COURSE GUIDE

PHS810
PHARMACOLOGY AND THERAPEUTICS IN PUBLIC HEALTH

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INTRODUCTION

Pharmacology in Public Health

PHS 810: Pharmacology and Therapeutics in Public is a biomedical science that is concerned with the study of drugs and their actions on biological systems (living cells, tissues, organs, whole animals) including the human body. This is the science that deals with all experiments, researches and preparations before pills, syrups, ointments and other pharmaceutical dosage forms come in retail to the drugstores. The importance of this science can hardly be exaggerated, since it is referred to the human health and person's well-being. Drugs can treat different illnesses and improve general physical and mental state of a person, but at the same time their wrong usage, mistaken dosage or at least minimally incorrect calculations can lead to unacceptable health outcome. A number of medical and disease conditions are attributed to improper use of drugs and chemical substances. In order to deal with such health situations professionally, the public health practitioner needs to be armed with the basic principles of pharmacology and a good understanding of the characteristics and dynamics of drug actions in man.

Understanding the population perspective of the availability and use of drugs and medicines have been referred to as public health pharmacology. The study is aimed at informing society about the required pharmaco-therapeutic resources and their best use for the common therapeutic good of the whole population and to fulfil the universal human right to adequate health care.

WHAT YOU WILLLEARN IN THIS COURSE

The course will bring to you the knowledge of pharmacokinetics, pharmacodynamics, metabolomics and Pharmacogenetic into focus as important phenomenon in drug actions and effects. Furthermore, therapeutic and adverse drug effects shall be studied in details to acquaint you understand the issues of drug compliance, substance abuse, drug interactions and toxicology needed by public health professional. Emerging public health issues related to pharmaceuticals and phytochemicals would be discussed under evidence-based pharmaco-therapeutics. The Courses consist of units and course guides. The course guides describe briefly the course and its specific objectives and also helps you to know how to go about your Tutor- Marked Assignment (TMT) which will form part of your overall assessment at the end of the course. Also, there will be regular tutorial classes that are related to this course, where you can interact with your facilitator and other students. Please, I encourage you to attend these tutorial classes.

COURSE AIMS

The course aims to you understanding ability to apply Pharmacokinetic/Pharmacodynamic principles in solving Public Health problems.

COURSE OBJECTIVES

To achieve the aims set out, the course has a set of objectives. Each unit has specific objectives which are included at the beginning of the unit. You should read these objectives before you study the unit. You may wish to refer to them during your study to check on your progress. You should always look at the unit objectives after completion of each unit. By doing this, you would have followed the instructions in the unit.
The comprehensive objectives of the Course are given below. By the end of the course/after going through this course, you will be able to:

- define the terms in Pharmacology
- identify the basic principles of Pharmacokinetics and Pharmacodynamics
- analyse mechanisms of drug action of drug used in various diseases
- explain therapeutics and adverse effects of drugs sufficient enough for a public health office to deal with situations involve in;
- describe drug compliance
- discuss substance abuse
- describe drug interaction and Toxicology
- manage emerging public health problems related to Pharmaceuticals and phytomedicines such as evidence medicine

WORKING THROUGH THE COURSES

To complete each course, students are required to read each course unit, read the recommended textbooks and other materials which may be provided by the National Open University of Nigeria.

Each course unit contains self-assessment exercises and at certain points in the course students would be required to submit assignments for assessment purposes. At the end of the course, there is a final examination. A course should take about a total of 20 weeks to complete. Below, you will find listed, all the components of the course, what you have to do and how you should allocate your time to each unit in order to complete the course on time and successfully.

This course entails that you spend a lot of time to read and holding group discussions. I would advise that you avail yourself the opportunity of

attending the tutorial sessions where you have the opportunity of comparing your knowledge with that of other people.

THE COURSE MATERIALS

i. The main components of a given course are:
ii. The Study Guide
iii. Study Units
iv. References/Further Reading
v. Assignments
vi. Presentation Schedule

STUDY UNITS

The course has 9 study units arranged in 3 modules as given below.

MODULE 1	**BASIC PRINCIPLESOF PHARMACOLOGY**
Unit 1	Basic Principles and Pharmacokinetics
Unit 2	Toxicology and Adverse Drug Reaction
Unit 3	Drug Discovery/Development/Toxicity /Phytomedicine
MODULE 2	**APPLIED PHARMACOLOGY IN PUBLIC HEAL TH**
Unit 1	Principles of Drug Action and Effects (Pharmacodynamics)
Unit 2	Mode of Action of Antimicrobial and Chemotherapeutic Drugs
Unit 3	Mode of Drug Action in Diseases
MODULE 3	**PHARMACOTHERAPEUTICS IN PUBLIC HEALTH**
Unit 1	Taking Drug History and Evidence Based Medicine
Unit 2	Pharmacovigilance/Pharmacovigilance in Public Health Programmes
Unit 3	Rational Use of Medicines/Drug Dependence and Substance Abuse

Module -1: This unit focuses on the basic principles of pharmacology and consists of three broad units. Unit 1, focuses on the nature and sources of drugs. Unit one is centred on pharmacokinetic processes which are

concerned with drug administration, absorption and bioavailability, distribution and elimination (by metabolism and excretion). The students will learn some basic description of pharmacokinetic characteristics of drug can provide a great deal of information of relevance therapeutically and/or toxicological effects. Consequences of metabolism (biotransformation), drug interaction, concept of renal clearance, pharmacokinetics changes in pregnancy and lactation, placental transfer of drugs, pharmacokinetics in children and the elderly and geriatric. Unit 2, focusses on toxicology and adverse drug reactions**.** The definition of terms in toxicology, purpose of toxicology, historical perspective of toxicology, toxicology sub-discipline, routes drug toxicity, mechanisms of drug toxicity, classification of toxic agents, and poisons that can heal. Adverse drug reactions are centred on adverse drug reaction classification, types and causes of adverse drug reactions, risk factors of adverse drug reactions and factors masking adverse drug reactions. In unit 3 of this module, the student will learn drug development and phytomedicine that deals with preclinical drug discovery, clinical drug development, (phases of development, ethics in clinical trials, clinical trial design, phases of clinical trials,) and how to appraise a clinical trial. Also, phytomedicine, its introduction and historical background, characteristics of phytomedicines, uses of herbal preparations, preparations of herbal medicines, standardized phytomedicines, routes administration of herbal medicines, safety issues in the use of phytomedicines, challenges of phytomedicine and the future of herbal medicine.

Module 2, Brings the understanding of the principles of drug action (pharmacodynamics), in man, types (mechanism) of drug action, receptor families, the basis of affinity and efficacy, graded drug dose response, potency and efficacy, therapeutic window, factors modifying drug effects in man, assaying receptor affinity and binding, and monitoring drug therapy. Basic mode of action of antimicrobial drugs, definition of terms in antimicrobials, types of antimicrobials, features of antimicrobial drugs, anti-infective drugs, anti-bacterial, antifungal, antiviral, cancer chemotherapy, general introduction and goals of cancer chemotherapy, cell cycle (cell proliferation), classifications and mechanisms of action of antineoplastic drugs, principles of cancer chemotherapy, factors that determine cancer drug response, resistance of cancer cells to chemotherapy. Adverse effects of antineoplastic drugs. Also, antiprotozoal and anthelminthic. Mode of action of drug acting on specific diseases, such as drug acting on the uterus (uterotonics and tocolytics), uterine relaxants, hypertensive disorders in pregnancy, anticonvulsants, contraception and pregnancy, anti-diabetes, drug acting on the heart, cardiac failure, antihypertension, drug acting on pain, drug action on pregnancy and lactation, drug therapy in young, drug therapy in elderly and geriatric.

Module 3, enables the student to learn pharmacotherapeutics issues relating to public health. unit 1 focusses on taking drug history &evidence-basedmedicine. This includes objectives obtaining medication history**,** taking drug history, information sources, challenges with difficult clients, questions to ask, tips for performing medication history, client education, tools, reconciliation and documentation. The other aspect of unit 1 introduces the students to the concepts of evidence-based medicine (EBM) as it relates to modern therapy, sources of Information for EBM general concepts of evidence-based medicine, theories and method, steps of emb model, some cases and examples of how to practice EBM, benefits, -why evidence-based medicine and limitations of EBM. unit.2: pharmacovigilance/pharmacovigilance in public health programmes. Pharmacovigilance as science of ADR reporting, origins of pharmacovigilance (era of safety monitoring, detection of adverse drug reactions, causality assessment, uses and limitation of causality assessment. Pharmacovigilance in public health programmes. unit+ 3, deals with rational use of medicines/drug dependence and substance abuse, example of over the counter (OTC) drugs, common inappropriate prescribing practices, irrational drug combinations, obstacles/reasons irrational use , factors underlying irrational use of drugs, impact of inappropriate use of drugs, the role of hcps in promoting rational drug use, objectives, changing a drug use problem: an overview of the process, strategies to improve use of drugs and, prescriber and dispenser. This unit drug dependence and substance abuse, the burden of substance abuse, classification of drug dependence/substance abuse, diagnosis of drug dependence / substance abuse, management of substance abuse/dependence.

FURTHER READING/ TEXTBOOKS/REFERENCES

Further reading links have been provided at the end of each module. This will help you in your exercises and forms part of your course materials where your assessment and final examination questions shall be derived. Ensure you download and read them.

ASSESSMENT

There are three aspects of the Assessment of the course. First is made of self- assessment exercise, second consists of the tutor marked Assignment (continuous assessment) and third is the final examination at the end of the course. You are advised to do the exercises and go through the further reading links provided at the end of each module. In tackling the assignments, you are expected to apply information, knowledge and techniques you gathered during the course. The assignments must be submitted to your facilitator for formal assessment in accordance with the assignment file. The work you will submit to your tutor for assessment

will count for 30% of your total course work. At the end of the course, you will need to sit for a final or end of course examination of about three-hour duration. The examination will count for 70% of your total course mark.

TUTOR MARKED ASSIGNMENTS (TMAs)

The TMA is a continuous assessment component of your course. It accounts for 30% of the total score. You will be given four (3) TMAs to answer. Three of them must be answered before you are allowed to sit for the end of course examination. The TMAs would be given to you by your facilitator and returned after you have done the assignment. Assignment questions for the units in this course are contained in the assignment file. You will be able to complete assignment from the information and the material contained in your reading, references and study units. However, it is desirable in all degree level of Education to demonstrate that you have read and researched more into your references, which will give you a wider view point and may provide you with a deeper understanding of the subject.

Make sure that each assignment reaches your facilitator on or before the dead- line given in the presentation schedule and assignment file. If for any reason, you cannot complete your work on time, contact your facilitator before the assignment is due to discuss the possibility of an extension. Extension will not be granted after the due date unless there are exceptional circumstances.

FINAL EXAMINATION AND GRADING

The end of course examination for Public Health Pharmacology will be for about two(2) hours and or has a value of **70%** of the total course work.

The examination will consist of questions, which will reflect the type of self-testing, practice exercise and tutor marked assignment problems you have previously encountered. All areas of the course will be assessed.

Use the time between finishing the last unit and sitting for the examination to revise the whole course. You might find it useful to revise yourself test, TMAs and comments on them before the examination. The end of course examination covers information from all parts of the course.

PRESENTATION SCHEDULE

There is a time-table prepared for the early and timely completion and submission of your TMAs as well as attending the tutorial classes. There are three modules and three units in each, followed by TMA. The course is of 15 weeks duration and you are expected to spend 3 hours per week

in your study and preparation (see table 2). You are required to submit all your assignments at the stipulated time and date. Avoid falling behind the schedule time. The presentation schedule included in this course guide provides you with important dates for completion of each e-tutor marked assignment (e-TMAs). You should therefore try to meet the deadlines.

