Section I

BASIC PHARMACOLOGY

Chapter

1

Drugs

Preview: *Pharmacology is an essential basic medical science that provides the foundation of clinical disciplines. The current CBME curriculum stresses more clinical-oriented Pharmacology. In this inaugural topic, students refresh the brief outlook of drug-related terminologies, asked during an assessment. The basic concept helps to assess a better understanding of exercises as recommended in different sections.*

The drug is used to prevent, diagnose, treat, and cure disease. Pharmacology is the discipline of medical science concerned with the scientific study of every aspect of a drug. Thus, drugs and pharmacology are complements of each other. This medical stream drives the international pharmaceutical industries to make mega profits.

PHARMACOLOGY

The word pharmacology is derived from the Greek word **pharmakon** (an active principle or drug) and **logos** (discourse in, science, treatise, study, or knowledge). Pharmacology is the science that deals with the **study of drug** and their interaction with the living system. Pharmacology is concerned with the study of all the aspects of the drug. This scientific discipline builds the intelligence to use the drug for good clinical practice.

Two main pillars of pharmacology are—pharmacokinetics (PK) and pharmacodynamics (PD). A substance (ingredient) that follows the principles of both criteria is considered pharmacologically active.

- **Pharmacokinetics** (*Kinesis* is a Greek word meaning *movement*)—pharmacokinetics is the study of the absorption, distribution, biotransformation, and excretion of drugs, i.e. **"What the body does to the drug"**. PK also denotes the relation between the dose and concentration of the drug, i.e. "**Dose-concentration"**. In brief, PK represents the journey of a drug in the body 'in, through and out'.
- **Pharmacodynamics** (*Dynamics* is a Greek word meaning *power*)—pharmacodynamics is the drug's physiological, biochemical, and therapeutic effects on the body and its mechanism of action, i.e. "**What the drug does to the body"**. PD also denotes the relation between plasma concentration and the effect of the drug, i.e. **"Concentration—effect"**.

DRUG

The drug is derived from the French word **drogue,** meaning a dry herb. WHO defines—A drug as any substance or product that is used or intended to be used to modify or

explore a physiological system or pathological state for the benefit of the recipient. Clinically, a drug is a substance used for the "diagnosis, prevention, treatment, and cure" of a disease.

Drug Vs Medicine

In clinical practice, both the terms 'drug and medicine' are commonly interchangeable but there is a minor difference. **Drug** is a broad term and includes all the pharmacologically active substances (natural, synthetic, or endogenous) used for prevention, diagnosis, cure, and treatment. **Medicine** is mainly used for the treatment of diseases and the clinical relief of patients. It includes both pharmacologically active 'drug' as well as pharmacologically inactive or inert substance 'placebo'. The word drug is linked with addiction in society. For all clinical purposes medicine is more appropriate.

Action Vs Mechanism of Action

There is a slight difference between action and mechanism of action. Better explained by the example—insulin is a hypoglycemic hormone that decreases blood glucose, this is action. But how does this happen? Insulin increases the utilization (uptake) of glucose by tissues via specific insulin receptors, this is the mechanism of action.

SOURCES OF DRUGS

Drugs are obtained from several sources—both natural and synthetic. From a commercial point of view, the majority of drugs are synthetic in nature.

Natural Sources

I. **Plants:** Atropine, morphine, quinine, digoxin.
II. **Animals:** Insulin, heparin, gonadotropins.
III. **Human:** Immunoglobulin, hCG.
IV. **Micro-organisms:** Antimicrobials like penicillin and cephalosporins.
V. **Minerals:** Iron, calcium carbonate, radio-isotopes.

Synthetic Sources

I. **Recombinant DNA technology:** Human insulin vaccines, factor VIII, interferon.
II. **Hybridoma technology:** Monoclonal antibodies (mab).
III. **Cell culture:** Urokinase.
IV. **Semi-synthetic:** Tetracycline, homatropine.
V. **Synthetic:** Fluoroquinolones, proton pump inhibitors.

Remarks

Based on physical and chemical properties, plant products are categorized as:

- **Alkaloids:** Basic insoluble substances that combine with acid to form a soluble salt, e.g. morphine sulfate.
- **Glycosides:** Combination of sugar with non-sugar (aglycone), e.g. digoxin, aminoglycoside, contains amino sugar.
- **Oils:**
  - **Fixed oils** (fat obtained from seeds with calorific value), e.g. castor oil.
  - **Volatile oils** (non-fat obtained from leaves, flowers, etc. without calorific value), e.g. turpentine oil.
  - **Mineral oils** (hydrocarbon mixture obtained from petroleum), e.g. paraffin.

- **Others:**
  - Tannins (non-nitrogenous, astringent compounds), e.g. catechu.
  - Resins (plant exudates, soluble in alcohol), e.g. oleoresin.
  - Gums (plant secretion form mucilaginous collides with water), e.g. gum acacia.

DRUG NOMENCLATURE

Every drug has three names.

i. Chemical Name

- Full chemical description of the drug.
- Usually lengthy, complex, and unsuitable for prescribing.
- Follow the rules issued by IUPAC (International Union of Pure and Applied Chemistry).

ii. Generic Name

- **Nonproprietary/approved/official name:** Assigned by a competent scientific authority such as USAN (United States of Adapted Name), BAN (British Approved Name), or an official agency like WHO (World Health Organization).
- Internationally accepted by WHO. After inclusion in the pharmacopeia, it becomes the official name.
- That could be the same all over the world.
- Similar spelling and pronunciation, so confusion does not arise.
- Convenient to prescribe.
- Economical (no promotional expenditure).
- Difficult for FDC, which has more than two ingredients.
- Quality control—sometimes may be substandard.

iii. Brand Name

- **Proprietary/trade/commercial name:** The name given by the manufacturer.
- Manufacturer is confined to ownership of the particular brand.
- The same drug may have different commercial names.
- Different brand names in different countries.
- Short, catchy, or smart name, but sometimes confusing.
- Suitable for FDC of several ingredients.
- Costly due to promotion and marketing of the brand.

Examples

- Para-acetyl aminophenol, N-acetyl para aminophenol (chemical name).
  Paracetamol, acetaminophen (generic name).
  Crocin, Metacin, Calpol, T-98 (brand name).
- 2-acetoxy benzoic acid (chemical).
  Aspirin, also called acetyl salicylic acid (generic name).
  Disprin, Majoral (brand name).

Name in Special Circumstances

Code name

- Coined during a clinical trial for simplicity, secrecy, and convenience.
- Denoted by alphabet letters (AXPZ) or some numbers (917) or both (MH49P).

Generic name

- Originally refers to genus or class, e.g. penicillins, benzodiazepines, etc. but later it is used as a synonym for the nonproprietary name.
- Usually, the generic name is universal throughout the world but there is some variation due to different systems used earlier. Some of the drugs still have two names, e.g. epinephrine (USAN) is also named adrenaline (BAN), similarly frusemide (furosemide) and lignocaine (lidocaine).
- Acetaminophen and paracetamol both generic names are commonly interchangeable. Paracetamol is British approved name. Paracetamol is derived from its chemical name **para acetyl aminophenol** (BAN) while Acetaminophen is derived from the chemical name **N-acetyl para aminophenol** (USAN)
- A generic version (other than the generic name) of the newly developed molecule is available after the expiry of the original patent.
- Branded generic drugs are those which have been given the commercial name. Such a drug has gone through the ANDA process of clinical trial after patent expiration.

Look-Alike and Sound-Alike (LASA) Name

- Also known as sound-alike and look-alike (SALA) name.
- Many medications appeared very similar when written(spelling) or spoken (phonetics).
- Can be classified as orthographic pairs (similar spellings) and phonological pairs (similar-sounding)
- Sometimes the names of different brands of drugs are very close to each other. Such sound-alike names create confusion, e.g. Allegra (fexofenadine) and Viagra (sildenafil).
- Some medications share similar letters, referred to as look-alike medication, e.g. DTap (diphtheria, tetanus toxoids, acellular pertussis), Tdap (tetanus, reduced diphtheria toxoids, acellular pertussis).
- These confusing names are one of the main causes of medication errors.

Examples

- Cycloserine (antibacterial) and cyclosporin (immunosuppressant) .
- Cotrimoxazole (antibacterial) and clotrimazole (antifungal).
- Eltroxin (thyroxin) and Althrocin (erythromycin).
- Nasivion (decongested) and Evion (vitamin).
- Livogen (iron and folate) and Levozin (levocetirizine).

DRUG TERMINOLOGIES

Prototype Drug

- A drug that represents a **particular group or class**.

- Prototype drug is the ancestral drug from which other drugs of the same class are developed.
- Characteristics or properties of other agents are based on the reference from the prototype drug.
  For example, morphine is a prototype drug of the narcotic analgesic group. Other agents, like codeine and pethidine are concerning morphine.

Drug Generation

- It is a group of pharmacologically similar or related drugs developed or produced in a **particular period**.
- The next group developed after a certain time interval with some modifications from the previous group.
- New group is generally more advanced than a prior counterpart given safety, coverage, and side effects.
- The only limitation is cost and sometimes doubtful safety profile of newer inclusion.
  For example, cephalosporins—I, II, III, IV,V generation; sulphonylureas—I, II generation.

Drug Choice

- Preference is given to the **particular drug**, based on maximum therapeutic benefits.
- Described as **first choice** (preference) or **next choice** (maybe second, third …. as per declined benefits).
  For example, penicillin is a drug of the first choice for the treatment of syphilis. Other drugs are the next choice in case of contraindication and are less effective than the first choice.

