVID-19 Patients April 22, 2020
- Pharming reported positive results from COVID-19 patients treated with its C1 esterase inhibitor Ruconest (conestat alfa) in a compassionate use program in Switzerland.
- **Ruconest is approved for treatment of hereditary angioedema (HAE), an immune disease caused by low levels or improper function of C1-esterase inhibitor.**
- The drug was administered to five COVID-19 patients with severe pneumonia. Fever resolved in four of the five patients within 48 hours and inflammation significantly decreased, the company said.

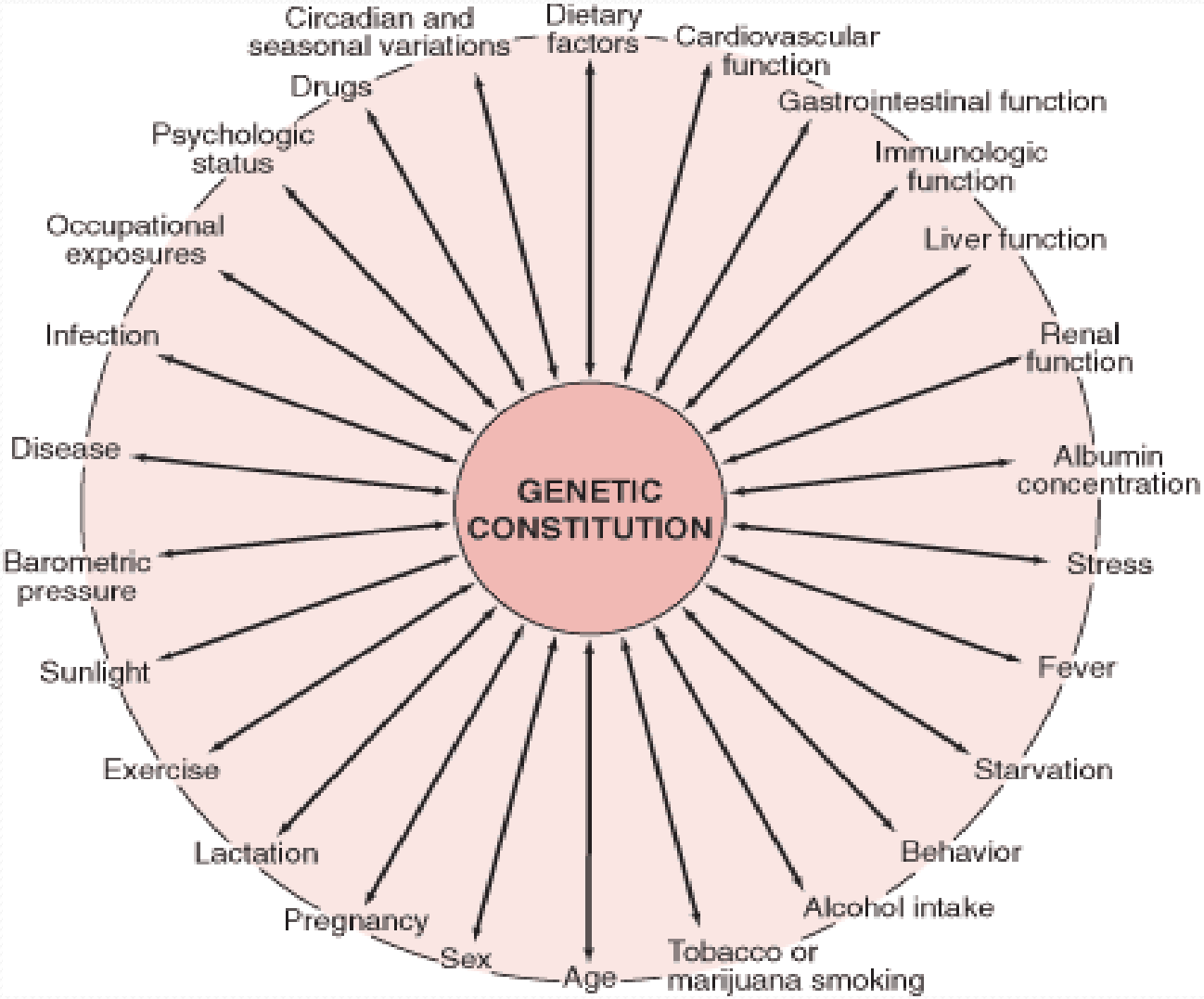
- Michael Osthoff of University Hospital Basel said: "**Although this is an uncontrolled, small treatment experience, the results demonstrate the potential effectiveness of using Ruconest as an anti-inflammatory approach to inhibit the complement and contact systems after SARS-CoV-2 infection.**"
- He added: "We are now in the midst of planning a multinational, randomized controlled trial in up to 150 patients to further understand the safety and efficacy of this approach in preventing deterioration in COVID-19 patients."