TABLE 1: COURSE MARKING SCHEME

Assignment	**Marks**
Tutor Marked Assignment – 3	Three Tutor Marked Assignments, three marks of 10%each, 30% of the course marks
End of course Examination	70% of overall course marks
Total	100% of course materials

Table 2: COURSE OVERVIEW

Unit	**Title of Work**	**Weeks Activity**	**Assignment (End of Units)**
	Course Guide	**Week**	
1	Basic Principles of Pharmacokinetics	Week -1	Assignment1
2	Toxicology &Adverse Drug Reaction	Week -2	Assignment2
3	Drug Development/Toxicity/Phytomedicine	Week -3	Assignment3
1	Principles of Drug Action (Pharmacodynamics)	Week -4	Assignment4
2	Mode of Action of Antimicrobial & Chemotherapeutic Drugs	Week-5	Assignment5
3	Mode of Drug Action in Diseases	Week -6	Assignment6
1	Taking Drug History & Evidence Based Medicine	Week -7	Assignment7
2	Pharmacovigilance/Pharmaco. in Public Health Programmes	Week -8	Assignment8
3	Rational Use of Medicines/Drug Dependence and Substance Abuse	Week -9	Assignment9

HOW TO GET THE MOST OUT OF THIS COURSE

In distance learning, the study units replace the university lecturer. This is one of the huge advantages of distance learning mode; you can read and work through specially designed study materials at your own pace and at a time and place that suit you best. Think of it as reading from the teacher, the study guide tells you what to read, when to read and the relevant texts

to consult. You are provided exercises at appropriate points, just as a lecturer might give you an in-class exercise. Each of the study units follows a common format. The first item is an introduction to the subject matter of the unit and how a particular unit is integrated with the other units and the course as a whole. Next to this is a set of learning objectives. These learning objectives are meant to guide your studies. The moment a unit is finished, you must go back and check whether you have achieved the objectives. If this is made a habit, then you will significantly improve your chances of passing the course. The main body of the units also guides you through the required readings from other sources. This will usually be either from a text- book or from other sources. Self-assessment exercises are provided throughout the unit, to aid personal studies and answers are provided at the end of the unit. Working through these self-tests will help you to achieve the objectives of the unit and also prepare you for tutor marked assignments and examinations. You should attempt each self-test as you encounter them in the units.

The following are practical strategies for working through this course

i. Read the Course Guide thoroughly.
ii. Organize a study schedule. Refer to the course overview for more details. Note the time you are expected to spend on each unit and how the assignment relates to the units. Important details, e.g. details of your tutorials and the date of the first day of the semester are available. You need to gather together all this information in one place such as a diary, a wall chart calendar or an organizer. Whatever method you choose, you should decide on and write in your own dates for working on each unit.
iii. Once you have created your own study schedule, do everything you can to stick to it. The major reason that students fail is that they get behind with their course works. If you get into difficulties with your schedule, please let your tutor know before it is too late for help.
iv. Turn to Unit 1 and read the introduction and the objectives for the unit.
v. Assemble the study materials. Information about what you need for a unit is given in the table of contents at the beginning of each unit. You will almost always need both the study unit you are working on and one of the materials recommended for further readings, on your desk at the same time.
vi. Work through the unit, the content of the unit itself has been arranged to provide a sequence for you to follow. As you work through the unit, you will be encouraged to read from your text books.
vii. Keep in mind that you will learn a lot by doing all your assignments carefully. They have been designed to help you meet the objectives of the course and will help you pass the examination.

viii. Review the objectives of each study unit to confirm that you have achieved them. If you are not certain about any of the objectives, review the study material and consult your tutor.

ix. When you are confident that you have achieved a unit's objectives, you can start on the next unit. Proceed unit by unit through the course and try to pace your study so that you can keep yourself on schedule.

x. When you have submitted an assignment to your tutor for marking, do not wait for its return before starting on the next unit. Keep to your schedule. When the assignment is returned, pay particular attention to your tutor's comments, both on the tutor- marked assignment form and also that written on the assignment. Consult you tutor as soon as possible if you have any questions or problems.

xi. After completing the last unit, review the course and prepare yourself for the final examination. Check that you have achieved the unit objectives (listed at the beginning of each unit) and the course objectives (listed in this course guide).

FACILITATORS / TUTORS AND TUTORIALS

These are 20 hours of tutorials provided in support of this course you will be notified of the dates, times and location of these tutorials as well as the name and phone number of your facilitator, as soon as you are allocated a tutorial group. Your facilitator will Mark and comment on your assignments, keep a close watch on your progress and any difficulties you might face and assistance will be provided to you during the course. You are expected to mail your Tut or Marked Assignment to your facilitator before the schedule date (at least two marking days are required). They will be marked by your tutor and return to you as soon as possible. Do not delay to contact your facilitator by telephone or e-mail if you need assistance.

The following might be circumstances in which you will find assistance necessary, hence you will have to contact your facilitator if:

- You do not understand any part of the study or the assigned readings.
- You have difficulty with the self –tests.
- You have a question or problem with an assignment or with the grading of an assignment.

You should endeavour to attend the tutorials. This is the only chance to have face to face contact with your course facilitator and to ask questions which are answered instantly. You can raise any problem encountered in the course of your study. To gain much benefit from course tutorials,

prepare a question list before attending them. You will learn a lot from participating actively in discussions.

SUMMARY

You should endeavour to attend the tutorials. This will afford you an opportunity to have face to face contact with your course facilitators and to ask questions which are answered instantly. You can raise any problem encountered in the course of your study.

This course is a study unit of clinical skills. But tutorials and practical clinical skills – will be covered only by a practical attachment in hospital. To gain more benefits from the course tutorials, please prepare a list of questions before attending them. You will learn a lot from participating actively in discussions. I wish you success in the course and I hope that you will find it both interesting and useful.

MAIN COURSE

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MODULE 1 BASIC PRINCIPLESOF PHARMACOLOGY

Unit 1 Basic Principles and Pharmacokinetics
Unit 2 Toxicology and Adverse Drug Reaction
Unit 3 Drug Discovery/Development/Toxicity/Phytomedicine

UNIT 1 BASIC PRINCIPLES OF PHARMACOKINETICS

CONTENTS

1.0 INTRODUCTION TO PHARMACOKINETICS

Pharmacokinetics principles and processes are concerned with the absorption, distribution, and elimination (by metabolism and excretion) of drugs. In pharmacokinetics we try to answer the following questions; 1. Is the drug getting into body (through serum/plasma concentration estimate)? 2. Is the drug getting to the site of action and at what rate/extent (bioavailability, steady state concentrations)? 3. How long does it stay before the body gets rid of it (half-life, metabolism and excretion)? and 4. Are the pharmacological activities being translated into therapeutic effects (therapeutic process)?

Thus, proper mathematical description of pharmacokinetic characteristics of a drug can provide a great deal of information of relevance to both the pharmacological and the therapeutically or toxic effects. By the study of pharmacokinetic process individual and inter-individual variability in absorption, distribution, metabolism and excretion of drugs can be defined. Such studies have contributed much to our understanding of the variability of response to drug.

2.0 OBJECTIVES

By the end of this unit, you will be able to:

- identify basic concepts and scientific underpinnings of the pharmacological sciences
- list various terminologies used in Pharmacokinetics and Pharmacodynamics
- describe both the theoretical and applied aspects of pharmacokinetics like bioavailability, bioequivalence, half-life, order of kinetics, steady state plasma concentration.

- explain how the total clearance of a drug determines its steady state plasma concentration through continuous administration
- state theoretical and clinical significance of drug metabolism, clearance, drug - drug interactions and Pharmacokinetic changes in Pregnancy.

3.0 MAIN CONTENT

3.1 Definition of Terms

i. **Drug:** (There is no single satisfying definition) but can be defined as chemical agents that interact with specific target molecules, thereby producing a biological effect.
WHO 1996 Define drug as any substance or product that is used or intended to be used to modify or explore physiological system or pathological states for the benefit of the recipients.
Dutch word "droog" means dry, used for treatment of disease, for the prevention of illness of pathologic states and for diagnosing disease condition.

ii. **Pharmacology:** Pharmacology is defined as ***(from the Greek word; pharmakon = "drugs" (δάρμaĸ0υ) i.e. drug and the word logos (λόɤϚ), study, explore or science)***Is the scientific study of the origin, nature, chemistry, effects, and uses of drugs. It deals with how drugs interact within biological systems to effect function. A branch of knowledge that has to do with the chemicals that have biological effects.

Pharmacology Simply: the science of drug actions and uses.

Pharmacologists work to identify drug targets in order to learn how drugs work. Pharmacologists also study the ways in which drugs are modified within organisms. A fundamental knowledge of the underlying biological processes is required to achieve these objectives and to identify new targets for future therapeutic intervention. Thus, pharmacologists study many basic aspects of cellular and molecular biology. **Pharmacy:** often confused with pharmacology, is a wholly separate profession concerned with the preparation, dispensing and use of medications. Whereas pharmacy can be viewed as a profession that is part of health care delivery and information systems, pharmacology is a basic biomedical scientific discipline.

In recent years, there has been a dramatic increase in the rate at which novel drugs are discovered and marketed. As a consequence,

it is essential to train a new generation of pharmacologists who will meet the challenges this opportunity presents.

iii. **Clinical pharmacology:** is the division which deals with the pharmacological effects of drugs in man. It provides information about the usefulness, potency, and toxicity of new drugs in humans. It is of great importance for the effective and safe use of drugs in man.

iv. **Medicine:** Is a chemical preparation, which usually but not necessarily contains one or more drugs, administered with the intention of producing a therapeutic effect, *(Medicine usually contain other substances (excipients, stabilisers, solvents etc.)*

Note: To count as drug the substance must be administered as such, rather than released by physiological mechanism.

Toxicology (Greek toxikon means poison) Toxicology is the science of poisons, their sources, chemical composition, action, tests for detection and antidotes. It forms a major part of forensic and environmental medicine. All drugs are potential poisons when given in high doses.

v. **Clinical toxicology** deals with the detection, diagnosis and treatment of poisoning.

vi. **Toxicodynamic**: describes the harmful effects that the poison produces on the body. **Toxicokinetic**: encompasses the absorption, distribution, biotransformation and elimination of the poison.

vii. **Pharmacogenetics:** is a relatively new field, which deals with the study of genetically determined variation in drug response.

viii. **Pharmacokinetics:** Literally, movement of the drug within the body ("what the body does to the drug").

ix. **Pharmacodynamics:** Is study of the biochemical and physiological effects of drugs as well as their mechanism of action. Simply. The study of what the drug does to the body – The mechanism of drug actions in living tissues, Mechanisms of action ("what the drug does to the body").

x. **Therapeutics:** Use of drugs for intended clinical benefits – cure of a disease, relief of symptoms etc.

xi. **Pharmacotherapeutics.** – study of how drug may be used in the treatment of disease – which among the drugs would be most

effective or appropriate for a specific disorder or what dose would be required. – Use of drugs and clinical indications of drugs to prevent and treat disease.

xii. **Pharmacogenetics.** – The study of genetically-determined reactions of drugs in the human body.

xiii. **Absorption**: is how the drug enters the blood
xiv. **Distribution**: how the drug travels in the blood and how it goes into and out of other areas of the body.

xv. **Metabolism**: how the body changes a drug usually in intestine and liver.

xvi. **Drug Elimination**: how the body gets the drug out via kidneys through urine or via liver though stool.

3.2 The Nature and Sources of Drugs

3.2.1. Sources of Drugs Include

1. **Plant sources:** Plants Important source of chemicals developed into drugs e.g. Digitalis, morphine, atropine, Quinine and some vitamins
2. **Animal sources** e.g., Animals Products e.g. Insulin =Cow and pig pancreas tissue, Thyroid drugs (thyroxine),& growth hormones = animal thyroid/hypothalamus tissues

3. **Mineral sources:** Mineral/Inorganic Products Elements with therapeutic effects in human body e.g. lithium, Liquid paraffin, magnesium sulfate, Aluminium, Fluoride etc.

4. **Microorganisms** e.g. penicillin's cephalosporins & other antibiotics

5. **Synthetic** e.g. Aspirin, Sulfonamides, benzodiazepines, phenothiazines, some vitamins

6. **Bioengineered (recombinant DNA technology)** e.g. human insulin, human growth hormone.

3.3 Pharmacokinetics (Pk) Processes

The term 'pharmacokinetics' refers to the rate and manner in which a drug is absorbed, distributed, metabolised and eliminated within and from the body. It is a tool for describing the movement of drug through the body over time, and deals with the processes of absorption from the site of administration, distribution throughout the body, metabolism or conjugation of the drug and elimination from the body. Study of the relationship between dose, amount of drug in the body and therapeutic or toxic effects of a drug

The study of drug therapy encompasses four main processes; Pharmaceutical process, Pharmacokinetic process, Pharmacodynamic process and Therapeutic process

i. **Pharmaceutical Process:** i.e. is the drug getting into the patient? Drug in dosage form, GIT, Hepatic Metabolism
ii. **Pharmacokinetic Process:** Is the drug getting to the site of action? Extracellular fluid (protein bound), tissue site of action,
iii. **Pharmacodynamic Process:** Is the drug producing the required Pharmacological effects?
iv. **Therapeutic Process:** Is the pharmacological Effect being translated into a Therapeutic effect?