Drug Line

- Preference is given to the **group of drugs** based on the maximum therapeutic benefits and fewer adverse effects.
- Described as the **first-line** (more efficacy, fewer side effects) or **second-line** (less efficacious and more toxic than the first line) or third-line, e.g. anti-tubercular drugs—isoniazid, rifampicin, pyrazinamide, and ethambutol are used initially as the first line. Second-line macrolides, fluoroquinolones, aminoglycosides, etc. will be indicated under special conditions.

SPECIAL DRUG TERMS

Designer Drug

This term is used for illegal, lab-made synthetic drugs that mimic the existing drug by molecular modification. It mostly includes psychoactive drugs, that are not only illegal but also harmful to society. Thus, designer drugs are synthetic substitutes for commonly used recreational drugs, produced in small clandestine labs (clandestine means done secretly or kept secret). They are functional analogs, that have been designed to mimic the pharmacological effects of existing original drugs while avoiding being kept under illegal drugs. They are also designed to bypass the drug rules governing manufacturing and marketing. Because the efficacy and safety of these substances have not been evaluated in clinical trials, their use may result in unexpected outcomes.

A new designer opioid China white, developed from a modification of fentanyl, was several times more potent as well as dangerous than its original counterpart. (Insulin analogues are popular as designer insulin, not a designer drug but named designer as produced by modification of the basic design of insulin.)

Club Drug

Also known as '**rave or party drugs'** are used by youths or dancers in nightclubs, bars, concerts, and parties for pleasure and mood, e.g. LSD, MDMA, PCP, ketamine, etc., more often in combination with illegal sedative-hypnotics. Club drugs become even more dangerous and potentially fatal when combined with alcohol.

Me-Too Drug

A drug structurally similar to a prototype or other known drug with an identical mechanism of action but is now marketed by a new pharmaceutical company and is considered a new drug in terms of efficacy, compliance and side effects. It is also known as a '**follow-on drug**'. Thus, it is similar to a pre-existing drug usually by making minor modifications to prototype profiles and used to treat the same clinical condition. Beta-blockers, PPI, and ACEI are commonly used.

Hit and Run Drug

The medications whose duration of action is quite longer than their stay in the body are called "hit and run drugs", e.g. reserpine, PPI . Reserpine acts by combining with the storage vesicle of nerve endings and depletes noradrenalin from vesicles. Its action returns only when new vesicles are synthesized, which takes time. Similarly, PPI has a short half-life but irreversibly inhibits (paralyzes) the pump longer, thus their action persists for one day.

Gateway Drug

As the name indicates, a gateway drug is an introductory habit-forming drug that can lead to the subsequent use of other more addictive drugs. Alcohol and tobacco are commonly used. Marijuana (dried leaves of cannabis sativa/ganja) opens the gate for cocaine use.

Hard and Soft Drug

Hard drugs are liable to disable the individual as a functioning member of society by inducing severe psychological depression and physical dependence such as heroin or cocaine. **Soft drugs** are less dependence-producing. These results are mainly psychological but very little or less physical dependence on alcohol, tobacco, and sedatives.

Blockbuster Drug

A drug that generates huge profits for the pharmaceutical industry, is a major factor in the success of pharmaceutical companies. Tagamet, Lipitor, Advair, Humira, Vioxx, Zoloft and COVID-19 vaccines are some examples of all-time biggest blockbuster drugs.

Smart Drug

Substances commonly referred to as nootropics are claimed to improve human cognitive abilities, creativity, intelligence, and motivation. Such drugs, e.g. caffeine, ginseng, and

ginkgo is used to improve memory, thought, learning, and mood. Methylphenidate is commonly used by students, also called a **study drug**.

Truth Drug

Commonly known as 'truth serum', is a conversational name for a range of drugs used to obtain information from subjects who are unable or unwilling to provide it. Agents such as scopolamine, midazolam, and sodium thiopental are used for this purpose to make a person answerable. Legal and human rights issues are still there.

Auxilliary Drug

A drug that does take care of an important issue of the overall treatment, e.g. use of anesthetics during operation (an auxiliary label is a label added to a dispensed medication package to provide supplementary information regarding the safe administration and storage of medication).

Wonder Drug

A drug (usually newly discovered) that elicits a dramatic positive response in the clinical condition of a patient. Also known as a **miracle drug**, is highly effective with the least side effects and is most widely prescribed. Aspirin has often been called a wonder drug partly because of its effectiveness in many health problems. Penicillin during World War, because of its remarkable effects on infectious diseases.

Recreational Drug

Drug use alters the state of consciousness and creates feelings and emotions. LSD a hallucinogen is commonly used for this purpose. Some recreational agents like tobacco, alcohol, betel nut, gutkha, and caffeine are widely used worldwide.

Orphan Drug

Some drugs are meant for diagnosis, prevention, or treatment of 'rare disease '. A rare disease is called an orphan disease and sufferers as patients/health orphans (orphan receptors are receptors for which there is no endogenous ligand). Orphan drugs may be lifesaving but they are commercially difficult to obtain. There are several orphan diseases out of which about 80% are genetic. Approximately 1000 drugs have orphan status, e.g. miltefosine (kala-azar), anagrelide (polycythemia vera), and deferiprone (iron overload in thalassemia).

Orphan drugs are not easily available due to manufacturing reasons. Such drugs remain unattended due to economic reasons like the enormous cost of production. Manufacturers apathy and lack of interest due to limited demand and less profit. Drug development for such rare diseases may not be able to recover the cost incurred. Orphan drugs receive priority at all stages of drug development. Orphan drugs are developed by the government and offer incentives like tax relief and subsidies.

PHARMACEUTICAL PRODUCTS

The use of FDC is very popular, so students practice differentiating the rational or irrational combinations. Banned drugs and orphan drugs also need attention. Pharmacological particulars such as antimicrobials, hormones, vaccines, nutrients as well as counterfeit drugs and OTC drugs are very common in the pharmaceutical market.

FIXED DOSE COMBINATIONS

A large number of pharmaceutical preparations contain two or more drugs in a definite ratio. Such combinations are popularly known as 'fixed dose combinations (FDCs)'. FDCs are innovative forms of drug therapy that offer distinct advantages to patients as well as physicians. Rational combinations of FDC are efficacious but irrational combinations may be dangerous. WHO has approved authentic combinations in the Essential Medicine List (EML).

As the name indicates, a fixed-dose combination is a formulation of two or more active ingredients (in a fixed ratio) combined in a single dosage form, e.g. drug A + B + C ... in a single preparation.

Common FDCs in clinical practice are anti-microbial, antitubercular, anti-diarrheal, anti-HIV, anti-hypertensive, analgesics, antacids, cough mixtures, nutrients combinations (hematinic, multivitamins and tonics), etc.

Criteria of Drug Combination

- The basis for combining drugs must be sound.
- Each drug component must have an independent mode of action.
- Cannot affect pharmacokinetics as well as pharmacodynamics of each other.
- Combination must be synergistic, antagonistic, or complementary in their effect.
- Both components should have different side effects; preferably one may counter the other.

Advantages

- Better patient compliance.
- Convenience in terms of reduced frequency of administration.
- Synergistic combinations improve therapeutic potential, e.g. addition of clavulanic acid in amoxicillin.
- Prevention of drug resistance, commonly seen with single-drug therapy after prolonged use, e.g. antimicrobial.
- Enhances efficiency and ensures when more than one agent has to be administered, e.g. anti-tubercular, anti-HIV.
- Side effects of one component may be counteracted by another, e.g. combination of potassium-sparing and losing diuretic.
- Only one expiry date simplifies dosing, whereas single products may have different expiry dates.

Disadvantages

- Pharmaceutical irrational combinations.
- Effects of pharmacokinetics and pharmacodynamics of each other.
- Antagonism of action.
- Additional adverse effects.
- Difficult to adjust the individual dose or flexibility in dose.
- Interaction among different components.
- Different time courses of action and inappropriate dose intervals.
- Difficult to trace out causative agents during drug reactions.

- Contraindication to any component means contraindication of FDC.
- Confusion of the therapeutic aims and false sense of superiority due to the addition of agents in combination.
- Additional cost burden, if a patient does not need all the ingredients in combination.

Regulation of FDC

New drug discovery and clinical trials are very costly affairs. A newly invented drug fails even at phase III of the trial and this puts a huge financial burden on the pharmaceutical company. The introduction of FDC is the least expensive. When well-known drugs combine as an FDC, the new formulation just requires approval and license from the authority. The introduction of a new FDC is more economical and profitable for pharmaceutical companies, in place of spending huge amounts on clinical trials. An FDC is treated as a new drug because combining two or more drugs' safety, efficacy, and bioavailability of individual ingredients may change. WHO approved only a few rational combinations in the latest essential medicine list.

COUNTERFEIT DRUGS

Despite official regulation, fraudulent drugs are flooding the pharmaceutical market worldwide and present a serious health problem. Such drugs are popularly termed counterfeit, spurious, or imitation drugs. Spurious drugs are formulations manufactured concealing the true identity of the product and made to resemble another drug, especially in some popular brands to deceive the buyer and cash on the popularity of original products. Some common practices are:

- Correct ingredient but less quantity (tablet paracetamol 500 mg contains less).
- False label—wrong or low-cost ingredient (strip of ofloxacin has ciprofloxacin inside).
- Non-bioequivalence (poor quality of correct ingredients with correct amount)
- No active ingredient at all (use of placebo).
- Adulteration—something is added to an active drug.

