Introduction to Pharmacology

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Pharmacology

- Pharmakon = Drug; Logos = Science

- (The study of drugs and their interactions with living Systems)

Wide term which includes:
- The investigation of the biochemical and physiological effects of drugs
- The study of drug absorption; distribution; metabolism and excretion
- The knowledge about the history; sources; physical and chemical
Definitions

- **Drug:**

  WHO
  
  “Any Substance or product that is used and intended to be used to modify or explore the physiological system or pathological state for the benefit of the recipient.”

- A chemical substance that is primarily used to reverse a pathophysiological defect =
Drug

- FDA approved definition of drugs
  A chemical substance that is mainly used to treat, control, prevent, or diagnose a specific disease or to prevent pregnancy!!!
- Chemical nature of drugs.
  - Acidic; Aspirin, barbiturates...etc
  - Basic or alkaline; Morphine, Atropine, Alkaloids...etc
Drug

- A substance recognized in an official pharmacopoeia or formulary.
- A substance other than food intended to affect the structure or function of the body.
- Any animal, vegetable or mineral substance used in the composition of medicine.
### Sources of Drug Information

<table>
<thead>
<tr>
<th>Pharmacopoeias (official)</th>
<th>Formulary (non official)</th>
</tr>
</thead>
<tbody>
<tr>
<td>British pharmacopoeias</td>
<td>Pharmaceutical codex(by pharmaceutical Society of Great Britain)</td>
</tr>
<tr>
<td>United states Pharmacopoeias</td>
<td>National Formulary (by American Pharmaceutical Association)</td>
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<tr>
<td>Indian Pharmacopoeias</td>
<td>National Formulary of India</td>
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</table>
Drug Sources:

- Natural
  - Plants (atropine, digoxin), animals (insulin), human (growth hormone), Micro organisms: Penicillin, streptomycin and many other antibiotics.
  - Minerals: Liquid paraffin, magnesium sulfate, magnesium trisilicate, kaolin, etc.
  - Genetic engineering: Human insulin, human growth hormone etc.
  - Semisynthetic (human insulin)
  - Synthetic (agonists; antagonists)

Out of all the above sources, majority of the drugs currently used in therapeutics.
Major Objective

- To Have Drug at Site of Action in Proper Concentration Good Enough to Reverse Defect Without Producing Side or Toxic Effects.
Differences Between Drug and Poison

- All the substances are poisons!
- There are no distinct borderline between them.
- Any drug will be toxic once they are overdosed.
- All drugs are toxins but not all toxins are drugs.
- Toxic dose; lethal dose
Drug Categories

- **Prescription drugs**: Are used under only medical supervision and dispensed by an order of medical practitioner only.

- **OTC (Over The Counter) drugs**: Can be sold over the counter without prescription.
DRUG CLASSIFICATION

There is no fixed rule; classification is usually done according to their:

1. Therapeutic use: e.g. anti-hypertensive drugs; anti-microbial drugs; anesthetics; hypoglycemic drugs; anticoagulants,.....

2. Type of pharmacological action:
This should be precise. e.g. local or general anesthetics; vasodilators; anticoagulants OR according to molecular or cellular site of action in target cells e.g. enzyme inhibitors, receptor blockers, ion channel blockers, inhibitors of transporters, antimicrobials acting on cell wall, DNA, or ribosomes.
3. Physiological systems on which they act: Drugs acting on cardio-vascular system; drugs acting on GIT or CNS or respiratory system

4. Chemical nature or Source:

Common chemical groups or structures can be used to classify drugs that have similarity in their pharmacological profile e.g. benzodiazepines, steroids. For drugs derived from nature, both the plant species or genus and drug chemistry are included e.g. belladonna.
Questions to be answered!!!!!!

- Pharmaceutical process; drug in dosage form:
  - Is the drug getting into patient?

- Pharmacokinetic process:
  - Is the drug getting to its site of action?

- Pharmacodynamic process:
  - Is the drug producing the required pharmacological effect?

- Therapeutic process (clinical pharmacology):
  - Is the pharmacological effect being translated into therapeutic effect?

- Pharmacogenetics
  Individual variations in responding to drugs +
Sub divisions of Pharmacology

**Pharmacokinetics**
- Deals with ADME process i.e. what the body does to the drug.

**Pharmacodynamics**
- Deals with the biological effect of the drug, its mechanism of action and relation b/w its plasma concentration, its response and duration of action i.e. What the drug does to the body.

**Pharmacotherapeutics**
- Clinical application of pharmacodynamics and pharmacokinetics information to cure.

**Clinical pharmacology**
- Deals with the comparative clinical evaluations of new drug for developing its therapeutic efficacy and safety.