3.3.1 Why study pharmacokinetic?

You administer drugs (*dose*) because you seek a certain effect (*response*). A complex chain of events links the administered dose to the observed response. Pharmacokinetics determine the blood concentration from a prescribed dosing regimen. More often the plasma concentration for analytical purposes. Pharmacokinetic data help us understand: dose and schedule (once a day vs. twice a day, etc.), dose adjustments due to drug interactions and other issues. ***Pharmacokinetics is essential for determining dosing regimens.***

An understanding of pharmacokinetics should therefore help the clinician to:

i. Appreciate how dosage regimen are devised
ii. Tailor a dosage regimen to the individual requirements of the patient (e.g. in renal failure)
iii. Determine what may be wrong when a patient fails to response to treatment
iv. Determine why a drug has caused toxicity
v. Elucidate the mechanism of drug interactions.

3.3.2 Why study Pharmacokinetic?

Pharmacokinetic study enables the clinician ask, am I getting the dose, right?

Achievement of the correct dose for individual patients is fundamental to clinical practice. Below a certain threshold concentration, the drug is inactive and above a certain concentration, side effects appear. Therefore, the dose should be aimed to be within the therapeutic **window.** Fig. (1) The therapeutic dose can vary between patients depending on a number of factors.

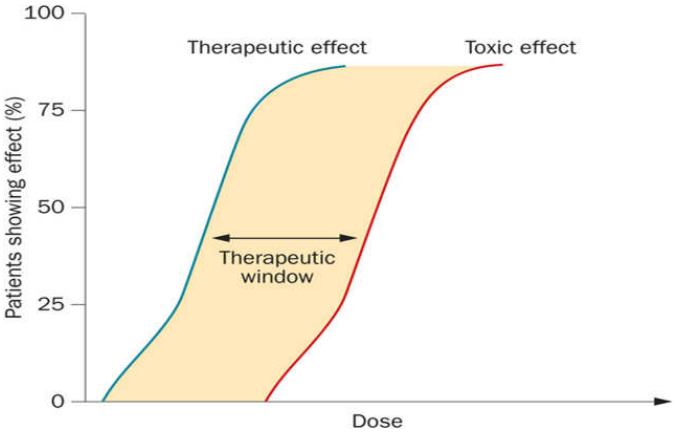


Figure 1: Therapeutic Range of a right dose. (Mathijssen (2014)

3.3.3 Importance of drug concentration

i. Ideally, drug concentration should be measured at the receptor.
ii. Blood or plasma level is used as a measure to reflect the concentration.
iii. You need to identify the ideal concentration-time profile.
iv. Knowledge of individual pharmacokinetic parameters allows you to manipulate dosage regimens.
v. You need to understand the pharmacokinetic characteristics of the drug and the physiological processes that are going on.
vi. Pharmacokinetics is based on the analysis of drug concentrations. In the graphic, after one or more doses, the drug concentration in the desired matrix is measured.

3.4 Absorption

Drug Absorption is the process by which drug proceeds from the site of administration to the site of measurement (blood stream) within the body.

Irreversible transfer processes, which a drug from its site of administration to the systemic circulation.

Absorption is the movement of unchanged drug from the site of administration into the blood. Drug absorption is nnecessary for the production of a therapeutic effect. The movement of drug through membranes is an essential step in absorption and is influenced by the

i. Routes of administration
ii. Physicochemical properties of the drug
iii. The nature of the membrane
iv. The perfusion of the absorption site and the local pH.
v. Formulation, for example, tablets, capsules or solutions

For most drugs, there are a direct relationship between pharmacological response and concentration at the receptor; thus, to be biologically active, drug must gain access to the systemic circulation. Plasma drug concentration depends on both drug kinetics and the design of the drug delivery system.

Table 1: Routes of drug absorption

Oral	Sublingual: drug dissolved under the tongue and absorbed through mucous membranes into bloodstream		Transdermal
Rectal	Inhalational	Intestinal	Parenteral: intravenous, intramuscular and subcutaneous

3.4.1 Oral administration

The most commonly used delivery systems involve absorption of drug from the gastrointestinal tract following buccal, sublingual, rectal or most often, oral administration. Commonly encountered oral drug forms include: includes *Solution, Suspension, Capsules, Tablets, Coated tablets and Modified-release tablets.*

i. ***Coated tablets*** – it is possible to alter the delivery and apparent kinetic of a drug by changing the dissolution characteristics of the tablet. Thus, a table may be enteric-coated to prevent breakdown in the stomach, ensuring that it remains intact until it reaches the small bowel. This approach is commonly used to protect drugs that are destroyed by gastric acid (e.g. omeprazole).
ii. ***Modified-release tablets***– the excipients of a tablet may be modified to improve drug delivery by controlling the rate, amount and duration of drug release over a 24-hour period. This approach is used for drugs with a short $t_{1/2}$ which required frequent dosing to

maintain therapeutic level (e.g. theophylline, verapamil, nifedipine).

iii. ***Prodrugs***– a similar effect may be achieved by using a prodrug. Prodrugs are inactive compounds which are activated by biological fluids or metabolising enzymes following administration (e.g. enalapril is converted to its active form enalaprilat).

For drugs administered orally, absorption may begin in the mouth and stomach. However, most drugs are usually absorbed from the small intestine. The drug passes through the intestinal wall and travels to the liver before being transported via the bloodstream to its target site. The intestinal wall and liver chemically alter (metabolise) many drugs, decreasing the amount of drug reaching the bloodstream. Consequently, these drugs are often given in smaller doses when injected intravenously to produce the same effect

3.4.2 The advantages and disadvantages of oral Absorption

Oral absorption has the following advantages:

i. Convenience and accuracy of dose.
ii. Administration does not require special skills
iii. No aseptic preparations are necessary
iv. In case of drug poisoning or adverse reactions, reversal with antidotes are possible.
v. It is non invasive
vi. Buccal and sublingual modes of administration have added advantage of avoiding first-pass effects and circumvention of the exposure of the acidic digestive fluids.
vii. The disadvantages of oral administration include:
viii. Slow onset of action –at least 15-30mins onset time
ix. First –pass effect
x. Gastric irritation- hence nausea, anorexia and vomiting and diarrhoea

3.4.3 Parenteral administrations

These includes intravenous, intramuscular, subcutaneous, intrathecal, inhalational, intranasal and sublingual/buccal/rectal. Drugs given intravenously (iv) enter the systemic circulation directly. However, drugs injected intramuscular (i.m) or subcutaneous (sc) must cross one or more biologic membranes to reach the systemic circulation. If protein drugs with a molecular mass > 20,000 g/mol are injected i.m or SC, movement across capillary membranes is so slow that most absorption occurs via the lymphatic system. In such cases, drug delivery to systemic circulation is slow and often incomplete because of first-pass metabolism (metabolism

of a drug before it reaches systemic circulation) by proteolytic enzymes in the lymphatics.

Perfusion (blood flow/gram of tissue) greatly affects capillary absorption of small molecules injected im or sc. Thus, injection site can affect absorption rate. Absorption after i.m or sc injection may be delayed or erratic for salts of poorly soluble bases and acids (e.g., parenteral form of phenytoin) and in patients with poor peripheral perfusion (e.g., during hypotension or shock).

Controlled-Release Forms; Controlled-release forms are designed to reduce dosing frequency for drugs with a short elimination half-life and duration of effect. These forms also limit fluctuation in plasma drug concentration, providing a more uniform therapeutic effect while minimising adverse effects. Absorption rate is slowed by coating drug particles with wax or other water-insoluble material, by embedding the drug in a matrix that releases it slowly during transit through the GI tract, or by complexing the drug with ion-exchange resins. Most absorption of these forms occurs in the large intestine. Crushing or otherwise disturbing a controlled-release tablet or capsule can often be dangerous.
Transdermal controlled-release forms are designed to release the drug for extended periods, sometimes for several days. Drugs for transdermal delivery must have suitable skin penetration characteristics and high potency because the penetration rate and area of application are limited.
Many non-iv parenteral forms are designed to sustain plasma drug concentrations. Absorption of antimicrobials can be extended by using their relatively insoluble salt form (e.g., penicillin Gbenzathine) injected im. For other drugs, suspensions or solutions in non-aqueous vehicles (e.g., crystalline suspensions for insulin) are designed to delay absorption.

Intravenous administration is most commonly used when a rapid onset of action and careful control of plasma levels are required.
The drug may be given as a bolus injection, slow infusion or continuous infusion

Slow infusion is used when excessively high transient plasma levels are undesirable (e.g. phenytoin). **Continuous infusion** is used when the drug has a short $t_{1/2}$ or when its therapeutic index is narrow and sustained controlled blood levels are required.

3.4.4 Advantages and Disadvanges Intravenous administration

Advantages Intravenous administration

Advantages intravenous administration includes

i. 100% bioavailability
ii. allow for easy measurement of plasma drug concentration at any time "t"
iii. Modes of actions is faster
iv. First-pass effects is avoided

Disadvanges include

i. require special skills to administer
ii. in case of emergency reversal of effects is almost impossible
iii. completed dosing regimen with fatal outcome
iv. sepsis, embolism may be complications
v. require aseptic procedure for administration

Other modes drug administration includes;
Topical, inhalational and ophthalmic etc.

3.4.5 Mechanisms of Transport (Absorption)

i. Transport and the Cell Membrane Transport?

Transport is any process in which movement of matter and / or energy occurs from one part of a system to another. If a substance can cross a membrane, the membrane is said to be **permeable** to that substance, if a substance is unable to pass, the membrane is impermeable to it. The plasma (cell) membrane is selectively permeable in that it permits some particles to pass through while excluding others. Across the cell membrane without any assistance, substances can pass through if they are lipid soluble and if they are of small particle size.

The small intestine is where the majority of drug absorption takes place. The small intestine has:

A much larger **surface area:** small intestine = 200 m^2, stomach = 1 m^2

A much better **blood flow** (for perfusion rate-limited absorption) small intestine = 1000 mL/min through intestinal capillaries, stomach = 150 mL/min

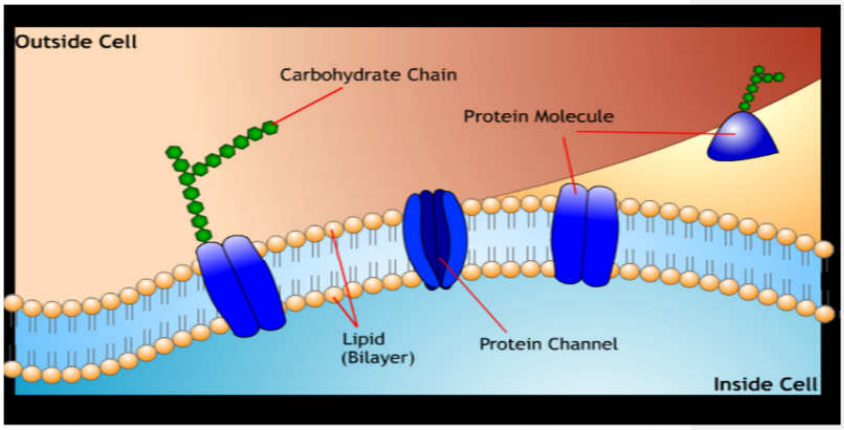
Better **permeability:** intestinal membrane>stomach

The small intestine, which is more **basic in pH**, favours absorption of weakly basic drugs:

GI transit: Transit time in the small intestine is slower than in the stomach. Rate of gastric emptying is a controlling step for rapid absorption

i. Transport across Cell Membrane

Following movement into the small intestine, the drug must cross the intestinal epithelial membrane to reach the systemic circulation. Drugs can cross cell membranes by: **Passive diffusion, Facilitated passive diffusion and Active transport.**



Schematic representation of the cell (or plasma) membrane showing the phospholipid bilayer and embedded proteins

Figure2: Schematic Representation of the cell membrane showing the Phospholipid bilayer and embedded Protein (@open source 2019).

ii. Passive diffusion

Drugs diffuse across a cell membrane from a region of high concentration (e.g., GI fluids) to one of low concentration (e.g., blood) until equilibrium is reached. Diffusion rate is directly proportional to the gradient but also depends on the molecule's lipid solubility, size, degree of ionization, and the area of absorptive surface. Because the cell membrane is lipoid, lipid-soluble drugs diffuse most rapidly.

It also depends on physicochemical properties of the molecule including:
Lipophilicity: Lipid-soluble drugs diffuse most rapidly.

Size: Small molecules tend to penetrate membranes more rapidly than larger ones.