Preventive measures are enforcement of the Drug Regulation Act and quality control of preparation. Regular check-ups and raids by drug inspectors.

OVER-THE-COUNTER DRUGS

Drugs that a person can buy without a prescription. Such easily available non-prescription drugs are known as, over-the-counter (OTC) or more commonly OTC drugs (explained in communication pharmacology).

SOME INTERESTING TERMS

Drug holiday (drug vacation, medication vacation): It stands for deliberate interruption of long-term therapy to restore effectiveness or reduce the risk of tolerance or toxicity. Discontinuation for three weeks may temporarily improve responsiveness in some conditions. The concept is not useful in practice due to fear of resistance (anti-tubercular drugs) or aggravation of symptoms (anti-angina, antiepileptic). The patient sometimes starts their drug holiday for compliance.

Drug honeymoon (honeymoon period/effect/phase): A time span during which problems known to exist are either not manifest or are ignored, just like the **honeymoon period** during which newlywed couples are most cordial and passionate with each other. In medical science, the honeymoon period is a brief period of disease remission, which follows the diagnosis of a disease and before its impact is felt (as seen in Type I diabetes during which no insulin therapy is required). The **honeymoon effect** is an initial period of temporary efficacy followed by a loss of effectiveness (as seen with antiepileptics in epilepsy). The **honeymoon phase** is a term for the early stage of illicit drug use before the development of addiction, during which the abuser is enjoying the buzz without recognizing his growing dependence.

Drug bank: A comprehensive freely accessible online unique bioinformatics resource. The database contains detailed information on drug (chemical, pharmacological, pharmaceutical) data with comprehensive drug targets (protein, sequence, structure). Data was released at an interval of 2 years. The first version was released in 2006. The most recent is the 5.0 version which contains approximately 15000 drug entries.

Bioterrorism: Some agents have the potential to be used as biological weapons. Such stable agents have been produced easily and kept to be used when required against mankind. *Yersinia pestis*, *Bacillus anthracis*, *Clostridium botulinum*, *Brucella*, and *Francisella tularensis* can result in plague, anthrax, botulism, brucellosis, and tularemia, respectively. The most recent incident is a worldwide pandemic of coronavirus-induced COVID-19 that resulted in a global lockdown.

EXERCISE

The inclusion of general consideration aims to imprint an image in the brain about all possible drug-related terminologies, commonly used in day-to-day practice. Although this is an addition, it helps in the memorization of students. A brief overlook definitely adds to the getting more scores because of its content frequently asked during an oral examination.

Chapter

2

Routes of Drug Administration

Preview: *The route of administration is the way by which drug formulations, fluids, and other substances are introduced into the body. Knowledge of routes is important for the administration of various dosage forms (an exercise of the new curriculum).*

There is a correlation between medicinal formulation and their application in the body. For the proper delivery of various dosage forms (the forms in which a drug is administered), there is a need for a specific route of administration. Selection criteria for routes depend on:

1. **Drug properties:**
   - **Nature:** Solids (orally), gases (inhalation), liquid (oral as well as parenteral route).
   - **Solubility:** Water-soluble drug (oral route), oily drug (IM), irritant drug (IV route).
2. **Amount:**
   - **Large volume:** IV route via infusion.
     Oral, inhalation, topical, and enema according to indications.
   - **Small volume:** All routes.
3. **Therapeutic indication:**
   - **Site:** GIT (oral), lung (inhalation), and skin (topical).
   - **Need:** General (oral), emergency (parenteral).
4. **Patient clinical condition:**
   - Conscious, cooperative—oral route.
   - Unconscious, irritable, severe emesis, breathlessness, shock—parenteral route.

A drug formulation can be administered in the body by following major routes—**enteral**, **parenteral,** and **topical.** Administration routes can be divided according to drug action. **Systemic action** is produced by the enteral and parenteral routes while **local action** is by the topical route.

ENTERAL ROUTE

- Most natural and accepted mode of drug administration.
- Drug is mainly given by oral route (PO), which enters into GIT (*Enteron = intestine*).
- Sublingual (buccal) and rectal modes are also considered under the enteral route, but the drug does not enter directly into GIT.

- Drugs used by the SL route are lipophilic in nature with short onset of action.
- Dosage forms are both solid such as tablets (DT, SR, EC, MD), capsules, powders, etc., and liquid like drops, syrups, suspensions, mixtures, linctus, elixirs, etc.

Advantages

- Safe and convenient.
- Self-administration (no need for assistance).
- Non-invasive, painless.
- Economical (does not need devices).
- Drugs intended for local GIT action, e.g. anthelmintic and laxative are better utilized orally (neither absorbed nor destroyed).

Disadvantages

- The pathway involved in drug absorption is more complicated.
- Lesser bio-availability (first-pass metabolism).
- Onset of action may be slow (not suitable for emergencies).
- Food, milk, and other drugs interfere with absorption.
- Non-palatable and irritant drugs cannot be administered.
- Difficult to use in patients with severe vomiting.
- Cannot be given to unconscious, non-cooperative, and bedridden patients.
- Demerits of the oral route can be minimized by specific modifications of formulation such as enteric-coated, sugar-coated, and sustained-release tablets.

PARENTERAL ROUTE

- As the name indicates, the parenteral route means all routes other than enteral or gastrointestinal *(per = beyond, the enteral = intestine).*
- Drug is administered directly into blood or body fluid to achieve maximum bio-availability.
- This route is used for drugs that are poorly absorbed, irritant, unstable, or degradable in GIT.

Advantages

- Rapid and predictable action.
- Gastric irritant drugs can be given.
- Maximum bioavailability (bypass first-pass metabolism).
- Used in patients with severe emesis and diarrhea.
- Can be used in unconscious and non-cooperative patients.

Disadvantages

- Poor patient compliance.
- Self-medication is difficult.
- Inconvenient, as it needs assistance and devices like a syringe, needle, etc.
- Risk of infection and local irritation at the injection site.
- Mandatory aseptic precaution.
- Injections are painful and not generally accepted.

- Injury to adjacent tissues possible.
- Immediate side effects can develop.
- Expensive.

Parenteral drugs are administrated by following major routes—injections, transmucosal, inhalational, and transdermal.

(i) Injections

Drug injected into specific tissue or site (vein, muscles, dermis, etc.) through a syringe and needle. Common modes are:

- **Intramuscular (IM):** In large skeletal muscles.
- **Intravenous (IV):** In a superficial vein (bolus or infusion).
- **Intradermal (ID):** In the dermis of the skin (very small quantity).
- **Subcutaneous (SC):** In subcutaneous space under the skin.

Special modes

- **Intra-arterial:** In the artery.
- **Intra-cardiac:** In the heart.
- **Intra-peritoneal:** In the peritoneal cavity.
- **Intra-thecal:** In the subarachnoid space.
- **Intra-articular:** In the joint.
- **Intra-medullary:** In the medulla of long bone.
- **Intra-lesional:** Directly into the lesion.
- **Others:** Intra-penile, intra-vesicle, and retro-bulbar, etc.

(ii) Transmucosal

Drugs are absorbed across the mucous membrane (rich blood supply). It includes three routes:

- **Sub-lingual/ buccal:** Drugs (lipid-soluble, nonirritant tablet) kept under the tongue.
- **Intra-nasal:** Drug introduced through the nostril by nasal spray.
- **Rectal:** The drug (irritant) can be put into the rectum by enema or by suppository (sublingual and rectal routes are also kept under the enteral route)

(iii) Inhalation

Drugs (gases, volatile liquids, aerosol, etc.) are directly given into the respiratory tract. Lungs provide a large surface area for absorption. Meanwhile, alveoli are thin and vascular, allowing the inhaled drug's rapid onset of action and maximum bioavailability. Common aerosol devices used as—metered-dose inhalers (MDI), nebulizers, dry powder inhalers (DPI), etc.

(iv) Trans-cutaneous (dermal)

Highly lipid-soluble drugs are applied over the skin for slow and sustained action. Common modes are **inunction, jet injector, and adhesive patches.**

TOPICAL ROUTE

- Drugs are applied on the skin or mucous membrane of nasal, aural, oropharyngeal, conjunctival, vaginal, and anal areas, etc. for localized actions.

- Effects depend upon lipid solubility, duration, and area of exposure.
- Hydrated skin has more permeability than dry skin.
- Dosage forms are cream, paste, gel, dusting powder, ointment, gargle, lotion, lozenges, paint, etc.

Advantages

- Convenient, self-application.
- Excellent patient compliance.
- None or very few systemic side effects.

Disadvantages

- Local hypersensitivity reactions.
- Risk of infection after prolonged use.

EXERCISE

Routes of drug administration are very important as per the therapeutic efficacy of a drug. This exercise can be clubbed with dosage forms for clarity of explanation. Students must know different types of routes, their advantages and disadvantages.

Chapter

3

Uses of Drugs

Preview: *A drug has been used for medical (therapeutic) and nonmedical (social) purposes. It is the dose, that decides the fate of a drug either as medicine or poison. Students must be aware of the prevention, therapeutic, and emergency use of drugs.*

DOSE

It is the amount of drug required for therapeutic actions**.** Posology is concerned with the study of the dose of drugs. To achieve the desired effect, a drug can be administered by following major routes**—enteral** (oral/*enteron-intestine*), **parenteral** (other than oral/*per-beyond, enteral-intestine*), and **topical** (surface). Types of dosage are based on the following characteristics.