RUCONEST

- The cost for Ruconest intravenous powder for injection 2100 intl units is around **$6,518 for a supply of 1 powder for injection,** depending on the pharmacy you visit. Prices are for cash paying customers only and are not valid with insurance plans.

Why do Patients vary in their response to Drugs?

Genetic, environmental, and developmental factors that can interact, causing variations in drug response among patients



The Origin of patient to patient Variability

- **Genetics (PHARMACOGENOMICS)**
- **Disease**
- **Age (weight)**
- **Concomitant drugs**
- **Gender**
- **Non-compliance - underestimated**
- **Route of Administration - bioavailability**
- **Food - protein malnutrition**
- **Pollutants - smoking/herbicide residues**
- **Timing - chronopharmacology**

PHARMACOKINETICS

Pharmacokinetics involves drug movement through the body (ie, “what the body does to the drug”) to reach sites of action, metabolism, and excretion. Specific processes are absorption, **distribution, metabolism (biotransformation), and excretion.**
Overall, these processes largely determine serum drug levels, onset, peak and duration of drug actions, drug half-life, therapeutic and adverse drug effects, and other important aspects of drug therapy.

PHARMACODYNAMICS

Pharmacodynamics involves drug actions on target cells and the resulting alterations in cellular biochemical reactions and functions (ie, “what the drug does to the body”). As previously stated, all drug actions occur at the cellular level.

Pharmacodynamic Variables

- ***Maximum Effect*** **(all pharmacologic responses must have a maximum effect (Emax). No matter how high the drug concentration goes, a point will be reached beyond which no further increment in response is achieved.**
- ***Sensitivity*** **(the sensitivity of the target organ to drug concentration is reflected by the concentration required to produce 50% of maximum effect, the EC50. Failure of response due to diminished sensitivity to the drug can be detected by measuring—in a patient who is not getting better—drug concentrations that are usually associated with therapeutic response. This may be a result of abnormal physiology—eg, hyperkalemia diminishes responsiveness to digoxin—or drug antagonism—eg, calcium channel blockers impair the inotropic response to digoxin.**

Drug-Related Variables

- ***Dosage***
- ***Route of Administration***
- ***Drug–Diet Interactions***
- ***Drug–Drug Interactions:***
  - **Increased Drug Effects (*Additive effects, Synergism* or *potentiation, Interference* by one drug with the metabolism or elimination of a second drug, *Displacement* of one drug from plasma protein-binding sites by a second drug increases the effects of the displaced drug)**
  - **Decreased Drug Effects - *Interactions in which drug effects are decreased are grouped under the term* antagonism *(Example:* naloxone (a narcotic antagonist) + morphine (a narcotic or opioid analgesic) >relief of opioidinduced respiratory depression. Naloxone molecules displace morphine molecules from their receptor sites on nerve cells in the brain so that the morphine molecules cannot continue to exert their depressant effects.**

Client-Related Variables

- *Age*
- *Body Weight*
- *Genetic and Ethnic Characteristics*
- *Gender (*except during pregnancy and lactation, gender has been considered a minor influence on drug action).
- *Pathologic Conditions*
- *Psychological Considerations*

WHO Definition of ADRs

Any noxious, unintended, undesired effect of a drug which occurs at doses used for prophylaxis, diagnosis, or therapy, excluding therapeutic failures, intentional and accidental overdose and drug abuse, and does not include ADRs due to errors in drug administration.

Drug Safety has always been a concern …. and should remain so -

'First do no harm … *it is a good remedy sometimes to use nothing*.'

(Hippocrates, 5th Century BC)

'All things are poisons and there is nothing that is harmless … *the dose alone decides that something is a poison*.'

(Paracelsus, 1500s)

'Patients may recover in spite of drugs … *or because of them*.'