Degree of ionisation

The **area** of absorptive surface

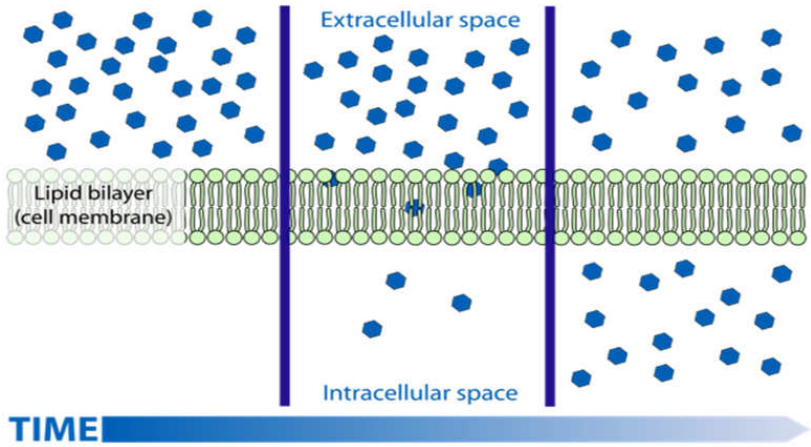


Figure 3: Schematic Representation of the cell membrane showing Drugs diffuse across a cell membrane from a region of high concentration(https://en.wikipedia.org/**)**

Most drugs are weak organic acids or bases, existing in un-ionized and ionized forms in an aqueous environment. The un-ionized form is usually lipid soluble (lipophilic) and diffuses readily across cell membranes. The ionized form has low lipid solubility (but high-water solubility i.e., hydrophilic) and high electrical resistance and thus cannot penetrate cell membranes easily. The proportion of the un-ionized form present (and thus the drug's ability to cross a membrane) is determined by the environmental pH and the drug's pK_a (acid dissociation constant). The pK_a is the pH at which concentrations of ionized and un-ionized forms are equal. When the pH is lower than the pK_a, the un-ionized form of a weak acid predominates, but the ionized form of a weak base predominates. Thus, in plasma (pH 7.4), the ratio of un-ionized to ionized forms for a weak acid (e.g., with a pK_a of 4.4) is 1:1000; in gastric fluid (pH 1.4), the ratio is reversed (1000:1). Therefore, when a weak acid is given orally, most of the drug in the stomach is un-ionized, favouring diffusion through the gastric mucosa. For a weak base with a pK_a of 4.4, the outcome is reversed; most of the drug in the stomach is ionized. Theoretically, weakly acidic drugs (e.g., aspirin) are more readily absorbed from an acid medium (stomach) than are weakly basic drugs (e.g., quinidine). However, whether a drug is acidic or basic, most absorption occurs in the small intestine because the surface area is larger and membranes are more permeable.

Table 2: Passive diffusion efficiency

Efficient	Inefficient
Lipids	Ionized molecules
Hydrocarbons	Carbohydrates
Anaesthetics drugs	Proteins
Alcohol	Ethanol
Most drugs	Aspirin and Quinidine

iii. **Facilitated passive diffusion:** Facilitated passive diffusion requires binding between the drug or molecule with a specific membrane- embedded channel or carrier proteins. It allows the entry of specific groups of molecules while excluding others. **It is a passive process:** Molecules move down their concentration gradient. Molecules cannot be transported against their concentration gradient. **It is a saturable process.** The availability of carriers limits the process.

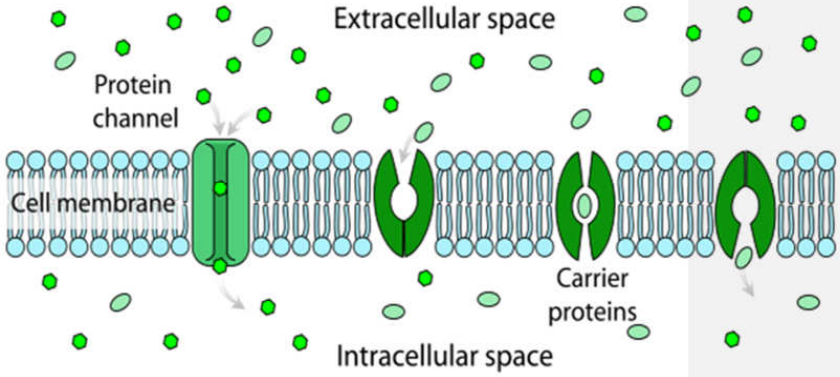


Figure4: Schematic Representation of the cell membrane facilitated passive diffuse across a cell membrane (@open source 2019).

vi. **Active Transport:** Active transport is a selective process. It requires a structurally specific transporter to transport drugs of a certain conformation.

- It requires energy expenditure.
- It can move molecules across the membrane against their concentration gradient. From a low concentration to a high concentration
- It is also a saturable process.

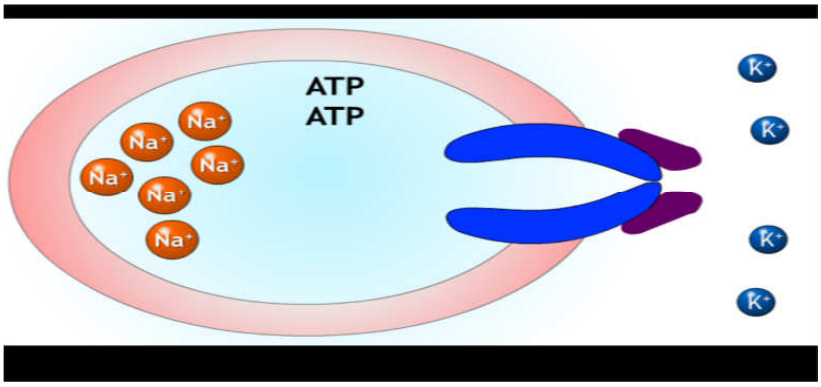
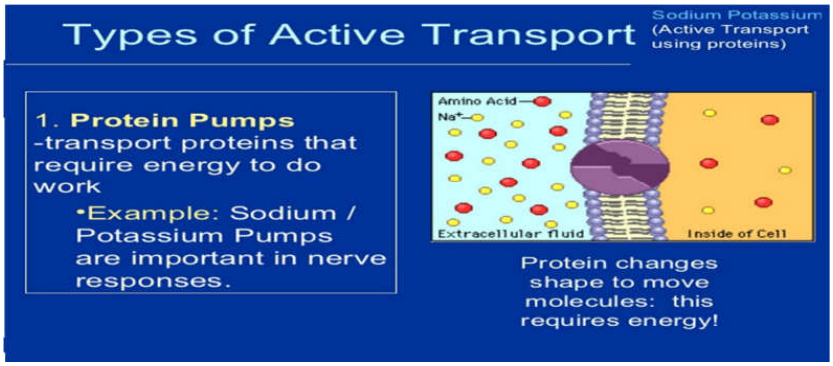
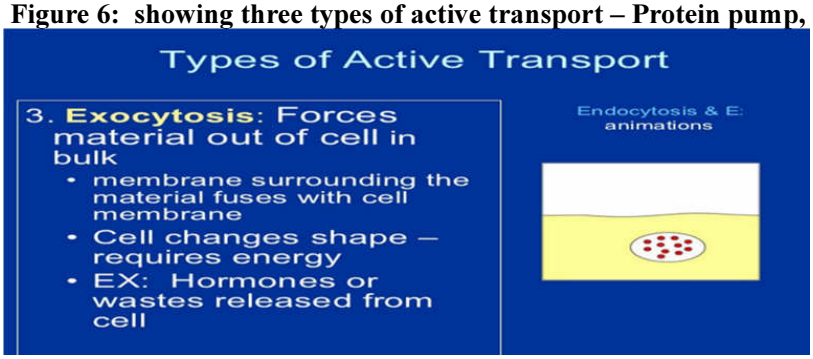


Figure 5: Schematic Representation of the cell membrane showing active across a cell membrane against concentration gradient (@open source 2019)



Exposure to transporters

Figure 6: showing three types of active transport – Protein pump,



Endocytosis and Exocytosis *(@open source 2019)*

3.4.6 Barriers to absorption: An orally administered drug must survive additional encounters in the systemic circulation. First-pass effect through the liver and hepatic portal system,

3.5 Bioavailability (F)

Bioavailability (F) describe the rate and concentration (the extent) at which the. administered drug reaches the circulation *intact***. It is the proportion of administered drug available to produce a pharmacological response.**

The drug, its route of administration and its galenic formulation determine the amount of administered dose absorbed into the circulation. Patient dependant factors also influence bioavailability.
When the drug is administered orally the bioavailability depends on several factors:

i. Physicochemical properties of the drug and its excipients that determine its dissolution in the intestinal lumen and its absorption across the intestinal wall.
ii. Decomposition of the drug in the lumen.
iii. pH and perfusion of the small intestine.
iv. Surface and time available for absorption.
v. Competing reactions **in the lumen (for example of the drug with food).**
vi. **Hepatic first-pass effect**: Orally administered drugs are absorbed from the **GItract** and reach the **liver** via the portal circulation. In the **liver** they undergo first pass metabolism before they enter systemic circulation, which decreases the bioavailability of the drug. Rectal and sublingual by pass the first past effects and the drug is absorbed directly through the blood stream.

Bioavailability can also be determined for other extravascular routes of administration such as intramuscular, subcutaneous, rectal, mucosal, sublingual, transdermal etc. Sublingual and rectal routes are often used to bypass hepatic first-pass effect. Bioavailability of most small molecular weight drugs administered i.m or S.C. are perfusion rate-limited. Large molecules administered i.m or S.C. enter the blood in part via the lymphatic pathway.

3.5.1 Clinical implications

When changing the route of administration or the formulation of a drug, the dose must be adapted with regard to the respective bioavailability of each route. Bioavailability of a drug administered intravenously is by definition 100%. Bioavailability is less or equal to 100% for any other route of administration.

3.5.2 Absolute and relative F

The term absolute bioavailability is used when the fraction of absorbed drug is related to its I.V. bioavailability. A drug given by the intravenous route will have an absolute bioavailability of 1 (F=1 or 100% bioavailable). The term relative bioavailability is used to compare two different extravascular routes of drug administration.Drugs given by other routes usually have an absolute bioavailability of less than one.

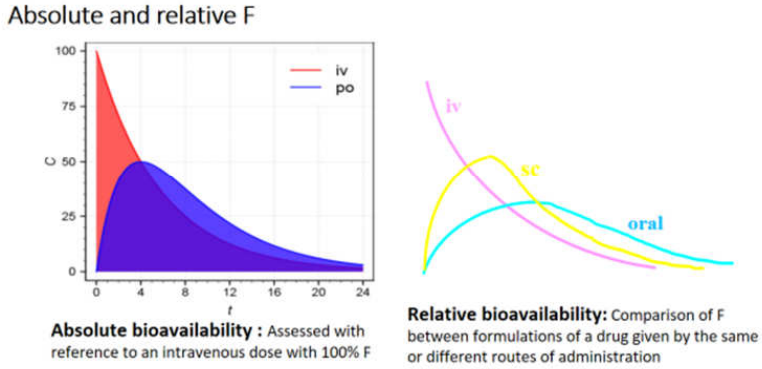


Figure7: absolute bioavailability is the area under curve (AUC) non-intravenous divided by AUC intravenous (Roy SK @ Novartis 2004)

3.5.3 Bioavailability (assessment) Pharmacokinetic study

Bioavailability is proportional to the total area under the plasma concentration- time curve (AUC). To determine the bioavailability of a drug, you must carry out a pharmacokinetic (PK) study to obtain a blood/plasma concentration versus time plot for the drug in question.
The relative bioavailability of drug 1 compared to drug 2 can be calculated using the following equation:

$$F = \frac{AUC_2}{AUC_1} * \frac{D_1}{D_2}$$

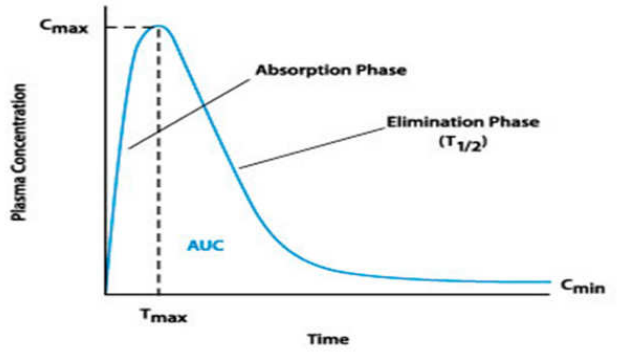


Figure 8: Area under the plasma concentration curve (AUC)

- Cmax = The peak plasma concentration of a drug after administration
- Tmax = The time to reach Cmax

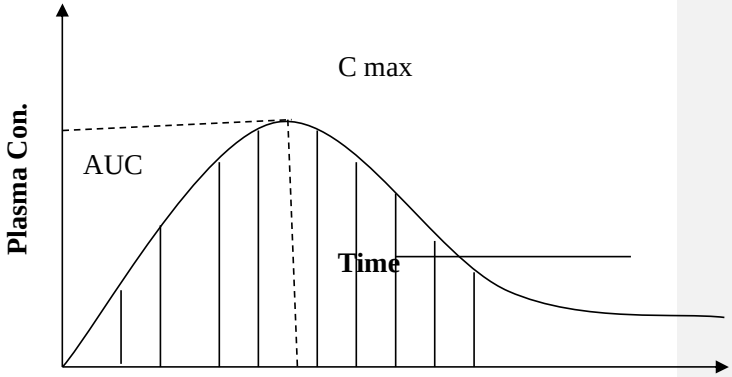


Figure 9: Theoretical Plasma concentration over time. (Roy SK @ Novartis 2004

***C_{max}** = the peak plasma concentration which is the function of speed and extent absorption, **t_{max}** = the time taken to reach the peak which is a function of the speed of absorption, **AUC** = the total area under the plasma curve – a function of absorption*

3.5.4 Causes of Low Bioavailability

A number of other factors may affect the absorption and bioavailability of a drug taken by mouth. Physiological characteristics include, how long the stomach takes to empty, what the acidity (pH) of the stomach is and how quickly the drug is moved through the digestive tract. Other factors include a person's age, sex, level of physical activity, and level of stress.