(i) **Use of a drug:**
- **Prophylactic dose:** Dose of a drug used for prevention of disease.
- **Therapeutic dose:** Dose of a drug used for treatment and cure of disease.

(ii) **Frequency of administration:**
- **Single-dose:** Only a single dose is needed.
- **Multiple doses:** Dosages are administered at a definite interval.

(iii) **Amount of drug:**
- **Fixed-dose:** A fixed amount of drug (high safety profile) used.
- **Variable dose:** Dose is adjusted according to clinical parameters.

(iv) **Tolerability of drug:**
- **Minimum tolerated dose:** Normal dose (maximum dose sometimes) at the start, gradually decreasing later, to restore normal physiology, i.e. downward titration.
- **Maximum tolerated dose:** The minimum dose at the start with a gradual dose increment of very low safety margin drugs, i.e. upward titration.

(v) **Schedule of drug dosing:**
- **Loading dose:** Administered large dose initially, to attain a steady state.
- **Maintenance dose:** Smaller doses, later on, to maintain therapeutic plasma concentration

(vi) **Miscellaneous dose:**
- **Standard dose:** Average dose to all irrespective of age and weight.
- Lethal dose, toxic dose, minimum dose, maximum dose, etc.

THERAPEUTIC APPLICATIONS

The drug is used for the diagnosis, prevention, treatment, and cure of a disease in human

- **Diagnosis:** Use of radio-contrast media (barium for skiagram).
- **Prevention:** Use of vaccines (BCG for Koch's disease).
- **Treatment:** Use of hormones (insulin for diabetes).
- **Cure:** Use of antimicrobials (ampicillin for pneumonia).

Indication Vs Contraindication

Indication: Referred to as the use of the drug in clinical conditions. Indication varies from drug to drug. Some drugs may be used for a **single indication**. e.g. metformin is indicated in noninsulin-dependent diabetes mellitus, similarly adenosine in PSVT. Most drugs have **multiple indications—**aspirin is indicated as an analgesic, antipyretic, anti-inflammatory, and anti-platelet agent. Apart from malaria chloroquine is also indicated in hepatic amoebiasis, rheumatoid arthritis, and photosensitivity reaction.

Contraindication: Referred to as the non-use or avoidance of a drug in a particular condition due to safety reasons. Drugs should not be used due to specific age, sex, disease conditions, and possible toxicity considerations, e.g. aspirin is not advised in children with influenza and varicella due to the risk of fatal hepatic-encephalopathy (Reye's syndrome). Teratogenic drugs, e.g. sodium valproate and steroids, are not indicated in pregnancy (preferably in the first trimester—the period of organogenesis) due to the impending risk of foetal malformation.

Special Indications

Off-label use of drugs: Drugs can be used in a way different from approved drug labels. It means, the unapproved use of an approved drug for a disease that is not approved to treat. Off-label prescribing of medicine is prevalent worldwide because it gives freedom physicians to apply new therapeutic options based on the latest evidence. It might be useful in some patients but it can expose them to unknown health risks. Some examples of off-label uses are—azathioprine in atopic dermatitis and psoriasis, lidocaine in post-herpetic neuralgia, intranasal desmopressin in nocturnal enuresis, and sildenafil in children's pulmonary hypertension.

Drug-repurposing (repositioning/reprofiling/re-tasking): A strategy for identifying new uses for approved drugs that are outside the scope of the original medical indication. This concept offers several advantages over developing an entirely new drug as it reduces the risk, cost, and time of the drug development process. Aspirin was initially marketed as an analgesic but after nine decades, its low dose was used as an antiplatelet agent in cardiac conditions.

Therapeutic diagnostic uses of a drug: Sometimes, clinical symptoms, signs, as well as investigations do not confirm the diagnosis but the patient still has problems with a specific disease. In such a situation, the most suitable therapeutic agent(s) will be advised on a trial basis, e.g. antimalarial, and antitubercular drugs. Improvement of symptomatology after appropriate drug administration will confirm the diagnosis.

DRUG AND PREVENTION

'Prevention is better than cure'. Prophylaxis is concerned with the use of specific agents to prevent the development of disease states. This is an outdated concept mentioned in

Indian medicine. Its main objective is related to good health and a disease-free state. Common approaches are:

- Use of specific agents to prevent disease in the future:
  - Immunization by vaccine.
- To prevent deficiency state:
  - Iron to prevent anemia.
- Use of agents for a particular purpose:
  - Contraceptive agents to prevent conception.
- Use of a drug in suspected/high-risk subjects:
  - Chemoprophylaxis in tuberculosis, malaria.
- Special situations:
  - Anti-HIV agents in high-risk persons (pre-exposure).
  - Anti-rabies vaccine in high-risk (pre-exposure) .
  - Addition of iodine in common salt (to prevent goiter).

Immunization Vs Vaccination

Immunization is the process of inducing immune responses which may be cellular or humoral. It is one of the most cost-effective health interventions known to mankind. Eradication of smallpox and now polio from the world is a landmark achievement of global immunization in medical science.

Vaccination is the process of inoculating the vaccine (live attenuated, inactivated, killed, and recombinant). The vaccine induces antibody production thereby conferring longer-lasting active immunity, such as GOI sponsored Mission Indradanush for childrens. In special circumstances, there is a need for temporary, curative but immediate protection by the use of readymade immunoglobulin and antisera.

DRUGS AND MEDICAL EMERGENCIES

Some of the drugs are extensively used during emergencies due to their immediate life saving potential. Apart from being important instruments, such drugs are an integral part of the emergency unit. Each well-equipped critical care unit must have an emergency tray that contains specific drugs. The list of common drugs (alphabetical) along with their indications is presented here:

- Adrenaline: *Cardiac arrest, shock, anaphylaxis.*
- Aminophylline: *Severe bronchospasm.*
- Atropine: *Bradycardia.*
- Adenosine: *PSVT.*
- Aspirin: *Acute coronary syndrome.*
- Calcium gluconate: *Hypocalcemia.*
- Dopamine: *Hypotension, shock.*
- Dexamethasone: *Anaphylaxis, shock.*
- Dobutamine: *CHF.*
- Digoxin: *Atrial fibrillation.*
- Furosemide: *Fluid overload, CHF.*
- Glucose: *Hypoglycemic coma.*
- Hydrocortisone: *Shock, anaphylaxis, asthma.*
- Heparin: *Acute coronary syndrome.*

- Lignocaine: *Ventricular fibrillation, tachycardia.*
- Mannitol: *Raised ICT, intraocular pressure.*
- Magnesium sulfate: *Eclampsia, convulsion.*
- Morphine: *MI, acute pulmonary edema.*
- Nitroglycerine: *Angina*.
- Pheniramine maleate: *Angioedema, anaphylaxis, urticaria.*
- Pethidine: *Obstetrics analgesia, postoperative pain.*
- Potassium: *Hypokalemia*.
- Sodium bicarbonate: *Metabolic acidosis*.
- Sodium nitroprusside: *Hypertensive crisis.*
- Streptokinase: *MI, pulmonary thromboembolism*.
- Vasopressin: *Variceal bleeding*.

Oxygen, plasma expanders, IV fluids, blood, blood products, etc. are other agents as needed.

MANAGEMENT SKILLS

Students must know ADCDE of emergency management. All clinicians must have skills in the emergency management of patients regardless of their specialty. Clinicians should have a basic knowledge of **ABCDE** of resuscitation.

"**A**irways, **B**reathing **C**irculation, **D**rugs, **E**xposer"

- Ability to decide action plan after integrated correlation of history (from relatives), physical and clinical examinations.
- Should have the expertise to perform basic procedures such as venipuncture, suturing, stomach wash, and wound care.
- Management of common poisoning with the antidote is essential.
- Monitoring of patients, both clinical as well as via equipment.

PLACEBO

A drug is an active substance with specific pharmacological action. But in contrast to a drug the placebo is an inert form without specific pharmacological action. It acts by psychological means rather than pharmacological means. Placebo is a Latin word that means—*I may please you/I shall be pleasing or acceptable.* Both drugs and placebo are used in the treatment of human beings.

Dummy medication resembles actual preparation in appearance in context with colour, flavour, strong taste, and odd shape producing more psychological impact, thereby more placebo effect. All forms of the treatment have some placebo effect. The placebo effect is not limited to medicine but is also seen with diagnostic procedures, surgery, and physiotherapy.

A placebo is indicated to benefit a patient psychologically, when the active drug does not require, and as a control in a clinical trial, to compare and assess whether the new compound is significantly better or just like a placebo.

DRUGS USED IN SOCIETY

Drugs are considered an integral part of society because most of them are used in various forms in routine life. Although drugs are generally used as medicine for the welfare of

mankind. There are certain fields where the drug is used for a purpose other than medicine. Certain things are commonly used in the routine life of the community in the form of drinks (tea, coffee, wine) and mouth fresheners (tobacco), etc. Consumption of such agents is habit-forming and becomes a part of routine activities but their excess may endanger life.