(Gaddum, 1959)

Incidence of Reactions

- 5% adults in US are allergic to
- ≥1 drugs
- 30% of medical inpatients develop an ADR
- 3% of all hospital admissions are due to ADRs
- Risk of an allergic reaction is approximately 1-3% for most drugs

Importance of ADRs - 1

- **Causes considerable morbidity and mortality; treating this is very expensive**

- **Data on incidence is poor considering the scope of the problem**

- **Typical figures for the USA (where most studies have been done) suggests:**

  - **precipitate 1-4% of acute medical admissions**
  - **4-9% of inpatients suffer an ADR**
  - **7,000 deaths per annum directly reflect an ADR**
    - **some sources put the figure closer to 100,000**
  - **Cost for the US health care system > $100b/year**
    - **UK estimate £400m??**

Importance of ADRs - 2

- **Majority are preventable**

- **Strategies for prevention include:**

  - **Ward pharmacists**
  - **Electronic prescribing and dispensing**
    - **Already in Primary Care/GPs**
    - **Extension to Hospitals**

  - **Better education**

Classification of Adverse Drug Reactions

Severity	Description
Mild	No antidote or treatment is required; hospitalization is not prolonged
Moderate	A change in treatment (eg, modified dosage, addition of a drug), but not necessarily discontinuation of the drug, is required; hospitalization may be prolonged or specific treatment may be required
Severe	An ADR is potentially life threatening and requires discontinuation of the drug and specific treatment of the ADR
Lethal	An ADR directly or indirectly contributes to a patient's death

UNPREDICTABLE REACTIONS

- Dose-independent
- Not related to drug's actions
- Related to immune response (allergy)

PREDICTABLE REACTIONS

- Dose dependent
- Related to drug's actions
- Occur in normal patients
- 80% of adverse effects
- Overdosage or toxicity
- Side effects
- Secondary/Indirect effects
- Drug interactions

CLASSIFICATIONS OF ADR

- **A (Augmented)**
- **B (Bizarre)**
- **C (Continuous)**
- **D (Delayed)**
- **E (Ending Use)**
- **F (Failure of Efficacy)**

Broadly

Type- A (Predictable)- Based on pharmacological properties

Type- B (Non-predictable) – Based on Immunological response and genetic makeup of person

TYPE A- AUGMENTED

- These are based on the pharmacological properties of the drug so can be predicted.
- They are common and account for 75% of ADRs
- Dose related and preventable mostly reversible.

Examples:-

- Anticoagulants (e.g., warfarin, heparin) – bleeding
- Anti-hypertensives (e.g.. α1-antagonists) – hypotension
- Anti-diabetics (e.g. insulin) - hypoglycemia

Predictable

TYPE B- BIZZARE OR UNPREDICTABLE

- Have **no direct relationship** to the dose of the drug or the pharmacological mechanism of drug action.
- Develop on the basis of:
  - Immunological reaction on a drug (**Allergy**)
  - Genetic predisposition (**Idiosyncratic reactions**)
- More serious clinical outcomes with higher mortality and morbidity.
- Mostly require immediate withdrawal of the drug.

Un-predictable

TYPE C – CHRONIC (CONTINOUS) USE

- They are mostly associated with **cumulative-long term** exposure

Example:-

Analgesic (NSAID)– interstitial nephritis, papillary sclerosis, necrosis

Predictable

TYPE D – DELAYED

- They manifest themselves with significant delay
  - **Teratogenesis -**Thalidomide – Phocomelia (flipper-like fore limbs)
  - **Mutagenesis/Cancerogenesis**

Others:

Tardive dyskinesis – during long time administration of Antipsychotic drugs

Predictable

TYPE E – END OF USE

- Drug withdrawal syndromes and rebound phenomenons
  - Example – sudden withdrawal of long term therapy with **β-blockers** can induce rebound tachycardia and hypertension
  - **TYPE F- Failure of treatment**

Predictable

PHARMACOVIGILANCE (DAUP)

The '**science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems**'

The information generated is useful in educating doctors and in the official regulation of drug use.

It has an important role in **rational use** of medicines, as it provides the basis for assessing **safety** of medicines.

Various activities involved in pharmacovigilance are:

- **Postmarketing surveillance** and other methods of ADR monitoring such as voluntary reporting by doctors prescription event monitoring.

- **Dissemination of ADR data** through 'drug alerts', 'medical letters,' advisories sent to doctors by pharmaceuticals and regulatory agencies.