Food, other drugs, and digestive disorders can affect drug absorption and bioavailability. For example, high-fibre foods and calcium supplements may bind with a drug and prevent it from being absorbed. Laxatives and diarrhoea, which speed up the passage of substances through the digestive tract, may reduce drug absorption. Surgical removal of parts of the digestive tract (such as the stomach or colon) may also affect drug absorption.

3.5.5 Bioequivalence: Two proprietary (galenic formulations) preparations of a drug are said to be bioequivalent if they exhibit the same **bioavailability** when administered in equal doses. **Bioequivalence** indicates that the drug products, when given to the same patient in the same dosage regimen, result in equivalent concentrations of drug in plasma and tissues. **Therapeutic equivalence** indicates that drug products, when given to the same patient in the same dosage regimen, have the same therapeutic and adverse effects. Bioequivalent products are expected to be therapeutically equivalent. Therapeutic non-equivalence (e.g. more adverse effects, less efficacy) is usually discovered during long-term treatment when patients who are stabilised on one formulation are given a non-equivalent substitute. Bioequivalence;

i. It can provide useful information about the:
ii. Dosage or dosage regimen of a given drug
iii. Performance of a drug formulation compared to other formulations
iv. It is quoted as a percentage (43%) or a decimal (0.43) and has no units.
v. Intravenous (IV) administration equals 100% bioavailability.
vi. For a non-IV dose, F ranges from 0 to 100%.

Table3: Variation of drug Bioavailability

Drug	**Foral (5)**
Gentamycin	< 5
Verapamil	22
Lignocaine	35
Digoxin	75
Phenytoin	98
Valproate	100

3.6 Elimination Half-Life

The half-life ($t_{1/2}$) of a drug is the time taken for the circulating concentrations of the drug to fall by 50%. By definition, the plasma concentration of a drug is halved after one elimination half-life. Therefore, in each succeeding half-life, less drug is eliminated. After one half-life the amount of drug remaining in the body is 50% after two half-lives 25%,

etc. After 4 half-lives the amount of drug (6.25%) is considered to be negligible regarding its therapeutic effects.

A concentration-time curve (figure… below) can be constructed by administering the drug intravenously and removing blood for assay at frequent intervals. With most drugs, the curve is a strength line when the concentration (vertical axis) is expressed on a logarithmic scale, enabling $1_{1/2}$ to be determined easily Complete drug elimination occurs in 4-5 half lives. After that drug will reach steady state concentration in the plasma. (Drug administered=drug eliminated)

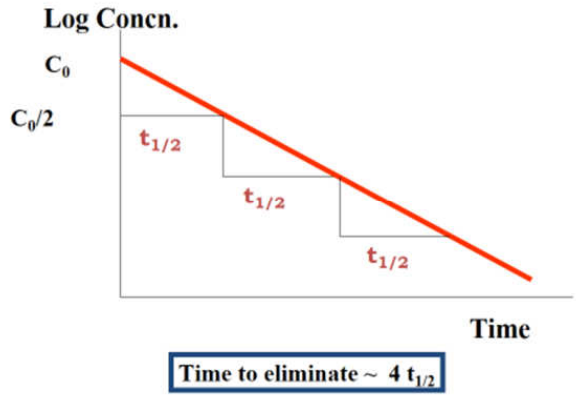


Figure10: Time to elimination half life (Roy SK @ Novartis 2004

= 1-50 %
= 2-75% (50+25)
= 3-87.5% (50+25+12.5)
= 4-3.75% (50+25+12.5+6.25)

The half-life can be calculated with the following formula: **t 1/2 = 0,693•Vd/CL**

Where Vd is the volume of distribution at the steady-state, and CL is the clearance.

Importance:

i. it denotes how quickly a drug is removed from the plasma by biotransformation or excretion.
ii. Since drug requires a minimum concentration in the plasma to produce pharmacological action, a drug which is eliminated quickly requires more frequent dosing than a drug with a long half-life.

iii. It thus indicates the duration of action of drug and therefore it determines the frequency of administration of dose of the drug for therapeutic effectiveness.
iv. The half-life of a drug depends on its clearance and volume of distribution. The elimination half-life is considered to be independent of the amount of drug in the body.

3.6.1 Therapeutic window

Therapeutic Window: Therapeutic window is a range of doses that produces therapeutic response without causing any significant adverse effect in patients.

Generally therapeutic window is a ratio between minimum effective concentrations (MEC) to the minimum toxic concentration (MTC). The levels of drug should always be between MEC and MTC in order to provide risk free therapeutic effects. If any drug crosses MTC then it will surely elicit toxic effects and if drug is unable to surpass MEC then it will cause therapeutic failure. MEC is also called as minimum inhibitory concentration (MIC).

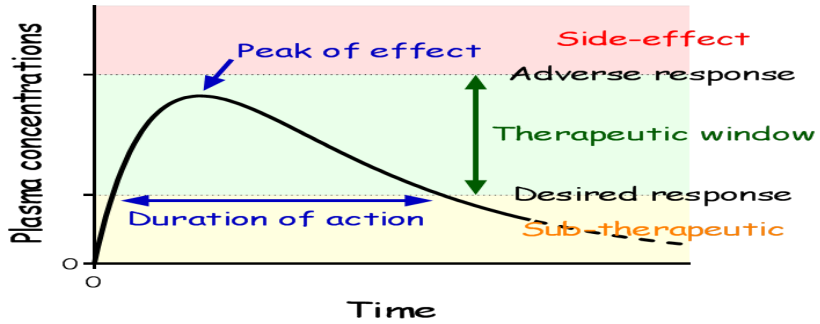


Figure 11: Therapeutic window (@ medimoon.com 2018)

Therapeutic Index

Therapeutic index (TI) describes a relationship between the doses of a drug that causes lethal or toxic effects with the dose that causes therapeutic effects. It is also called as therapeutic ratio.

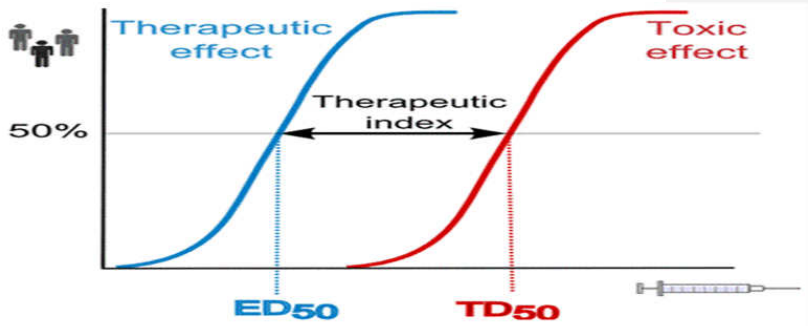


Figure 12: Showing Therapeutic index (TI) (@ medimoon.com 2018)

Therapeutic Index = $\frac{\text{TD50 or LD50}}{\text{ED50}}$

Where

LD_{50} is the minimum amount of drug that causes adverse effects in 50% of the population. L**D50** could also be replaced with Toxic dose (TD_{50})
ED_{50} is the quantity of a drug that can produce desired therapeutic effects in 50% of the population. Such types of studies are usually conducted in animal models.

The higher the **TI** the better the drug. **TI's** vary from 1.0 (some cancer drugs) to: >1000 (penicillin). Drugs acting on the same receptor or enzyme system often have the *same* **TI**: (e.g. 50 mg of hydrochlorothiazide about the same as 2.5 mg of indapamide)

Ideally any drug that requires more amount to produce toxic or adverse effects in 50% of population will have wider therapeutic index and vice versa. Drugs having wider therapeutic index are safer in comparison to those having low therapeutic index because minor modification in the dose of such drugs (aspirin, acetaminophen) will not produce toxic effects.

For examples NSAIDs have wider therapeutic index and warfarin has narrow therapeutic index as it has therapeutic index less than two. Some common potent drugs having low therapeutic index; Digoxin, Lithium, Warfarin, Theophylline, Phenytoin, Gentamicin, Amphotericin B and 5-fluorouracil etc.

3.6.2 Steady-State Concentrations

Steady-state concentration: Steady-state concentration (C_{ss}) is defined as the time during which the concentration remains stable or consistent when the drug is given repeatedly or continuously (IV infusion). The time to reach steady-state is a function of $T_{½}$ and is achieved when the rate of the drug entering the systemic circulation equals the rate of elimination. For most drugs, the C_{ss} is reached in approximately five half-lives. The time to reach steady-state is independent of dose size, dosing interval, and number of doses.

In case of multiple dosing, when a drug is administered in a fixed dose at fixed intervals, the plasma concentration increases exponentially to a plateau or steady-state with a half time of increase that is equal to the $T_{½}$ of the drug. As indicated previously, 50% of the steady-state level is achieved in one $T_{½}$, 75% (50+25) is achieved in two, 87.5% is achieved in three, and more than 99% is achieved in seven half-lives. In practice, a useful estimate of time to reach a steady-state is obtained by the following equation: ½Time to 95% steady-state = 4.3×t½

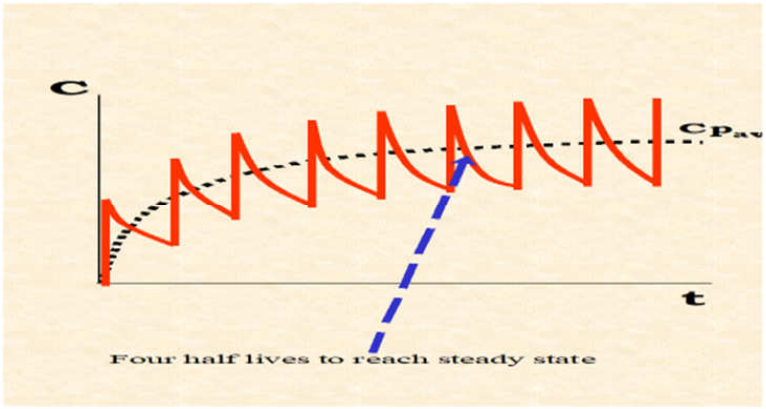


Figure 13: Steady state giving after every half-life*. (Linear PK Example.png 2014)*

Therefore, the shorter the half-life, the more rapidly the steady-state is reached, and vice versa. Steady-state occurs after a drug has been given for approximately five elimination half-lives. At steady-state the rate of drug administration equals the rate of elimination and plasma concentration - time curves found after each dose should be approximately superimposable.

Steady state pharmacokinetics are important for chronically administered drug products. Understanding the basic concept that a drug reaches steady state once the rate of drug input and elimination are equivalent helps simplify the concept of steady state.

3.7 Drug Distribution

Drug distribution describes the reversible transfer of a drug from one location to another within the body. After a drug enters the systemic circulation, it is distributed to the body's tissues.