Tea, Coffee and Cola Drinks

These drinks contain methylxanthines as a principal constituent. There are three xanthines, namely caffeine, theophylline, and theobromine found in plants. They are qualitatively similar but differ markedly in potency. Caffeine is the main xanthine found in tea, coffee, and cola drinks as well as in chocolates. In addition, tea contains theophylline while a bar of chocolate contains theobromine. Caffeine is more potent than theophylline, both stimulating mental activity and improving physical performance. In general, caffeine induces feelings of alertness, well-being, and euphoria. Meanwhile, the onset of boredom, fatigue, inattentiveness, and sleepiness is postponed. Regular use of caffeine-containing drinks as part of normal social life. Slight tolerance to the effects of caffeine may occur. A withdrawal symptom, attributable to psychological and mild physical dependence occurs and includes headache and irritability.

Wine

The history of alcohol is part of the 'history of civilization'. Alcohol may be useful as a blind energy source (7 calories per gram). Consumption of wine and other alcohol-containing drinks is common in various strata of society. Although alcohol is widely used in medicine, misuse is quite common. Alcohol is a cerebral depressant, that results in sedation and sleep. It also imparts recent memory. Excess may produce a phenomenon of blackout after which the drinker has no memory of his behaviour. Dependence varies among drinkers for whom companionship is the principal factor. Reasons behind the development of dependence are the amount, frequency, and duration of abuse.

Tobacco

Chewing of tobacco in beetle, gutkha, and in the form of smoking (cigar, hukka, and cigarette) is very common. The principal components are nicotine and tar. The composition of tobacco smoke is complex (over 500 compounds have been identified, and most are carcinogens). Both smoking and chewing tobacco produce pleasurable effects for a short time but are major risk factors for respiratory and oral carcinoma.

NON-MEDICAL USES

Drugs are not only used as diagnostic or therapeutic agents but they are also used for other purposes in different fields. Non-medical uses may be endangering life.

Lifestyle Drugs

These can be considered agents used for good health-related purposes and well-being. Lifestyle drugs are used by both sexes, mainly due to the current trend of looking 'fit and smart' or 'health conscious'. Some examples are—orlistat, rimonabant (reduces body weight) minoxidil, finasteride (re-growth of hair), botulinum toxin (removes wrinkling), alcohol, tobacco (recreational), tea, coffee, and soft drinks (mood change).

Drug and Sports

The rewards of competitive sports, both financial and personal as well as national prestige are the cause of determination to win at any cost. Drugs are used to enhance performance in different capacities such as for 'strength sport' (to improve body weight and strength) and 'endurance sport ' (to enhance the oxygen-carrying capacity of blood). Some examples are erythropoietin (marathon race for long period endurance), caffeine, amphetamine (to increase energy for a short period), beta-blockers (shooting for steadiness of hand), and anabolic steroids (wrestling and weight lifting). The use of such agents is accompanied by the risk of diseases, and metabolic and electrolytes disturbance.

EXERCISE

Students must remember the wider use of drugs in therapy, in society, and in special circumstances. They must know about the types of formulations, strengths, administration routes, indications, and precautions. This part can be accompanied by some project work such as preparing an emergency tray by incorporating specific drugs.

Chapter

4

Drug Reactions

Preview: *No drug is safe. All drugs are responsible for reactions that range from mild to severe presentations. Such unfavourable reactions to drugs are referred to as adverse drug reactions (ADRs). This segment refreshes the overview of drug reactions because reporting adverse drug reactions is an important exercise in the new curriculum.*

A drug is nothing but a two-edged sword, that can damage not only the enemy (disease) but also can affect the user (adverse effects). ADR is most common in children, pregnant women, and patients who have hepatic, renal and cardiac diseases. The activities relating to the detection, assessment, understanding and reporting of adverse drug effect is conducted under pharmacovigilance.

ADR Vs ADE

Two interesting terms related to adverse outcomes are **adverse reaction** (seen from the point of view of a patient) and **adverse effect** (seen from the point of view of the drug).

Adverse drug reaction (ADR), as defined by WHO, any response to a drug that is noxious and unintended and that occurs at doses used in man for the prophylaxis, diagnosis, or therapy of disease or modification of physiological functions.

Adverse drug event (ADE) is an unwanted medical occurrence, which may present during the treatment with pharmaceutical products but does not necessarily have a causal relationship with the treatment.

Classification

ADRs are classified into types A to U, as under:

Type A (Augmented)

- Most common, expected, and predictable reaction.
- Related to dose and pharmacological action of the drug.
- Non-serious, corrected by dose adjustment.
  For example, dryness of mouth by atropine (side effect, at usual dose). Ototoxicity by streptomycin (toxic effect, exaggerated side effect).

Type B (Bizarre)

- Uncommon, unexpected, and unpredictable reactions.
- Not related to dose and pharmacological drug action.

- May be idiopathic, genetically determined, or immunological.
- Require stoppage of therapy, which can result in mortality.
  For example, chloramphenicol induced aplastic anaemia (idiopathic). Haemolytic anaemia by primaquine in G6PD deficiency (genetic). Anaphylaxis by penicillin (immunological).

Type C (Continuous use)

- Results after long-term use of the drug.
- Dose as well as time-related.
- This may be due to adaptation and cumulation.
  For example, Cushing syndrome by prednisolone (immunosuppression). Analgesic nephropathy, drug dependence.

Type D (Delayed)

- Appears sometime after the use of the drug, i.e. time-related
- Mostly results in serious consequences.
  For example, thalidomide induced phocomelia (teratogenicity). Cancer by hormones, radioisotopes (carcinogenicity).

Type E (Ending of use)

- Manifest soon after withdrawal or sudden stoppage.
- Seen in chronic drug users.
  For example, MI after sudden atenolol (prophylaxis) withdrawal. Corticosteroids may lead to acute adrenal insufficiency.

Type F (Failure)

- Next common, after type A reaction.
- Result from drug interactions.
  For example, contraceptive failure from rifampicin (enzyme inducer).

Type U (Unclassified)

Reaction is not kept in the above types.

COMMON TERMINOLOGIES

Side Effects

Common, predictable, and unavoidable but manageable effects. Extension of pharmacological response produced at the therapeutic dose, e.g. hypoglycaemia from insulin, sedation from promethazine. A side effect that might be troublesome in particular conditions may prove to be useful in other circumstances, e.g. dryness is the side effect of atropine, it is useful as a pre-anesthetics medication.

By observing side effects, a new drug can be derived after some modification of the parent drug. Sulfonamide is used as a chemotherapeutic agent but hypoglycaemia is one of its side effects. After structural modification, a hypoglycaemic agent sulfonylurea is synthesized and is now used as an oral antidiabetic. Sometimes untoward and undesirable side effects may develop at therapeutic dose, e.g. diuretic-induced hypokalaemia.

Toxic Effects

Exaggerated forms of side effects develop when a drug is administered repeatedly. This may be due to cumulation, e.g. repeated injection of streptomycin results in ototoxicity. The toxic effects may also develop from large or higher doses, e.g. morphine in a normal dose stimulates respiration but can cause respiratory depression at a higher dose.

Secondary Effects

Indirect consequences of main drug action, i.e. effects are not due to direct drug action. The development of superinfection after prolonged antimicrobial use which suppresses important gut flora is a classic example. Pseudomembranous-enterocolitis is a condition of bloody diarrhoea developed after prolonged use of broad-spectrum antibiotics, e.g. Clindamycin, due to the multiplication of *clostridium difficile* as an opportunistic pathogen. Similarly, corticosteroid decreases host immunity.

Intolerance

Intolerance means failure to tolerate, better to say lower threshold to the normal action of the drug. A person may show an exaggerated response even with the usual therapeutic dose or small dose, e.g. single tablet of quinine results in symptoms of cinchonism.

Idiosyncratic Reactions

Qualitative drug reactions, could be due to:

(a) **Genetically determined:** There is an inherited abnormal response due to a definite gene defect. Development of hemolytic anaemia in a person deficient in G6PD, when exposed to oxidizing agents such as sulfonamide, primaquine, and salicylate.

(b) **Idiopathic:** No definite cause known. Aplastic anaemia develops in some users of chloramphenicol.

(**Pharmacogenomics** is a discipline concerned with the utilization of genetic information to understand and explain the variation of responses in individuals).

Hypersensitivity Reactions (Drug Allergy)

Immunologically mediated drug reactions are included in this group. Four types of allergic Reactions—types I, II, and III are immediate (seen within minutes to hours) while type IV is a delayed reaction (seen after days).

Type I is an **anaphylactic reaction** commonly encountered. It includes local anaphylactic reaction to the drug, pollen, dust, and atmospheric pollutants, e.g. rhinitis (nose) and bronchial asthma (lung). A systemic reaction popularly known as anaphylaxis proves to immediately endanger life, e.g. penicillin injection (a prior sensitivity test is needed).

Type II is a **cytotoxic reaction** in which certain drugs like sulfonamide; carbamazepine phenytoin, etc. will result non-urticarial rashes and blood dyscrasias such as agranulocytosis, haemolysis, and thrombocytopenia.

Type III is **immune complex-mediated hypersensitivity** and includes local 'arthus reaction' and systemic 'serum sickness reaction'. Drugs such as aminopenicillins, quinolones, antiepileptics, etc. develop classical dermatological manifestations. A few of them are Jarisch-Herxheimer reaction (JHR), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema nodosum leprosum (ENL).

Type IV is a **delayed hypersensitivity reaction** seen after 48–72 hours, e.g. contact dermatitis. This principle is used clinically for BCG vaccination and tuberculin skin tests.