- **Changes in the labelling** of medicines indicating restrictions in use or statuary warnings, precautions, or even withdrawal of the drug.

ADR detection methods

- Premarketing clinical trials
- Post approval spontaneous case reports
- Aggregate population-based data sources
- Computerized data collections
- Postmarketing studies
- Case reports

- The **Uppsala Centre (Sweden)** is the international collaborating centre for collecting and analyses all DARs.

- Ex: In India,
  - National centre is located at Ghaziabad
  - Peripheral Centres at Medical college levels and tertiary and above hospitals
  - Reports generated by doctors, paramedical staff--to peripheral centre…National centre…Uppsala Monitoring Centre…Compilation of data..analysis of data..causal association is confirmed..guidelines issued regarding the safe use of medicine or (restricted use or withdrawal from the market)

Categorized into:

- Side effects-
- Secondary effects
- Toxic effects
- Intolerance
- Idiosyncrasy
- Drug allergy
- Photosensitivity
- Drug dependence
- Drug withdrawal reactions
- Teratogenicity
- Mutagenicity and Carcinogenicity
- Drug induced diseases (Iatrogenic disorders or Iatrogenicity)

Beware of – Iatrogenic, Idiosyncrasy, Idiopathic, Intolerance

SIDE EFFECTS

- Unwanted often unavoidable Pharmaco-dynamic effects.
- Occur at therapeutic doses.
- Predictable

Examples.

Benzodiazepines- Motor in coordination

H1 Anti-histaminics- Sedation

An effect may be therapeutic in one context but side effect in another context

- Depression of A-V conduction is the desired effect of digoxin in atrial fibrillation, but the same may be undesirable when it is used for CHF.
- Constipation by codeine is side effect but can be used as therapeutic effect in patient with loose motions

TOXIC EFFECTS (Poisonous effect)

It is the dose and duration which makes a poison…. *Paracelsus*

- Over dose or prolonged use.
- The effects are predictable and dose related.

- The CNS, CVS, kidney, liver, lung, skin and bone marrow are most commonly involved in drug toxicity.

ADVERSE EFFECTS OF DRUGS

The term *adverse effects* refers to any undesired responses to drug administration, as opposed to *therapeutic effects,* which are desired responses.

Some adverse effects occur with usual therapeutic doses of drugs (often called side effects); others are more likely to occur and to be more severe with high doses.

- ***CNS effects*** may result from CNS stimulation (eg, agitation,confusion, delirium, disorientation, hallucinations,psychosis, seizures) or CNS depression (dizziness, drowsiness, impaired level of consciousness,sedation, coma, impaired respiration and circulation).
- ***Gastrointestinal effects*** (anorexia, nausea, vomiting, constipation, diarrhea)
- ***Hematologic effects*** (blood coagulation disorders, bleeding disorders, bone marrow depression, anemias, leukopenia, agranulocytosis, thrombocytopenia)

ADVERSE EFFECTS OF DRUGS

- ***Hepatotoxicity*** (hepatitis, liver dysfunction or failure, biliary tract inflammation or obstruction)
- ***Nephrotoxicity*** (nephritis, renal insufficiency or failure)
- ***Hypersensitivity*** or *allergy*
- ***Drug fever***
- ***Idiosyncrasy*** refers to an unexpected reaction to a drug that occurs the first time it is given.
- ***Drug dependence***
- ***Carcinogenicity*** is the ability of a substance to cause cancer.
- ***Teratogenicity*** is the ability of a substance to cause abnormal fetal development when taken by pregnant women.

Drug toxicity (also called poisoning, overdose, or intoxication) results from excessive amounts of a drug and may cause reversible or irreversible damage to body tissues.

SUMMARY

- Any drug can produce some form of ADR
- Significant untoward risks, costs, and increased hospital stays associated with ADRs
- Allergy, atopy, or asthma pts have been suggested to be at an increased risk
- Antibiotics, blood products, drug preservatives and polypeptides may be associated with a higher incidence of reactions
- Drug avoidance whenever possible is still the best method to avoid an ADR

The concept of Essential medicines

- Definition of essential medicines

Essential medicines are those that satisfy the priority health care needs of the population

(Report to WHO Executive Board, January 2002)

A limited range of carefully selected essential medicines leads to better health care, better drug management, and lower costs