3.7.1 The factors determining the pattern of distribution:

Distribution is generally uneven because of differences. The factors determining the pattern of distribution are the

i. tissular delivery of drug by blood,
ii. the ability of the drug to cross membranes,
iii. the binding of drug with blood and tissues components (e.g., because of lipid content),
iv. its partitioning between water and fat, and
v. Its ability to undergo active transport through cell-membrane carriers (e.g. P-glycoprotein).

After the drug reaches the bloodstream, it is initially distributed in the most vascularised organs.

The entry rate of a drug into a tissue depends on the rate of blood flow to the tissue, tissue mass, and partition characteristics between blood and tissue. Distribution equilibrium (when entry and exit rates are the same) between blood and tissue is reached more rapidly in richly vascularised areas, unless diffusion across cell membranes is the rate-limiting step. After equilibrium, drug concentrations in tissues and in extracellular fluids are reflected by the plasma concentration. Metabolism and excretion occur simultaneously with distribution, making the process dynamic and complex

Table 4: Blood flow to tissues: Good blood supply is vital for efficient drug delivery.

Organ	**Blood flow ml/min**	**Organ mass/kg**	**Blood flow ml/min**	
Cardiac output	5,600	-	-	
Myocardium	250	0.5	833	Highly Perfused
Liver	1,700	2.5	680	
Kidney	1,200	0.3	4,000	

CNS	800	1.3	615	
Fat	250	10	25	Slowly perfused
Other (Muscle, etc.)	1,400	55	25	
Total		69.4		

i. Plasma protein binding: A drug's efficiency can be affected by the degree to which it binds to the proteins in the blood. The drug binds to specific sites on plasma proteins, which results in sequestering of the drug, making it unavailable to its site of action. Competition for plasma protein binding sites can sometimes occur when another drug is given in combination with your drug of interest, resulting in displacement of the drug and increasing its unbound concentration in the blood plasma. Such competition can be very significant clinically

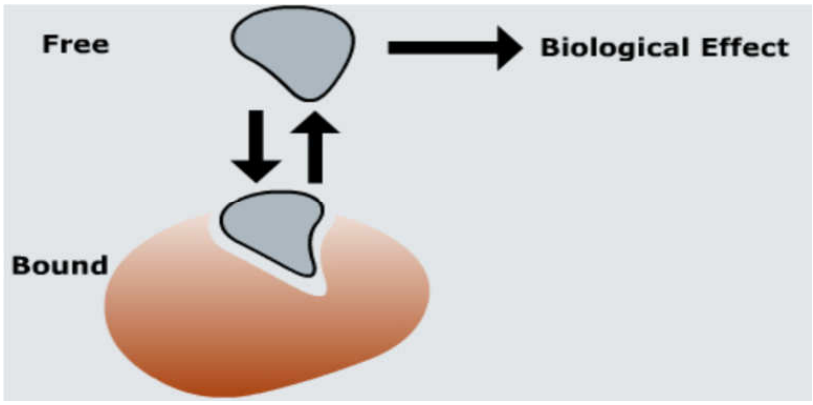


Figure 14: demonstrating competitive Plasma protein binding (Roy SK @ Novartis 2004

Consider the anticoagulant Warfarin as an example. It is approximately 98% protein-bound. So, for each 5 mg dose, only 0.1 mg of the drug is free. The patient takes a normal dose of aspirin at the same time, which occupies 50% of binding sites; the aspirin displaces some of the Warfarin. If 96% of the Warfarin dose is protein-bound, 0.2 mg of Warfarin is now free. The dose has been effectively doubled.

Common blood proteins: Common blood proteins that drugs bind to are:

Human serum albumin: *Most concentrated protein in blood plasma*: Acidic drugs

-α1 – acid glycoprotein: Basic drugs
α, β, and γ globulins: Steroid hormones

Drug binding to plasma proteins is generally reversible and rapid. •The extent of binding is determined by quantifying the free drug fraction (*fu*). The extent of binding can vary widely among drugs. **Plasma albumin:** This table shows examples of the extent of plasma albumin binding to various drugs. The unbound fraction of some drugs is dependent on the concentration of plasma proteins and can be altered in disease states that produce hypoalbuminemia. An example of this type of drug is phenytoin

Table5: Showing examples of the extent of plasma albumin binding to various drugs

Acidic Drugs	**% Bound**	**Basic Drugs**
Ibuprofen Warfarin Aspirin phenobarbitone	100%	Diazepam Methadone Erythromycin Pethidine
Ampicillin	< 50%	Theophylline

i. Volume of Distribution

The volume of distribution (Vd), or apparent volume of distribution, is: A theoretical volume that the total amount of drug administered would need to occupy to provide the same concentration as in blood plasma. It is not a physical volume, nevertheless, the volume of distribution of a drug gives information on its distribution in the body.

The Vd is calculated as the ratio of the dose present in the body and its plasma concentration, when the distribution of the drug between the tissues and the plasma is at equilibrium.

An equilibrium concept that relates the amount of drug in the body (A) to either the plasma or blood concentration (C): **Vd = D/C**

Example: A patient is administered an intravenous analgesic at a dose of 75 mg. A few minutes later, a blood sample is taken and the concentration of the analgesic in the blood is 0.65 μg/mg. What is the volume of distribution (in litres) of the analgesic?

Vd = D/C = 75mg / 0.65 μg/mg = 75,000 μg / 0.65 μg/mg = 115,385 ml = 115.4 litres

Accordingly, a drug that accumulates in tissues as e.g. fat tissue, will have a relatively low plasma concentration with regard to the administered dose, and consequently, the calculated Vd will be high.
Volume of distribution provides little information about the specific pattern of distribution. Some drugs cannot enter cells because of their low lipid solubility. Interstitial fluids of most tissues, drug distribution rate is determined primarily by perfusion. For poorly perfused tissues (e.g., muscle, fat), distribution is very slow Vd (12-20 L), especially if the tissue has a high affinity for the drug

Drugs with a very small Vd (<10 L) are mainly confined to the intravascular fluid, thus the blood, corresponding to roughly twice the plasma volume. This may occur for two reason 1. The molecule is too large to leave this compartment and 2. The molecule binds preferably to plasma proteins (e.g. to albumin) and much less to tissue proteins. Competition for plasma protein binding sites can occur between such drugs or with endogenous substances.

Drugs that accumulate in organs either by active transport or by specific binding to tissue molecules have a high volume of distribution, which can exceed several times the anatomical body volume. Therefore, Vd should not be identified too closely with a particular anatomical compartment. Lipid-soluble drugs are stored in fat. Bone is a reservoir for drugs such as tetracycline and heavy metals.

Distribution coefficient: measure of hydrophobicity/hydrophobicity of a drug C (drug concentration in the organic solvent)/ C (drug concentration in water.

Table6: Showing each drug is uniquely distributed in the body

Volume of distribution	
High	**Low**
High lipid solubility (non – polar)	Polar
Low rates of ionization	More highly ionised
Low plasma binding capabilities	High plasma binding

Volume of distribution can be: Increased by renal failure or liver failure, Decreased in dehydration.

ii. **Real water distribution:** The body is composed of 'real' compartments that contain 'real' volumes of fluid:

Table 7: Distribution of Water in the Body for a 70kg Person

Compartment	Volume (V)	Percentage (%)
Total body water (TBW)	42	60
Intracellular Fluids (ICF)	28	40
Extracellular Fluids (ICF)	14	20
Interstitial	10	15
Plasma	4	0

Examples

Heparin: High molecular weight drug binds to plasma proteins extensively, and volume of distribution of about 4 litres. This correlates very well with the plasma volume. Such volume of distribution for this drug is considered a 'real' volume. The volume occupies 'real space ‘in the plasma volume. Heparin unable to transport out of the vascular system.

Atracuronium: Neuromuscular blocking agent of low molecular weight drug but is hydrophilic. Its volume of distribution of about 11 litres. This is equivalent to the volume in the extracellular compartment of the body. A very polar compound, Atracuronium is unable to transport across cell membranes and therefore remains in the extracellular fluids.

The majority of drugs, which bind strongly to tissues, have volumes of distribution higher than total body water. A minority of drugs that diffuse to intracellular fluid have a volume of distribution equivalent to TBW volume**.**

Table8: Example of drug variation in drug Vd

Compound	**Volume/Litres**	
Ethanol	38	
Caffeine	36	
Alfentanyl	56	
Fentanyl (Anaesthetics)	280	
Propofol (Anaesthetics)	560	
Digoxin (Cardiac drugs)	365	
Drug	**Volume**	**Location**
Aspirin	9.8	Located mainly in plasma, little in tissues
Amoxycillin	14	
Theophylline	35	Similar concentration in plasma and tissues
Diazepam	105	
Digoxin	490	Mainly located in tissue, very little in plasma
Haloperidol	1,750	
Values in litres for an average 70kf adult		

Clinical usefulness of drug distribution

i. The volume of distribution reflects the size of the distribution space, thereby giving you an idea of the localisation of the drug in the target organ.
ii. With a large volume of distribution, you will need a higher dose to load.
iii. With a low volume of distribution, you will need a lower dose to load.
iv. The volume of distribution is useful in estimating the dose required to achieve a given plasma concentration as $A = C \cdot Vd$, with A = amount of drug in the body (≈ dose, shortly after administration) and C = plasma concentration.
v. Gives us idea of variation of the peak plasma concentration of the drug. This is important when peak plasma concentration is essential for the therapeutic effect (e.g. hypnotics). Drug dosage must be adapted to the Vd for such drugs.
vi. Vd varies with individual height and weight. The most important causes of variation of Vd are accumulation of fat (for lipid-soluble drugs) such as for obese patients, or accumulation of fluids (for water-soluble drugs) such as ascites, oedema or pleural effusion. As the proportion of each body compartment varies with age, so does the Vd for most drugs.

3.8 Drug Metabolism (Biotransformation)

3.8.1 Introduction

Metabolism (biotransformation) is a process by which drugs are converted into more polar forms through a series of enzymatic reactions. This serves to increase the renal elimination of the substance, this usually, but not always, results in a less toxic form of the substance. The metabolites might still have potent biological activity (or might have toxic properties). An inactive or weakly active substance that has an active metabolite is called a prodrug. Is the main mechanism of drug elimination involving the enzymatic conversion of one chemical entity to another within the body? Occurs predominantly in the liver. Results in metabolites that are more polar than the parent drug and that can be excreted by the kidneys

Example of Metabolism

Barbital: It is water soluble and after metabolism, is excreted unchanged. Theoretical and measured half-life of 55-75 hours

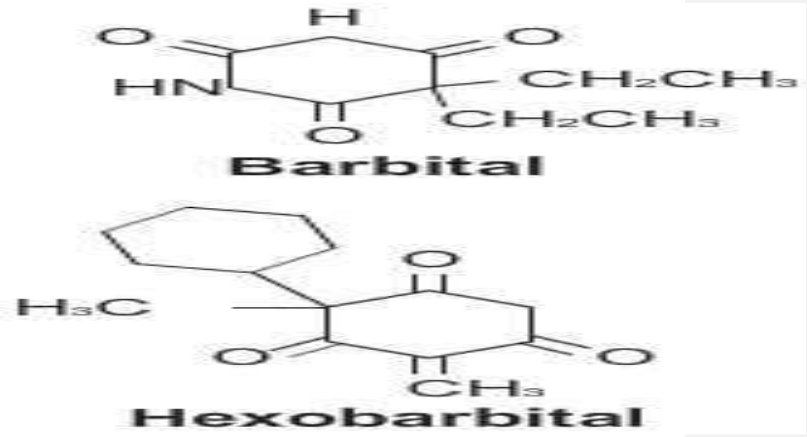


Figure 15: Metabolism of Barbital to Hexobarbital

Hexobarbital: A Lipophilic drug is metabolised. Its theoretical half-life of 2-5 months, while measured half-life of 5-6 hours.

3.8.2 Sites of metabolism: Metabolic enzymes are located in many different tissues and usually reflect tissues with a high exposure to xenobiotic. These include tissues of the Liver, Lungs, Nasal mucosa, Eye and - Gastrointestinal tract (GIT). The main site of biotransformation is the *liver* because of its size and concentration of enzymes.

3.8.3 First-pass elimination: Many xenobiotics are absorbed from the GIT by the liver and metabolised then. This is designed to prevent high levels of orally ingested xenobiotic reaching circulation. However, this first-pass metabolism can limit the bioavailability of some drugs. Alternative routes of administration avoid the first-pass effect. Notable drugs that experience a first-pass effect include imipramine, morphine, diazepam, demerol, cimetidine and lidocaine.