Other Reactions

Iatrogenic reaction/disease: Physician-oriented drug-induced disease, e.g. antitubercular-induced hepatitis, steroid-induced Cushing syndrome, and chloroquine-induced retinopathy.

Drug withdrawal reactions: Reactions seen from the sudden or abrupt cessation of the drug after prolonged use. This may manifest as: (i) rebound of disease, e.g. β-blocker precipitate angina or (ii) withdrawal symptoms after alcohol. Such situations can be better handled by gradual withdrawal.

Drug interactions: There may be an increase, decrease, or development of some new effects, when we prescribe two or more drugs *in vitro* or *in vivo*.

Teratogenicity: Ability of a drug to develop foetal malformation if administered in pregnant women during the period of organogenesis. A classic example was the thalidomide disaster in 1958–61, during which phocomelia, i.e. seal limb deformities were seen in newborns.

Mutagenicity and carcinogenicity: Drugs causing inherited genetic abnormality are mutagens. Carcinogens are drugs that have the potential to develop cancer. It includes anticancers, hormones, radioactive compounds, etc.

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) is testing, that measures the concentration of certain medicines in body fluids for therapeutic information. It is done to make sure the amount of medicine taken is safe and effective. TDM helps to increase efficacy, assess diagnosis, and decrease toxicity from relevant drugs.

General Considerations

- TDM is the pragmatic manipulation of the dose of a drug using plasma concentration as a guide to optimize its efficacy and identify toxicity.
- Plasma, serum, and blood are commonly used as samples which should be collected after steady-state concentration (4–5 $t_{1/2}$). Saliva, tears, milk, and urine can be used in special cases.
- It is done with special instruments. Proper sample collection is also mandatory for good results.
- Before conducting TDM, its limitations must be kept in mind that some low safety profile drugs are indicated for TDM.
- To fully utilize the TDM, results must be interpreted in the light of a complete clinical situation using all available information.

Indications

- Drugs that have a narrow therapeutic index or therapeutic window.
- Drugs that exhibit saturation kinetics.
- Drugs that exhibit wide inter-individual variation in metabolic rate, leading to marked differences and steady-state plasma concentration, especially in children in whom differences in body weight and metabolic rate are high.

- Drugs for which small changes in the plasma concentration of drugs are likely to exhibit large changes in drug response.
- When signs of drug toxicity are difficult to recognize clinically.
- When signs of under-dosing or over-dosing are indistinguishable.
- When there is a potential risk of drug interactions.
- When there is doubt about patient reliability in taking the drug.
- When the patient's condition is refractory to a dosage regimen.

TDM is indicated for antiepileptics, antipsychotics, antiarrhythmics, lithium, theophylline, digoxin, and aminoglycoside. While TDM is not needed for drugs whose dose can be correlated with clearly measurable indices such as blood sugar and BP. Therefore, safe drugs, tolerance-producing drugs and drugs responsible for hypersensitivity reactions or idiosyncratic reactions do not require TDM.

Methods

- Spectrophotometer and calorimeter: Economical but not specific.
- Enzyme-linked immunosorbent assay (ELISA): Economical as it uses enzymes.
- Radioimmunoassay (RIA): Expensive, as it needs radioisotopes.
- Fluorescence polarization immunoassay (FPIA): Accurate, precise, and time-sparing.
- Chromatography: Expensive but most specific measures both drug as well as metabolite. High-performance liquid chromatography (HPLC) is commonly used.

BANNED DRUGS

A drug is not recommended and forbidden, if there is no therapeutic justification.

Reasons of Ban

- Drug is less or non-curative, and a better option is available, e.g. terfenadine results in arrhythmia, and levocetirizine is safe.
- Risk of serious adverse effects but a safe alternative is available, e.g. nimesulide causes liver damage, paracetamol is a better alternative.
- Adverse effects could be more hazardous than the disease, e.g. nitrofurazone can cause carcinoma.
- Superior drugs with lesser adverse effects, are available, e.g. metformin is safe anti-diabetic while phenformin causes lactic-acidosis.

(i) Single drug preparation

Examples of some common banned drugs:

- Antiallergics: Astemizole, terfenadine, phenylpropanolamine.
- Anti-inflammatory: Valdicoxib, analgin, nimesulide (for children up to 12 years).
- Antidiarrheal/GIT drugs: Furazolidine, cisapride, tegaserod, quineodochlor.
- Antidiabetics: Phenformin, rosiglitazone.
- Anti-obesity: Fenfluramine, sibutramine.
- Miscellaneous: Human placental extract, carisoprodol.

(ii) Fixed Dose Combinations (FDCs)

Most of the FDCs are irrational. Some examples are:

- Anti-microbial combinations.
- Paracetamol with other NSAIM.
- Cough mixtures.
- Multivitamins and haematinics.

EXERCISE

Students can differentiate various types of drug reactions. They can make a list of common agents responsible for particular reactions. They make a list of different categories of banned drugs and a list of drugs that require therapeutic drug monitoring. They can search for banned drugs on the website and find out the reason for their ban. A group discussion-like activity may be conducted.

Chapter

5

Clinical Trials

Preview: *Curiosity arises in the mind about 'how a drug is born'? Drug discovery and further development are a very complex and time-consuming process. There are various ethical issues evolved from the conception to the delivery of a new drug. A brief overview is necessary for all medical students.*

DRUG DISCOVERY AND DEVELOPMENT

Drug discovery and development are among the most important translational scientific activities that contribute to human health. Drug discovery is the process of identifying compounds that have the potential to become therapies. Drug development is essential to bringing a new drug to the pharmaceutical market. How a drug is born? Lots of factors and processes are hidden behind from conception to delivery of a new one. There are several ethical issues involved. Drug discovery and development is a long, costly, and complex process that requires the coordinated collaboration of different departments including research, development, manufacturing, regulatory, marketing, and business management.

A newly born drug can never be used in human subjects for a particular indication. To prevent any unexpected adverse happening in humans, it first undergoes a series of tests in animals (or others) to predict the safety nature followed by human testing. The planned systemic scientific intervention of such an agent in human beings is popularly known as a 'clinical trial'. Thus clinical trials can be considered a special type of bioassay of new drugs in humans. A meticulously conducted clinical trial is the safest way to determine efficacious medical treatment. The clinical trial is a time-consuming and highly expensive process. Moreover, failure rates are quite high.

CRITERIA OF DRUG TO BE TESTED

- A new chemical entity (NCE)—any substance first time proposed to be developed as a new drug.
- A marketed drug that has already been approved for an indication by a certain route in a certain dosage regime, but is now being proposed to be for a new indication or by another route or in other dosage regimes.
- New drug combinations such as FDC (although approved individually), are proposed to be combined for the first time.
- If the drug is already approved or marketed abroad, then a phase III trial (multicentric) is usually required.

REGULATORY AFFAIRS

The clinical trial is an ethically designed human test for drug safety and efficacy before its widespread use for therapy. There are various rules, regulations, and amendments guiding the process of drug development. Some important ones are—**GLP** (good laboratory practice), **GCP** (good clinical practice), **GDP** (good documentation practice), **GRP** (good regulatory practice), and **GMP** (good manufacturing practice).

The drug discovery and development process is designed to ensure that only those pharmaceutical products that are both safe and effective are brought to market. Drug development is a very complex and time-consuming process. For convenience, the entire process can be divided into three steps:

(i) Drug discovery
(ii) Pre-clinical
(iii) Clinical trial phase, followed by review and post market monitoring.

DRUG DISCOVERY

Drug discovery involves the sequential phases of target selection (choosing a disease to treat and developing a model for that) and drug selection (finding a drug that works within that model system). Target selection helps us to find the right drugs for the right person. The discovery of a new compound is quite a lengthy and time-consuming process. Common ways of developing new drugs are:

- Identifying the active ingredient from traditional remedies.
- From natural products, plants, animals, and microorganisms.
- Random screening of natural and synthetic entities.
- A serendipity, i.e. observation by chance.
- By changing the structure of existing drugs.
- Bioinformatics/genomics.

Technology innovation has helped to speed up development processes and save time. Advances in cell biology and receptor technology have helped in developing automated screening systems for new drugs. The most popular techniques are—designing new drugs using computer-aided drug design (CADD) and high content screening (HCS) in which 'in vitro cell-based assays' are used to screen a large number of compounds for their effects. Other methods are combinatorial biosynthesis (to develop several compounds within a short period and systematically modify an existing compound chemically to act on a selected target), luminance-based assays (assay and screening of the compound), and techniques such as robotic high throughput screening (HTS) and more sensitive ultra-high-throughput screening (UHTS).

Hit to Lead (H2L)

With the help of computer-aided drug design (CADD), HTS, and HCS, hits and leads are identified. Newly discovered compounds, that first undergo the process of screening are referred to as **hits** (hit confirmation). Hit is a molecule with a confirmed structure, desired activity, and good profile through screening. If a compound is found fit for evaluation and undergoes optimization (to increase the affinity, efficacy, stability, and bioavailability) then it is identified as a **lead** compound (lead optimization). Therefore, a hit compound is a molecule that shows the desired type of activity in a screening assay. Lead compounds selected from a collection of hits show potential therapeutic benefits.