(Nu trebiue să lipsească din rezerva de M, trebuie să fie disponibile in orice moment in cantități suficiente, corespunzător ca formă farmaceutică și la preț accesibil pentru toți membrii comunității!)-

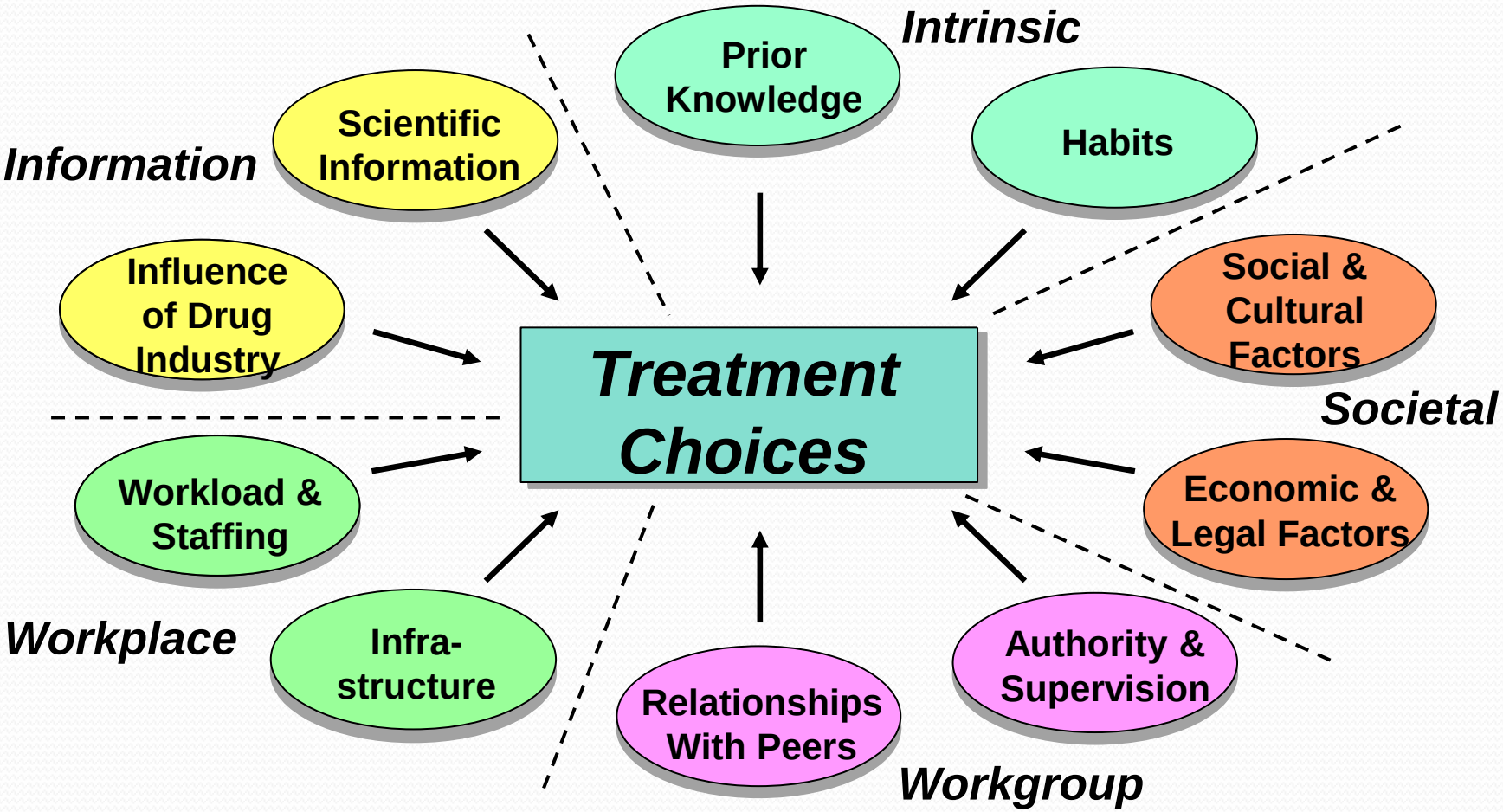
ARSENALUL FARMACOTERAPEUTIC AL UNUI STAT

The rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community.