**Toxicology**
- Deals with the toxicity and poisonous effects of various chemicals and also with the symptoms and treatment of poisoning.
<table>
<thead>
<tr>
<th>Pharmacology</th>
<th>Deals with the systemic infection or malignancy with drugs with selective toxicity for infecting organisms.</th>
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</thead>
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<tr>
<td>Pharmacogenetics</td>
<td>Deals with the study of inherited ((single\ gen\ mediated)) differences in the drug metabolism or drug response in humans.</td>
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<td>Pharmacogenomics</td>
<td>Deals with the genetic make up ((Genome)) of individual to choose drug therapy.</td>
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<tr>
<td>Pharmacoepidemiology</td>
<td>Deals with the study of use and effects of the drug in large population to establish risk: Benefit ratio of the drug.</td>
</tr>
<tr>
<td>Pharmacovigilance</td>
<td>Deals with the continuous monitoring for unwanted effects and other safety related aspects of marketed drugs. Science related to DAUP ((Detection,\ Assessment,\ Understanding\ and\ Prevention)).</td>
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Essential Medicines, as defined by the WHO are "those drugs that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in appropriate dosage forms, at a price the community can afford."
**Orphan Drugs**

- These are drugs or biological products for diagnosis/treatment/ prevention of a rare disease or condition, or a more common disease (endemic only in resource poor countries) for which there is no reasonable expectation that the cost of developing and marketing it will be recovered from the sales of that drug.

- e.g. sodium nitrite, fomepizole, liposomal amphotericin B, rifabutin, somatropin, digoxin immune Fab (digoxin antibody), liothyronine (T3) and many more.

Governments in developed countries offer tax benefits and other incentives to pharmaceutical companies for developing and marketing orphan drugs (e.g. Orphan Drug Act in USA).
- **Routes of administrations:**

1. Oral
2. Buccal
3. Sublingual
4. Inhalational
5. Parenteral
6. Topical
7. Rectal
8. Transdermal (patches)
9. Subdermal implants
Dosage Forms:

It is the physical form of drug product that is suitable for administration to man. It contains specified dose or amount of drug in a specified quantity or unit of the formulation.

1. Oral dose forms: It includes the followings
   A. Tablets [IR; SR], and capsules
   B. Liquid: Syrup, suspension, elixire
   C. Powder
   D. Herbal plants: seeds, leaves etc..

2. Inhalational:
   A. Aerosol  B. Inhaler  C. Vaporizer (Solutions)

3. Parenteral:
   A. Intradermal (ID)  B. Intramuscular (IM)
   C. Intraperitoneal (IP)  D. Intravenous (IV)
   E. Subcutaneous (SC)  F. Intrathecal (IT)
4. Topical:
   A. Cream, gel, ointment, lotion
   B. Eye drops (ophthalmic)
   C. Ear drops (otic)
   D. Skin patch (transdermal)

5. Rectal:
   • Suppositories

6. Vaginal:
   • Pessaries
Drug discovery & development

1. Starts with prediction—an idea & hypothesis
What helps?

- Awareness of the beneficial effects of plants and animal products (natural sources)
- Chemical identification of a wide variety of natural mediators and the possibility of modifying them
e.g. epinephrine, norepinephrine
- Acetylcholine
- Histamine
- Prostaglandins
- Endogenous Opioids
- Hormones...etc

- Avoid chemicals with highly reactive groups (toxic)
Design and synthesis of useful drugs or substances through simple techniques or with the help of advanced technology.

- **Plant** → fractionation, chromatographic experiments → identification of the active ingredients → isolation → purification → good drug (recently most drugs of plant source could be synthesized)
- **Animal** → isolation of a substance (insulin)

Simple peptides → a.a sequencing machine

Complex proteins → recombinant DNA technology

- **Receptology studies:**
Allowed synthesis of huge number of agonists and antagonists
Rational drug design:

- This implies the ability to predict the chemical structure of drug molecule on basis of 3-dimensional structure of its receptor, employing at present suitable computer programs. Only few drugs in clinical use at present were developed in this rational way. Most drugs were in the past developed through random testing of chemicals, or modified molecules of known drugs that are known to have some other pharmacological effect.

However, as more would become known about detailed structure of receptors, rational drug design with aid of computers will become more feasible.
# Drug development and approval

<table>
<thead>
<tr>
<th>Preclinical testing</th>
<th>Clinical trials</th>
<th>Post-marketing surveillance (Phase 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro studies</td>
<td>Long-term toxicity studies</td>
<td>NDA</td>
</tr>
<tr>
<td>Animal testing</td>
<td>Phase 1 – normal volunteers: safety, pharmacokinetics</td>
<td>1 year</td>
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<td></td>
<td>Phase 2 – selected patients: therapeutic efficacy, dose range</td>
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<td></td>
<td>Phase 3 – large populations of selected patients: therapeutic efficacy, safety in double blind studies</td>
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**Average years**
- IND: 1 to 5 years
- NDA: 2 to 10 years
- Post-marketing surveillance: 1 year
3. Preclinical studies
Studies on tissues and whole animals
- Determine efficacy
  - Isolated tissue e.g. bronchi → organ path → testing drug...etc
  - Animal models
    → drug ↓ BP
    → drug ↓ blood sugar level
- Determine pharmacokinetic parameters
  Absorption, distribution, metabolism...etc

- Determine pharmacodynamics (MOA)

- Assessment of drug toxicity=safety
  - Acute toxicity studies
    Determination of LD$_{50}$; Margin of safety...etc
  - Subacute and chronic toxicity studies.
  - Repeated dose studies.
Daily observation of animals (wt., food and water intake ..)