The leads (new drug molecule) have to be formulated into a suitable dosage form (tab, capsule, injection, patches, etc.) based on characteristics such as solubility, stability, compatibility, etc. The code name is coined during clinical trials for simplicity, secrecy, and convenience. The new compound is denoted by alphabet letters (AXPZ), some numbers (917) or both (MH49P). Now newly invented molecules are tested to determine their efficacy and safety in animals followed in humans. Ethical committee approval is mandatory before conducting studies on animals and humans.

PRECLINICAL EVALUATION

The aim of the preclinical evaluation is, to see whether the newly discovered molecule is 'safe or not'

- A compound has been first tested either in animals or alternatives by *in vitro*, *in vivo*, and in-silico methods for toxicity and safety.
- Pharmacological potential of the new entity involves the use of animals or alternatives such as isolated cell culture, tissues, enzymes as well as a computer model (GOI amendment 2023 replaces the use of animals in drug testing).
- Animal testing is done according to standards laid down as good laboratory practice (GLP). The animal house should be registered with CCSEA. This ensures the reliability and reproducibility of lab data with minimum human errors.
- Animals used for preclinical studies are small (guinea pig, mouse, rat, rabbit, etc.), and large (cat, dog, monkey). The choice of species is based on which will give the best correlation to human trials.
- At least two more species should be used. Preferably one species should be a rodent (due to genetic similarity to humans).
- At least two routes of administration should be used, one must be enteral and the other will be an expected route probably used in the future.
- Animal studies comprise preliminary pharmacological screening (dynamics and kinetics) and should integrate with special studies such as behaviour, reproductive, and toxic studies like teratogenicity, carcinogenicity as well as mutagenicity.
- Total study on average takes 1 to 2 years (sometimes 3–5 years) for its completion. and comprise acute (short studies), sub-acute, and chronic (large studies) components.
- After experimentation, most are euthanized for further analysis.
- Limitation of animal studies is a poor predictor of drug safety in humans. It is unreliable, time-consuming and expensive. Animals do not naturally get many diseases that humans do. Compounds indicate safety in animals will result in only 10–20 percent safety in human subjects.
- Use of 'alternatives '(substitutes) in place of animals (these alternatives have been defined by **3Rs—R**eduction, **R**efinement and **R**eplacement). *In vitro*/in silico techniques include tissue/organ culture, stem cells, DNA chips, chromatography, and computer analysis models. Comparatively, it is less expensive and yields quick results, disadvantage includes the lack of an appropriate alternative to study whole responses like animals.
- Best approach is, that a candidate compound is initially tested in alternatives. Studies in living animals have shown whether the compound works the same way inside the body as it did in the artificial environment of the lab.

- If an animal or alternative study indicates adequate efficacy and reasonable safety, then the compound will be subjected to study in human beings.

If a preclinical study reveals acceptable efficacy and safety, then the drug will be further studied scientifically in human subjects. A suitable formulation with stability of the appropriate dosage form is made based on the physiochemical properties of the new molecule. This is essential because such tested drugs cannot be used directly in a population just based on the results of animal studies due to differences in anatomical, physiological, and biochemical parameters. Human beings could not be treated as guinea pigs for drug testing. Their safety is the prime concern. Code of conduct, rules, and regulations protect them during the well-planned clinical trial.

After the successful completion of preclinical testing of the new drug, the pharmaceutical company files an 'investigational new drug (IND)' application to the regulatory authority for permission to test the drug in humans. Thus, the company gets legal status for a new investigational molecule as a new drug. IND becomes effective if the authority does not disapprove it within 30 days.

Types of Clinical Trials

Based on the objective and phases of a clinical trial, there are different types of trials:

- **Treatment trial:** Conducted to test a new treatment, new approach, and novel method.
- **Prevention trial:** To study medicine, vitamins, and minerals that lower the risk of developing the disease.
- **Screening trial:** Conducted to test the best way to find a disease.
- **Diagnostic trial:** To find a better test for procedures and diagnosis of a disease.
- **Vaccines trial:** To identify candidates and development of required antibodies.
- **Medical devices trial**, e.g. stents, intraocular lenses, and orthopedic implants.
- **Quality of life trial:** Study the benefit of treatment, side effects reducing drug and lifestyle changes, e.g. diet modification that improves the quality of life.

Clinical Trial Designs

Randomization, blinded trial (single as well as double-blind), cross-over trial, cross-sectional study, factorial trial, sequential trial, multicentric trial, and placebo control. These are essential to eliminate bias because researchers are unlikely to be deliberately biased. Randomization is a process by which volunteers are randomly selected. In the double-blind trial, both investigator and subject are unaware of the identity of the compound. The randomized, double-blind, and placebo-controlled trial is the most common standard design for a clinical trial.

Clinical Evaluation—Prerequisites

A clinical trial on new drugs must be conducted with written permission from the licensing authority designated by the government. In India, clinical trials are approved and monitored by DCGI under CDSCO. The procedure followed during the trial should comply with 'good clinical practice' (GCP) as recommended by the International Conference on Harmonization (ICH). Essential requirements to initiate a clinical trial are as under:

- In the Indian scenario a trial can, be conducted only after written permission from a licensing authority designated by the Central Government (as specified in rules 122A to E of drug and cosmetic rules). The office of the Drug Controller General of India (DCGI) under the Central Drug Standard Control Organization (CDSCO) has prime responsibility for regulating clinical trials in India or appropriate regulatory agency (FDA in the USA) to conduct clinical trials in the respective country.
- There must be the responsibility of sponsors and investigators, as specified in schedule Y of the drug and cosmetic rule (revised 2005). Good clinical practice (GCP) guidelines as issued by CDSCO. Ethical guidelines for biomedical research on human subjects, suggested by ICMR by the 'ethical principles of declaration of Helsinki'.
- All clinical trials should be registered with CTRI (Clinical Trial Registry of India).
- Investigational New Drug (IND) application to the authorized controlling body.
- Approval of the Institutional Ethics Committee (IEC) or Board (IRB) where the trial has to be conducted. The ethical committee/board is a multidisciplinary and multisectoral independent body of at least seven members or more constituted of medical professionals (clinicians, medical scientists) and non-medical members (legal experts, persons from the community). The chairperson should be from outside the institution.
- IEC should have a written standard operating procedure (SOP) and should maintain a record of its proceedings. The responsibility of the IEC is to ensure the protection of the rights, safety, and well-being of human subjects.
- Success of clinical trials has been based on strict adherence to the **protocol**. The protocol is a standard written document that describes how the clinical trial design will be implemented. The protocol is a document that states the background, objective, design, methodology, and statistical considerations.

Code of Conduct

Present-day guidelines on 'good clinical practice' have evolved through a series of regulations and policy formulations such as the Federal Food and Drug Act, 1906, Food Drug and Cosmetic Act, 1938, Nuremberg Code, 1946, Good Clinical Practice 1980-90 (Indian GCP 2001). Declaration of Helsinki 1964, and World Medical Association (WMA event of 'ethical guidelines for biomedical research on human subjects). To conserve the rights of participants there is the provision of well-planned informed consent.

INFORMED CONSENT

A clinical trial is generally conducted in adults of the age group 18 to 60 years. Children, elderly, pregnant, and nursing women are normally excluded from trial except in some special conditions. The provision of informed consent in writing is essential for the recruitment of subjects. An investigator does not have the right to conduct experiments on other human beings regardless of potential benefits to humanity. Therefore, proper written informed consent of the subject must be secured.

Informed consent is a process by which a subject (healthy individual or patient) voluntarily confirms his or her willingness to participate in a particular trial after having been informed of all the aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented using a written, signed, and dated informed

consent form in a language known to the participant. An informed consent document (ICD) is a document that describes the rights of participants and includes details about the study.

The informed consent form should be drafted in simple language (understood by the volunteer). The patient information leaflet contains all the details regarding clinical research including the purpose of research, study design, study procedure, benefit and risk to the subject, insurance, policy and compensation, etc. The volunteer is asked to read the consent form carefully if the subject is unable to read. A witness should be present during the entire discussion and should sign the form. An informed consent form should be signed and personally dated by the subject and by the investigator. An informed consent form should be signed in duplicate, one copy should be retained with the investigator and one should be given to the study participant. A parent or guardian must give legal consent if a child is under 18 years. As per CDSCO's new directives, there should be an audiovisual recording for vulnerable populations during the informed consent procedure.

Participants' safety is the prime concern. In the event of the occurrence of any serious adverse reaction, the subject shall be withdrawn from the study immediately. Participants receive free medical service and pay for the inconvenience. He should be reimbursed for expenses incurred in connection with their participation in research. All payments, medical services, and reimbursement should be approved by the ethics committee. There is a provision of insurance to the subject for trial-related injury.

Neither the investigator nor the trial staff unduly influences a subject to participate or to continue to participate in a trial. Participation is voluntary with an option to opt out of the study at any time without assigning any reasons. Confidentiality of the subject should be maintained.

CLINICAL TRIAL

- Clinical trial is a team work and it includes clinical pharmacologists, clinicians, preclinical staff, healthcare professionals, and social workers.
- The team has to screen volunteers for inclusion or exclusion from the trial.
- The team also bears the responsibility for the safety of trial participants.
- Stakeholders include sponsor/CRO, IRB, regulatory authority, investigators and study subjects.

Phases of Clinical Trial

Phase I: Human pharmacology/clinical pharmacology and toxicology.

Phase II: Therapeutic exploration/clinical investigation.

Phase III: Therapeutic confirmation/formal therapeutic trial.

Phase IV: Post-marketing surveillance/therapeutic use.