3.8.4 Cytochrome P450 Classification

Cytochrome P450: Cytochrome P450 (CYP) is a haemoprotein that plays a key role in the metabolism of drugs and other xenobiotics. Understanding the CYP system is essential for advanced practitioners (APs), as the consequences of drug-drug interactions can be profound.

Cytochrome P450s are classified by amino acid homology of the genes.

Cytochrome P450 pathways are classified by similar gene sequences; they are assigned a family number (e.g., CYP1, CYP2) and a subfamily letter (e.g., CYP1A, CYP2D) and are then differentiated by a number for the isoform or individual enzyme (e.g., CYP1A1, CYP2D6). Those with < 40% homology are put into separate families, with numbers as identifiers. Those with 40–55% homology have different sub-families and are given letter names. Those with > 55% homology are members of a different sub-family. These are given numbers as identifiers.

Drugs that share a common pathway have the potential for drug-drug interactions. The classification of CYP proteins will be the APs first hint of the potential for drug interactions. Not all drugs have CYP activity. However, drugs with CYP activity may be inhibitors, inducers, or substrates for a specific CYP enzymatic pathway, thus altering the metabolism of concurrently administered agents. Drugs that inhibit an enzymatic pathway of CYP may cause increased concentrations of other drugs metabolised by the same pathway, resulting in drug toxicity. Likewise, drugs that induce an enzymatic pathway of CYP may reduce concentrations of drugs metabolised by the same pathway, leading to sub therapeutic drug levels or treatment failure.

Role of sub-families: There are 74 families but only 17 families in humans and there are approximately 57 CYP genes. The important sub-families involved in drug metabolism are: CYP1A and CYP1B, CYP2A–D. CYP3A.

Found in every class of organism, including Archaea. For example, CYP1, CYP2 and CYP3 are found in the microsome and are involved in drug metabolism and CYP4 is found in the microsome but is involved in fatty acid metabolism. The p450 superfamily is believed to have originated from ancestral gene that existed over 3 billion years ago. In humans, they play central role in Phase 1 drug metabolism, significant problems in clinical pharmacology, drug -drug interactions, Inter-individual variation in drug metabolism and Genetic polymorphism resulting in marked metabolic activity e.g. CYP2D6

CYP structure: Cytochrome P450s are haem-containing proteins. They usually require a second enzyme for catalytic activity – something that provides electrons. In the endoplasmic reticulum (ER), or primary metabolic enzymes, this is NADPH-cytochrome P450 reductase. In mitochondria, the second enzyme is ferredoxin and ferredoxin reductase.

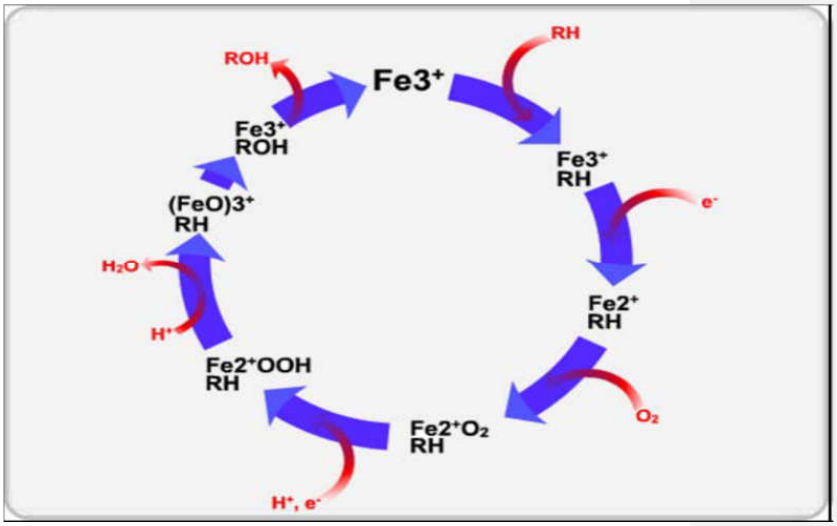


Figure 16: CYP structure (Roy SK @ Novartis 2004

The most common reaction catalysed by cytochromes P450 is a monooxygenase reaction, e.g., insertion of one atom of oxygen into the aliphatic position of an organic substrate (RH) while the other oxygen atom is reduced to water:

- RH + O2 + NADPH + H+ ROH + H2O + NADP+

3.8.5 Stages in Metabolism

i. Phase I

Introduces or exposes a functional group. – OH, - NH2, - SH and - COOH.

Only slightly increases polarity

There are three types of Phase I reaction: Hydrolysis, Oxidation and Reduction

Many Phase I products are not efficiently eliminated and may require a second conjugation reaction by Phase II enzymes to form a highly polar conjugate that can then be excreted in the urine.

CYP oxidation reactions involve;

i. Hydroxylation (aliphatic or aromatic carbon)
ii. Epoxidation of double bond
iii. Heteroatom (S-, N- and I-) oxygenation

iv. Heteroatom (O-, S-, N-, Si-) dealkylation
v. Oxidative group transfer
vi. Cleavage of esters
vii. Dehydrogenation

ii. Phase II metabolism

Phase II drug metabolising reactions are synthetic, anabolic reactions that involve conjugation whereby another molecule is added to the drug such as ***Glucuronidation, Sulfation, Acetylation, Methylation, Glutathione conjugation and Amino acid conjugation.*** These are primarily cytosolic reactions, and are much faster than Phase - I reactions.

i. **Glucuronidation:** Glucuronidation is the most common Phase II reaction. It is mediated by UDP-glycotransferases. Requires uridine diphosphate-glucuronic acid as a co-factor.
ii. Substrates include: Aliphatic alcohols and phenols Carboxylic Acids Secondary aromatic and aliphatic amines
iii. **Glucuronides:** The resulting glucuronide conjugates of drugs are secreted in bile or urine depending on their molecular weight. Those of low molecular weight are excreted in urine whereas those molecules of high molecular weight are excreted in bile. It is a very important reaction, particularly for drugs such as: Acetaminophen, Morphine, Propranolol, Diclofenac and Lamotrigine
iv. **Sulfation:** Sulfation is described as a higher affinity but lower capacity reaction than glucuronidation. It has similar substrates to glucuronidation and is catalysed by sulfotransferases. The reaction requires the co-factor, 3'-phosphoadenosine-5'-phosphosulfate (PAP), which is the reason for the low capacity of this reaction, that is, the limitation of PAP.
v. **Sulfate:** The sulphate conjugates are excreted in the urine or bile. Sulfation can activate some carcinogens, such as safrole. Many drugs are sulphated: Acetaminophen, Chloramphenicol, Dopamine and Ethanol.
vi. **Methylation:** Methylation is a relatively minor reaction that often decreases water solubility. It is mediated by methyltransferases, with the best-known being Catechol-O-methyltransferases. The co-factor is S-adenosylmethionine. Methylated drugs include: Catecholamines, Captopril, and Azathioprine.
vii. **N-acetylation:** N-acetylation is another major conjugation reaction, particularly for: Aromatic amines, Hydrazine. It is mediated by N-acetyltransferases (NAT). The co-factor is acetyl-coenzyme A. This can also decrease water solubility. There are two enzymes involved, NAT1 and NAT2.

Table 9: Major Enzymes involved in Acetylation

N-acetyltransferases (NAT)	
NAT1 preferentially conjugates	NAT2 preferentially acetylates
p-Aminosalicylic acid	Isoniazid
Sulfamethoxazole	Dapsone

Slow acetylation: NAT2 contains a number of polymorphisms that can decrease the rate of acetylation. Individuals who express this phenotype are known as slow acetylators. ~70% incidence in Middle East, 50% incidence in Caucasians, and <25% in Asians. Slow acetylators have an enhanced response to hydralazine (anti-hypertensive). Its increased nerve damage from isoniazid and dapsone

Xenobiotic activation: Cytochrome P450s biotransformation can lead to activation of some toxins and carcinogens. In some cases, the activation is desirable because it produces the active agent from a pro-drug.

Other CYP reactions: CYP450 enzymes can be induced or inhibited by many drugs and substances, resulting in drug interactions in which one drug enhances the toxicity or reduces the therapeutic effect of another drug.

3.8.6 Mechanisms of enzymatic Processes Drug Metabolism

The mechanisms are brought about by enzymatic Processes

i. Enzyme inhibition
ii. Enzyme induction
iii. Auto Induction

It should be noted that p450 Induction is not limited to drugs as other substrates such as, grapefruit juice can inhibit CYP3A4 mediated metabolism. Alcohol, chronic cigarette smoking, and even charbroiled meats can induce hepatic CYP450 enzymes

i. Inhibition of CYP: Inhibitors of CYP450s include: Cimetidine, Ciprofloxacin, Erythromycin, Fluoxetine etc. Inhibition can lead to adverse drug reactions due to altered metabolism. However, inhibition is typically reversible depending on the half-life of the drug and can be used to increase bioavailability of a drug, for example: Ritonavir inhibits CYP3A enzymes, Saquinavir is metabolised by CYP3A. A combination of ritonavir and Saquinavir is synergistic in HIV. Inhibition can be due to a number of factors including:

Competition for a CYP between two substrates

i. Competition with a non-substrate inhibitor e.g. Omeprazole and diazepam compete for CYP2C19, CYP2D6 metabolises dextromethorphan and is inhibited by quinine, Celecoxib inhibits CYP2D6, and Grapefruit juice inhibits CYP3A enzymes.
ii. Substrates that can also be converted to a suicide inhibitor e.g. Erythromycin inhibits CYP3A4, Furafylline inhibits CYP1A2, and Trienoic acid inhibits CYP2C9.
iii. Terfenadine is a non-sedating H1 antagonist.It is metabolised to an active agent by CYP3A4. This active metabolite does not cross the blood-brain barrier (BBB). Azole antifungals and macrolide antibiotics inhibit CYP3A4.This results in increased plasma levels of terfenadine. Terfenadine blocks cardiac K+ channels. This can result in torsade de pointes and even ventricular arrhythmias.

Table10: Examples of Common Drug-Drug Interactions Involving the Cytochrome P450 Enzyme System (@Lynch, T.et al 2007)

CYP	**Drug substrate**	**Inhibitor**	**Inducer**
1A2	Paracetamol (Acetaminophens) caffeine, odansetron, Phenacetin tacrine, tamoxifen, Theophylline	Furafylline	Smoking, charred foods
2A6	Coumarin, Caffeine	Dicarb sodium (Diethyldithiocarbamate)	
2C9	Diclofenac. Flurbiprofen, losartan, phenytoin, Piroxicam, acid, Tolbutamide	Sulfapenazole	Barbiturate, rifampicin (rifampin)
2C19	Diazepam, (S) – Mephenytoin, omeprazole, entamidine, Propranolol (R) – Warfarin		
26D	Defuralol, codeine, debrisoquine, haloperidol, nortriptyline	Quinidine	

2E1	Paracetamol, enflurane, caffeine, chlorzoxazone, theophylline	Dicarb Sodium	Alcohol, (ethanol) isoniazid
3A4	Clarithromycin, dapsone, Indinavir, codeine, midazolam, cyclosporine, erythromycin, Nifedipine Felodipine, diazepam, verapamil, Loxatan, quinidine	Gastrodne ketoconazole, itraconazole	Barbiturate, Rifampicin, dexamethasone, carbamazepine

Commented [U1]:

ii. **Induction of CYP:** Some drugs can enhance the expression of some CYP enzymes. This can be beneficial because induction increases the pool of enzyme available to catalyse specific drug metabolising reactions. However, other drugs can be metabolised much more rapidly than would be anticipated. This does not cause a toxic effect but results in sub-therapeutic levels of drugs, such as oral contraceptives.

Mechanism of induction is cytosolic receptor mediated: CYP1A and AhR (dioxin), - CYP2B and CARβ (phenobarbital), CYP3A and PXR (rifampin), CYP4A and PPARα (clofibric acid) and Activation of the receptors leads to gene induction and increased mRNA production.

iii. **Autoinduction: Polymorphisms:** Polymorphisms in the CYP family are considered to have the most impact on the fate of therapeutic drugs.

Functions

i. To function within phase, I Liver Detoxification
ii. To detoxify xenobiotic sources of toxicity, chemicals, alcohols and carcinogens, converting them into water and oxygen
iii. To assist endogenous sources of waste such as Bilirubin
iv. To assist in the synthesis of Vitamin D

For hormone synthesis: To effectively convert cholesterol into pregnenolone which then gets converted into other hormones like oestrogen, testosterone, cortisol and DHEA.