Obtaining biological samples (blood; urine)

Obtaining tissues (liver; spleen; stomach...etc) for histopathological exam or
- **Special toxicology studies**
  - Mutagenicity (genotoxicity) tests
    - Could define the induction of gene mutations (bacterial mutagenicity test or administration of drug to pregnant animals...etc)
    - Some mutations could result in the development of cancer
- **Carcinogenicity studies**
  - Not always required prior to early studies in man unless there is a high suspicion that the drug could be carcinogenic e.g. suspicion of mutagenicity; highly reactive groups on drug; histopathological abnormalities...
  - Required if the use of drug in man for more than one year or +ve mutagenic test
Clinical drug trials (mainly 4 phases)

- **Phase 0**
  - Phase 0 or first-in-human trials is a recent phase approved in accordance with the United States FDA’s 2006 Guidelines
  - Phase 0 trials are also known as human microdosing studies and are designed to speed up the development of promising drugs by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies
Distinctive features of Phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics and pharmacodynamics.

A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development.
Phase 0 studies enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data

Questions have been raised by experts about whether Phase 0 trials are useful, ethically acceptable, feasible, speed up the drug development process or save money, and whether there is room for improvement.
Phase I

Involves the use of a drug in humans for the first time

It establishes dose level at which signs of toxicity first appear

Conducted on 20-80 healthy men with ages 18-45 yrs
- Usually a single dose is used initially and if no side effects exhibited, the dose is increased progressively until sufficient serum level is achieved (therapeutic level) or some toxic effects appear.
- Such studies are conducted in hospital.
- If no side effects result from single dose, multiple dose studies should be initiated.
Phase II

If phase I studies prove that the **drug** is **safe** to continue, the new drug is administered to **patients** for the first time.

All patients should have only **one problem** (one disease). It assesses **efficacy** and establishes **optimal dose range** in patients (**dose-response studies** are important).

Phase II studies are conducted on **80-100 patients** (certain countries ask for **50-300 patients**), and the patients are observed for **toxicity** to assess the safety of the drug.
Phase III

- Similar to phase II but conducted on large number of patients (several hundreds to thousands; 250-1000 reasonable)
- It also assesses safety and efficacy
- Could detect effects/side effects not observed in phase II
Phase IV

Post-marketing studies

- Controlled and uncontrolled studies are often conducted after drug approval and marketing
- It further assesses **safety & efficacy** of drugs
- It allows for **comparisons between different drugs** used for the same disease
In addition, **phase IV** studies provide evidence of a **new use to the drug** e.g.

- Aspirin-antiplatelet
- Sildenafil citrate-ED

**Double-blind; single-blind placebo controlled studies are usually conducted**
After all these clinical drug trials the drug is usually approved by national or international regulatory authorities and is licensed for General prescribing.
Ethics of the use of drugs in humans

- Full detailed protocol has to be approved by the ethical committee, the institutional review board (IRB)
- All subjects should sign an informed agreement form
- All subjects should be insured for life and damage
Branches of pharmacology usually answer all of the following questions:

- How much of a drug to give? Dose
- How frequent a drug should be given? Related to the biological half-life \( (t_{1/2}) \)
- When to give it? Before or after meals; at bed time, PRN...
- How to give it? administration ... etc
- **Factors affecting the dose**
  - Age
  - Weight
  - Route of administration
  - Sex

- **Factors affecting administration**
  - Physicochemical properties of drugs
  - Site of action
  - Status of patient
  - Dosage interval
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<thead>
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<th>Schedule</th>
<th>Description</th>
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<td><strong>Schedule I</strong></td>
<td>Includes the drugs with high potential of Abuse Eg. LSD, Heroin, Marijuana, Flunitrazepam and Methaqualone</td>
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<tr>
<td><strong>Schedule II</strong></td>
<td>Includes morphine, codiene, pethidine, fentanyl, cocaine, amphetamine, methylphenidate, pentobarbital and secobarbital. These can be used under medical supervision only</td>
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<tr>
<td><strong>Schedule III</strong></td>
<td>The drugs with moderate physical and psychological dependence Eg. Stanzolol, ketamine, nalorphine, thiopental, suppository form of secobarbital and pentobarbital etc</td>
</tr>
<tr>
<td><strong>Schedule IV</strong></td>
<td>They have low potential for abuse and have limited physical and psychological dependence Eg. Long acting barbiturates, Benzodiazepines, Propoxyphene, Pentazocine, Premolineolpidem and Zaleplon</td>
</tr>
<tr>
<td><strong>Schedule V</strong></td>
<td>They have minimal use abuse potential and minimum dependence liability Eg Lamotil and formulation containing Codiene while others are OTC drugs.</td>
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Handout