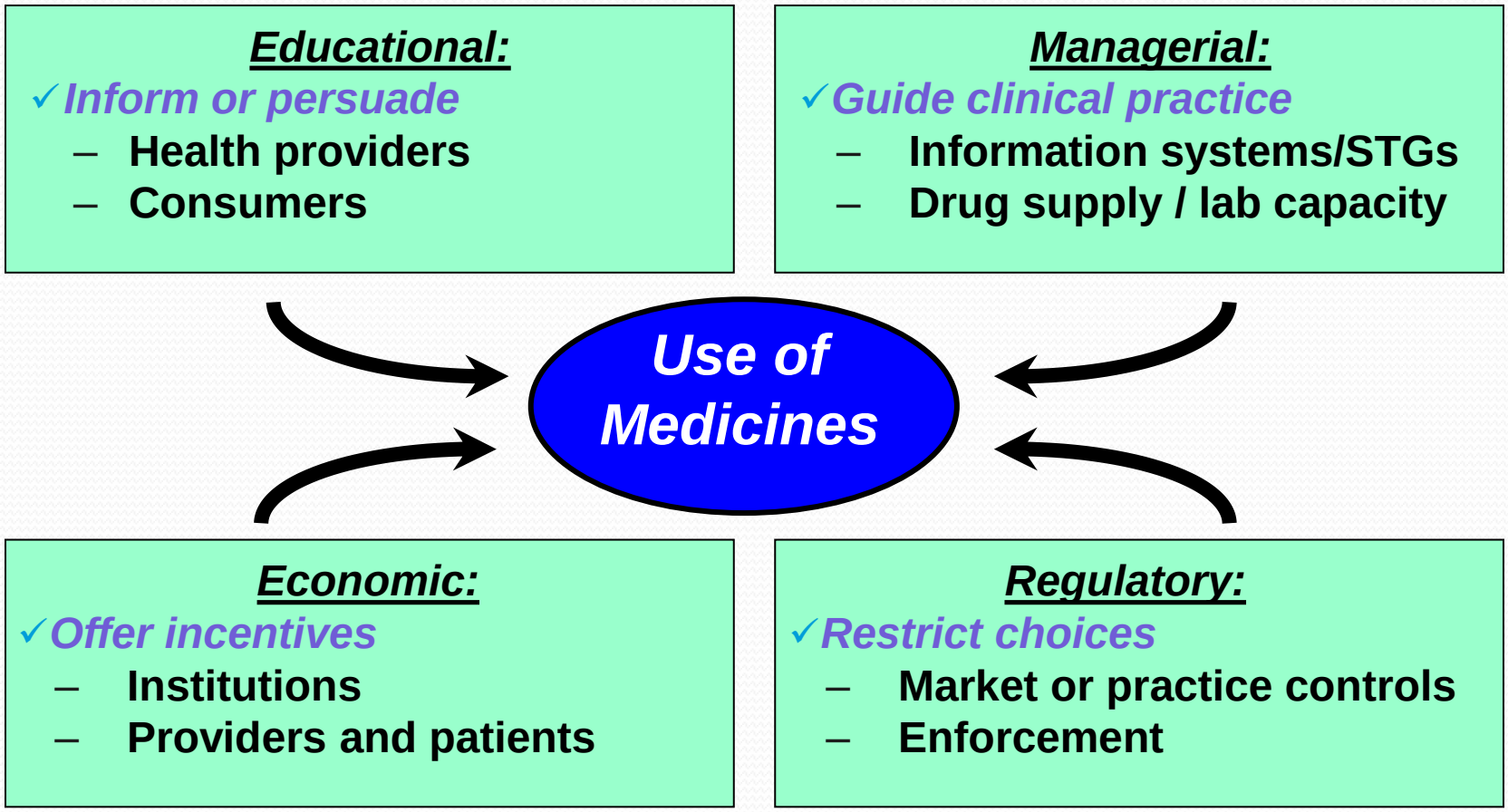
WHO conference of experts Nairobi 1985

- **correct drug**
- **appropriate indication**
- **appropriate drug considering efficacy, safety, suitability for the patient, and cost**
- **appropriate dosage, administration, duration**
- **no contraindications**
- **correct dispensing, including appropriate information for patients**
- **patient adherence to treatment**