SPECIFIC CONSIDERATIONS

- Phases I–III are premarketing studies while Phase IV is post-marketing surveillance.
- Nowadays, **Phase 0, Zero trial/Micro-dosing study—**a new addition is considered in some of the trials. It has no therapeutic intent. This makes the trial not only cost-effective but also spares time. This phase is initiated with a single micro-dosing

(sub-pharmacological dose or 1/100th of estimated human dose) of test drug in a small number (5–10) of subjects for a short time. This study yields human pharmacokinetics information. Meanwhile, the result may not be significant because the dose used in this phase is too small.

- Phase I to Phase IV are mandatory for clinical trials of newly developed molecules in almost all countries including India. FDA-approved addition of zero phase is not a compulsion.
- The location of the trial will depend on the organizer and type of study, common sites are medical institutions (colleges and universities), hospitals, community clinics, and industry-funded research sites.
- In all phases I, II, and III, the regulatory bodies can impose a clinical hold if the study is found to be unsafe.
- Study of the newer aspects/use of already approved drugs is highly rewarding because the drug is already in use with established safety. It is time-sparing and economical.
- The drug under a clinical trial should be compared with a placebo (a pharmacologically inactive substance) to nullify the subject bias.
- In a nutshell phase I is concerned with screening for safety, phase II establishes the effectiveness while phase III finally confirms safety and effectiveness. In a broad sense. Phase IV studies during the sales.
- Phase II is the most crucial, a poor predictor of drug success with maximum failure.
- For new drug substances discovered in India, clinical trials begin right from phase I.
- It is a compulsion to conduct a multicentric phase III trial for marketing a new drug developed outside India. This is mandatory to generate evidence of the efficacy and safety of the drug in Indian patients.
- If serious adverse effects (SAE) developed during the trial, report SAE to the sponsor within 24 hours and to the ethical committee within one week. The sponsor conveys this to the authority within 14 calendar days.

Phase I

- **Objective:** To determine the safety profile of the maximum tolerated dose.
- **Design:** Open or non-blind.
- **Duration of trial:** 3 to 12 months.
- **Number of subjects:** Generally 20–50 (100).
- Employ healthy volunteers, preferably males.
- **Aim** is to determine the safety, tolerability, and pharmacological profile (pharmacokinetics and dynamic) of the drug and to detect predictable toxicity.
- Preclinical study findings are confirmed in human beings.
- Drug is administered first time in humans, also called as First-in-human (FIH) phase.
- Begin the trial with 1/5th to 1/10th tolerated doses (mg/kg), as predicted from preclinical studies, and ascend stepwise to achieve the effective dose.
- The idea of testing the new drug in normal humans is based on the fact that healthy persons are more likely to tolerate the adverse effects of the drug than diseased persons.

- To minimize risk to the healthy volunteers, the trial should be done in patients with a particular disease if the drug is expected to have significant toxicity, e.g. anti-cancer, anti-HIV.
- Phase I study is the pivotal point around which the successful development of a new drug revolves. It laid the foundation for the planning of further human trials.

Phase II

- **Objective:** To determine efficacy in particular indication and dose range of test drug.
- **Design:** Open or single-blind/double-blind.
- **Duration of trial:** 1 to 3 years.
- **Number of subjects:** Involve 100–300 subjects.
- Drug is studied in patients of both sexes having target disease.
- **Aim** is to evaluate effectiveness in particular indication, safety, and dose regimen (minimum effective and maximum tolerated) in a diseased person.
- Both new drugs and placebo are used.
- Phase II data have been compared with that of standard drugs used for the same disease.
- The phase has further divided into early (II-a) and late (II-b) phases:
  (i) **Phase II-a:** Single-blind design and a limited number of patients are studied to observe the potential therapeutic benefits and dosing requirements. Here patients do not know whether they are receiving a drug or a placebo.
  (ii) **Phase II-b:** Double-blind design, conducted on a large number of patients to ensure the safety and efficacy of the new drug in a specific disease. Here the investigator and patient do not know which agent (or placebo) the patient is receiving.

Phase III

- **Objective:** To generate further expanded testing of efficacy and safety in both sexes of variable genetic and ethnic groups, i.e. to determine the drug's therapeutic benefits.
- **Design:** Large-scale randomized and double-blind parallel and cross-over design.
- **Duration:** Up to 5 years.
- **Number of subjects:** Conducted in a larger number of patients, 500 to 3000 or more.
- Multicentric studies at different centers but centrally coordinated.
- **Aim** is to obtain adequate data on patients with social, geographical, and environmental variations to confirm efficacy in a large population.
- Special categories of the patients such as children and the elderly are also involved.
- Dosage recommendations in special situations such as renal and hepatic disorders are also studied and finalized.
- Trial result is finally compared with placebo and previously established drug.
- Two designs used—parallel design, where a test drug is given to one group and compared with those administered established drug/placebo in another group. Crossover design, where the test drug is alternated with either a placebo or with an established drug in the same patient.

After completion of all three phases of the trial statistical analysis is performed and the data is submitted to drug control authorities for **NDA** (new drug application) to obtain permission for approval. Authority can review an NDA within six months and grant a product license (in case of non-approval explain the reasons, minor deficiencies can be corrected).

Phase IV

- **Objective:** To obtain additional information about rare adverse effects and benefits.
- **Design:** Open, no specific design, because this is post-licensing field surveillance.
- **Duration:** Usually 2 years, but no fixed duration of observation.
- **Number of subjects:** Involve a large number of patients, e.g. 2000–10,000 or more in a defined community.
- The drug can be used commercially but still monitored for long-term safety over several years. The study was performed after drug approval and related approved indication.
- **Aim:** To detect relatively rare side effects of low incidence, unknown drug interactions, and previously unknown and sometimes new therapeutic indications.
- Also compare cost and effectiveness with another drug already in use.
- Periodic Safety Update Report **(PSUR)** should be submitted to the regulatory authority, every 6 months for 2 years and then annually for the next 2 years, i.e. for 4 years. But can be extended in the interest of public health.
- The drug may remain in **new drug status** in controlled marketing for several years until the authority is confident of its release for unrestricted widespread marketing after assuring safety profile.

BIOSTATICS—INTERPRETATION OF CLINICAL DATA

Statistics is the lifeline of clinical trials. The involvement of a statistician saves a lot of money as well as time. After the completion of the clinical trial, the result is subjected to statistical analysis. Various statistical designs have been suggested. The basis of statistical analysis is variability in population because smaller groups of subjects (sample size) are included in the trial but their results are extrapolated for large populations. Biostatistics also imparts the outcome of a clinical trial to know whether a new drug is significantly better than an established older one or a placebo.

Duration and Outcome

The clinical trial is a quite lengthy affair. It takes approximately 5 to 15 years for completion. On average 3–4 years may be expended during preclinical development and 6–10 years on the different phases of the human trial including approval from DCGI (IND—permission to conduct the clinical trial, NDA—permission to market new drug). Suppose 1000 compounds are evaluated for preclinical testing then only very few will enter the clinical trial. After the successful completion of all phases, only one to two compounds get approved.

PATENT LIFE OF NEW DRUG

The life of a patent of a new drug is **20 years**. Usually, it takes 5(10)–15 years to develop the product. A patent cannot be extended beyond the term for which it is issued. Thus,

pharmaceutical will wish to manufacture it as early as possible and it can claim as much of the patent life as possible. Once the patent has expired (say in 5–10 years) other manufacturers can produce the product (now a generic version) and sell it at a lower cost.

A **generic drug** is a medicinal product with the same active ingredient as an innovator drug. As a rule, generic drugs should only be marketed after the innovator drug patent has expired. A generic drug is comparable to an innovator drug product in dosage form, strength, quality, and cost (less expensive because generic manufacturers do not have the investment cost of the development). A generic drug has same the active ingredient, risks, benefits, and use. Generic drug application or ANDA is termed as 'abbreviated' because they are generally not required to include preclinical and clinical data. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent to innovators. After documentation, the manufacturer can assign a brand name and register it. Thus a generic drug is an approved medicinal product, mentioned in 'orange book' with the same active ingredient as an innovator drug and can only be marketed after the innovator drug's patent has expired (Generic drugs contain identical ingredients as the innovator but **Biosimilars** are similar to reference biological products but not identical).

Contract Research Organizations

Contract research organizations (CROs) are service organizations that provide support to pharmaceuticals for research-related services. It provides a wide range of services from registration to commercialization of developed products. Its main aim is the reduction of time and expenses of a clinical trial in a planned way. Usually, a CRO comprises competent persons from different fields and has expertise in administration, technology, biostatistics, regulatory affairs, and marketing.

After successful clearance from the clinical trial, a developed drug is now ready to enter the pharmaceutical market. This is governed by several rules, laws, and schedules. Pharmaceutical medicine is the scientific discipline concerned with the discovery, evaluation, development, monitoring, registration, and medical aspects of the marketing of medicines for the benefit of the patient as well as the community.

Summary of a well-planned clinical trial

Discovery phase: Target identification → identify hits → screen out lead → **drug patent**

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Preclinical phase: Animal/alternative testing → IND

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Clinical phase: Pre-marketing phases 0, I, II, III → NDA, post-marketing phase IV

EXERCISE

During the study of pharmacology, every student knows how a drug is developed and marketed. Even though it is a very broad topic, they have a brief overview of ethical considerations and phases of clinical trials. This part can be clubbed into group discussions and interactive sessions.