Many Factors Influence Use of Medicines



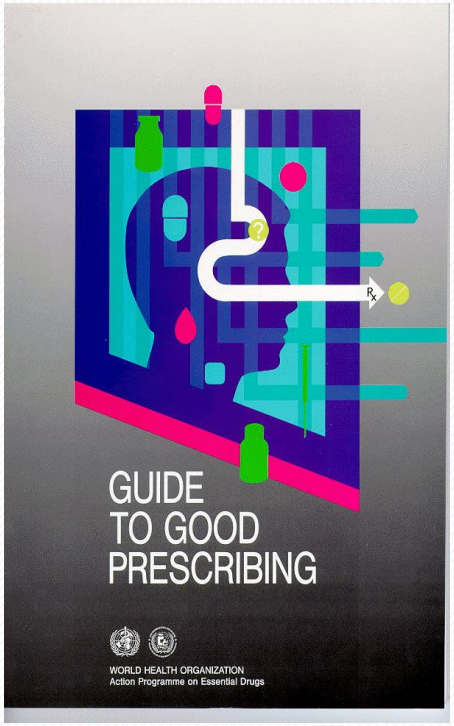
Strategies to Improve Use of Drugs



Training for prescribers

The Guide to Good Prescribing

- **WHO has produced a Guide for Good Prescribing - a problem-based method**
- **Developed by Groningen University in collaboration with 15 WHO offices and professionals from 30 countries**
- **Field tested in 7 sites**
- **Suitable for medical students, post grads, and nurses**
- **widely translated and available on the WHO medicines website**



Steps in choosing a P-drug

- I Define the diagnosis
- II Specify the therapeutic objective
- III Make an inventory of effective groups of drugs
- IV Choose an effective group according to criteria
- V Choose a P-drug

Choose an effective group/drugs according to criteria

During this process, 4 criteria should be used: **efficacy, safety, suitability and cost** of treatment. The easiest approach is to list these criteria in a table.

Of course, efficacy remains of first importance.

Cost of treatment is discussed later.

D-cul: Angină pectorală de efort

Scopul: Profilaxia acceselor anginoase

Grupele PM	Eficacitatea 0,5	Inofensivitatea 0,3	Costul 0,2	În total 1,0
B-adrenoblocante	8 (4,0)	7 (2,1)	8(1,6)	7,7
Nitraţi	7(3,5)	6 (1,8)	8(1,6)	6,9
Blocantele canalelor de calciu	8 (4,0)	8 (2,4)	8(1,6)	8,0

Criteriul acceptabilitate include:

- Contraindicaţiile
- Interacţiunea cu alte medicamente
- Gradul de comoditate la pacient.

Pacientul 45 ani:

- Angină pectorală de efort. CF III. Astm bronşic

Preparatele medicamentoase	Eficacitatea 0,5	Inofensivitatea 0,3	Acceptabilitatea 0,1	Costul 0,1	În total 1,0
Verapamil tab 0,04	8 (4,0)	8 (2,4)	8 (0,8)	7(0,7)	8,0-1
Nifedipin tab 0,02	8 (4,0)	6 (1,8)	7 (0,8)	7(0,7)	7,3-3
Diltiazem tab 0,03	8 (4,0)	7 (2,1)	8(0,8)	7(0,7)	7,6-2
Metoprolol tab 0,05	8 (4,0)	7 (2,1)	4 (0,4)	7(0,7)	7,2-4
Propranolol tab 0,04	8 (4,0)	5 (1,5)	0 (0)	7(0,7)	6,2-5
Izosorbid dinitrat tab 0,02	8 (4,0)	7 (2,1)	8 (0,8)	7(0,7)	7,6-2

Informarea, instructajul, atenţionarea pacientului

- Informarea despre:

- scopul tratamentului;
- modificările posibile după iniţierea tratamentului, RA;
- consecinţele refuzului la tratament sau administrării incorecte;

- Instructajul despre:

- modul, regimul de dozare detaliat şi durata curei de tratament;
- termenii de prezentare la medic;

- Atenţionarea pacientului

- riscurile la modificarea dozei,
- suspendării anticipate.

! Este necesar repetarea de către pacient a celei mai importante informaţii.

Regulatory strategies

Goal: to restrict or limit decisions

- **Drug registration**
- **Banning unsafe drugs - but beware unexpected results**
  - substitution of a second inappropriate drug after banning a first inappropriate or unsafe drug
- **Regulating the use of different drugs to different levels of the health sector e.g.**
  - licensing prescribers and drug outlets
  - scheduling drugs into prescription-only & over-the-counter
- **Regulating pharmaceutical promotional activities**

Only work if the regulations are enforced

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