For the synthesis of bile and bile acids, which are necessary for the assimilation of fat-soluble vitamins. Bile also contains many of the toxins conjugated in the liver, which then get dumped into the bowels for proper elimination.

3.8.9 Consequences of Metabolism (biotransformation)

The end product can involve
Active drug to Inactive metabolite: Pentobarbitone, Morphine, Chloramphenicol

Active drug to Active metabolite: Phenacetin
Inactive drug to active metabolite: Levodopa
Prodrugs: Inactive drug is converted to active metabolite

Advantages:

i. Increased absorption
ii. Elimination of an unpleasant taste
iii. Decreased toxicity
iv. Decreased metabolic inactivation
v. Increased chemical stability
vi. Prolonged or shortened action

3.9 Rug – Drug Interactions

A drug interaction occurs when a drug interferes in a negative way with another drug or medical condition. These interactions can occur between two drugs, by combining medications with particular foods or drinks, or by a drug interfering with another medical condition. It does not only happen with prescription drugs, it can happen with over the counter medications, vitamins and supplements, and illegal substances.

The objectives of a drug interaction study are to

i. Explore if a new agent significantly affects the metabolic elimination of approved drugs and vice versa
ii. Determine if any interactions are clinically significant to necessitate dose adjustment, warning or contraindication.
iii. Understand dose adjustments or how to avoid interaction, may allow marketing for drug that otherwise been associated with unacceptable level of toxicity.

3.9.1 Types of Drug Interactions

Two types of drug interactions

Pharmacokinetic (ADME) interactions: A drug usually alters absorption, distribution, protein binding, metabolism, or excretion of another drug.

Pharmacodynamic drug interactions: Pharmacodynamic drug interactions occur when one drug alters the sensitivity or responsiveness of tissues to another drug by:

i. Having the same effect (agonistic)
ii. Blocking effect (antagonistic)

For example, if fluoxetine is given with tramadol serotonin syndrome can result. This is a *pharmacodynamic drug interaction.* Fluoxetine and tramadol both increase availability of serotonin leading to the possibility of "serotonin overload" This happens *without a change in the concentration* of either drug)

These effects usually occur at the receptor level but may also occur intracellularly and can occur in one or 6 ways.

3.9.2 Pattern of Drug-Drug interactions: 6 patterns

i. Pattern1: An inhibitor is added to a substrate e.g. Paroxetine is added to nortriptyline, leading to an increase in the nortriptyline blood level.
ii. Pattern 2: A substrate is added to an inhibitor Nortriptyline is added to paroxetine, leading to a higher than expected blood level of nortriptyline at a given dose
iii. Pattern 3: An inducer is added to a substrate Carbamazepine is added to be haloperidol, leading to a decrease in the haloperidol blood level.
iv. Pattern 4: A substrate is added to an inducer Haloperidol is added to carbamazepine, leading to a lower than, expected blood level of haloperidol at a given dose
v. Pattern 5: Reversal of inhibition. An inhibitor and a substrate have been stably co-administered and then the inhibitor is discontinued. E.g. Cimetidine is discontinued in the presence of nortriptyline, leading to a decrease in the nortriptyline blood level
vi. Pattern 6: Reversal of induction. An inducer and a substrate have been stably co-administered and then the inducer is discontinued. E.g. a patient on clozapine abruptly discontinues smoking, leading to an increase in the clozapine blood level

3.9.3 Clinically significant interactions

Clinically significant interactions are often predictable and usually undesired.

Therapeutic effects

i. Co-administration of the two anti-retroviral drugs, lopinavir and ritonavir, to patients with HIV infection results in altered metabolism of lopinavir and increased serum lopinavir concentrations and effectiveness.
ii. Lopinavir/Ritonavir is now marketed as a fixed dose combination drug for the treatment of HIV infection, combining lopinavir with a sub-therapeutic dose of ritonavir. Kaletra (high-income countries) and Aluvia (low-income countries)

Table 11: Showing detail description and effects of drug interaction (@Lynch, T.et al 2007)

Interacting Drug	**Findings and Mechanism of Interaction**	**Recommendations/Comments**
Amiodarone	Increased risk for myopathy/rhabdomyolysis due to decreased metabolism of atorvastatin, lovastatin, and simvastatin. Amiodarone is a CYP3A4 and CYP2C9 (moderate) inhibitor	Do not exceed 40 mg lovastatin or 20 mg simvastatin. Consider limiting atorvastatin dose. Fluvastatin is primarily metabolised by CYP2C9. Amiodarone can potentially decrease its metabolism. Consider using pitavastatin, pravastatin, or rosuvastatin
Azole Antifungals Fluconazole, Itraconazole Ketoconazole, Nizoral,	Posaconazole, Voriconazole. Decreased metabolism of atorvastatin, fluvastatin, lovastatin, and simvastatin. Itraconazole, ketoconazole, are	Hold lovastatin and simvastatin during the course of itraconazole, ketoconazole, or Posaconazole treatment. Consider reducing lovastatin or simvastatin dose when used with Voriconazole. Hold atorvastatin during the

	strong CYP3A4 inhibitors. Fluconazole is a moderate CYP3A4 and CYP2C9 inhibitor	course of itraconazole treatment. Consider reduced atorvastatin dose if used with ketoconazole, or Voriconazole. Use caution when co-administering fluconazole with atorvastatin, lovastatin, simvastatin, or fluvastatin. Limit fluvastatin dose to 20 mg twice daily. Consider fluvastatin, rosuvastatin, or pravastatin rather than lovastatin, simvastatin, or atorvastatin with itraconazole or ketoconazole
Cimetidine	Decrease in TG-lowering effect of atorvastatin from 34% to 26%.	If atorvastatin TG lowering effect not satisfactory, use another H_2-antagonist. No data for rosuvastatin
Colchicine	Increased risk of myopathy/rhabdomyolysis with atorvastatin, lovastatin, and simvastatin. Colchicine is a P-glycoprotein inhibitor.	Use combination with caution/clinical monitoring
Glyburide	Increased glyburide levels due to fluvastatin inhibition of CYP2C9. Increased levels of fluvastatin due to competition for CYP2C9	Monitor response to glyburide with fluvastatin 80 mg
Grapefruit/Grapefruit Juice	Increased risk for myopathy/ rhabdomyolysis due to decreased metabolism of	Experts suggest avoiding grapefruit with atorvastatin, simvastatin, and lovastatin.

	atorvastatin, lovastatin, and simvastatin. Grapefruit juice inhibits CYP3A4 and P-glycoprotein	Consider using pravastatin, rosuvastatin, or Fluvastatin
Macrolide Antibiotics Clarithromycin (e.g., *Biaxin*, generics) Erythromycin	Increased risk for myopathy/rhabdomyolysis due to decreased metabolism of atorvastatin, lovastatin, and simvastatin.	Lovastatin and simvastatin should be held during treatment with these macrolides. Do not exceed atorvastatin 20 mg with clarithromycin. Also consider cautious dosing with erythromycin. Use azithromycin if treatment with a macrolide antibiotic is unavoidable (considered less likely to interact).
Nefazodone (U.S. only, generics)	Increased risk for myopathy/rhabdomyolysis due to decreased metabolism of atorvastatin, lovastatin, and simvastatin. Nefazodone is strong CYP3A4 inhibitor	Hold lovastatin and simvastatin during nefazodone use. Atorvastatin dose reduction recommended. Consider fluvastatin, pravastatin, or rosuvastatin
Phenytoin (*Dilantin*, generics)	Increased phenytoin levels due to fluvastatin inhibition of CYP2C9. Increased levels of fluvastatin due to competition for CYP2C9.	Monitor phenytoin levels with fluvastatin initiation or dosage change.Fluvastatin dose adjustment not necessary.
Protease Inhibitors Darunavir Fosamprenavi, Indinavir Lopinavir/Ritonavir, Ritonavir	Increased risk for myopathy/rhabdomyolysis due to decreased metabolism of atorvastatin, lovastatin, and simvastatin.	Do not use protease inhibitors with lovastatin or simvastatin. Do not exceed atorvastatin 20 mg with saquinavir/ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, or boceprevir.

Saquinavir	These antivirals are strong CYP3A4 inhibitors.	Do not exceed 40 mg atorvastatin with nelfinavir. Use lowest necessary dose of atorvastatin with atazanavir, indinavir, lopinavir/ritonavir, and ritonavir.
Rifampin	Dual mechanism: rifampin induces CYP450 enzymes but inhibits some non-CYP450 elimination pathways. Simultaneous rifampin/atorvastatin administration increases	Give rifampin and atorvastatin simultaneously. Limit pitavastatin dose to 2 mg with rifampin
Warfarin	Potential increase in INR due to decreased warfarin metabolism and displacement of warfarin from protein binding sites	Monitor INR closely when initiating, stopping, or changing the statin dose. Atorvastatin may be less likely to interact

Project Leader in preparation of this PL Detail-Document: *Melanie Cupp, Pharm.D. BCPS* Pharmacist's Letter 2012; 28(6):280606

3.9.4 Minimising Interactions

Clinicians should know all of their patients' current drugs. The fewest drugs in the lowest doses for the shortest possible time should be prescribed. Patients should be observed and monitored for adverse effects, particularly after a change in treatment.

Effects that are influenced by enzyme induction may take more than one week to appear. Drug interactions should be considered as a possible cause of any unexpected problems.

Prescribers should determine serum concentrations of selected drugs being taken, consult the literature or an expert in drug interactions and adjust the dosage until the desired effect is produced.

If dosage adjustment is ineffective, the drug should be replaced by one that does not interact with other drugs being taken.

3.10 Drug Clearance (Excretion)

3.10.1 Routes of Drug Elimination

i. **Renal Clearance (excretion):** Consists of elimination of chemically unchanged drug or its metabolites from the body. Occurs in the kidney most drugs leave the body in urine, either unchanged or as polar metabolites. Also occurs at other sites such as the liver, the lungs, stool and skin. This is not always for example while drugs like Amiloride, Frusemide etc. can be metabolized and excreted 100%, 80% Amphetamine, 85% Digoxin, 50% Ampicillin, metronidazole, trimethoprim, 60% Flucloxacillin. Because some drugs remain unchanged in the body, excretion is important for the termination of the drug's effect. Other major routes of elimination include biliary, pulmonary, skin and two minor but significant forms of excretion are mammary and salivary.

ii. **Biliary excretion:** Excretion in the bile is similar to excretion in the kidney and occurs by active secretory transport. When plasma drug concentrations are high, secretory transport may approach an upper limit. Substances with similar physicochemical properties may compete for excretion. Drugs with a molecular weight of > 300 g/mol and with both polar and lipophilic groups are more likely to be excreted in bile. Smaller molecules are generally excreted only in negligible amounts. The molecular weight of most drugs is too low for efficient biliary excretion. Conjugation to glucuronic acid often increases molecular weight sufficiently for biliary excretion. Conjugation to acetate or glycine is generally too small. Bile is a significant route of excretion for: Glucuronide conjugates (morphine) and a limited number of ionised drugs with very high molecular weight (cromoglycate)

iii. **Pulmonary excretion:** Pulmonary excretion refers to excretion through the lungs and breath. This is a significant route of excretion for some volatile molecules, especially anaesthetics.

iv. **Excretion through the skin: sweat -** Drugs can be excreted through the skin. Drugs are secreted into sweat by passive diffusion. – This depends on the plasma/sweat partition coefficient (sweat pH: 4–6.8). There are also some active secretion mechanisms by which drugs can be excreted into sweat.

v. **Mammary: milk -** Mammary excretion is a minor route but can be clinically important. There is no active excretion, just passive diffusion. Concentration in milk reflects free concentration in blood. As milk is slightly acidic (with a pH of 7 compared to blood with a pH of 7.4), the ionisation of the drug may differ slightly between the milk and the blood — thus affecting its partitioning. Erythromycin in milk has pH of breast milk: 7.0 and pH of blood: 7.4.

vi. Drugs in milk: clinical significance

The clinical relevance of the effect of a drug is evident when considering breastfeeding a baby, for example; Tetracyclines are incorporated into teeth, which become weakened and 'mottled'. Chloramphenicol can result in bone marrow toxicity and 'grey baby' syndrome, where babies cannot metabolise the drug effectively.

vii. **Saliva:** Excretion through saliva is a minor route but can be significant because of possible use in drug monitoring. Pharmacokinetic experiments often need a number of blood samples (10 or more) so there are doubts about ethical approval. Saliva sampling is non-invasive. For neutral molecules, salivary concentrations will reflect free concentrations in plasma. Ionised drugs are a problem. Saliva pH is variable so, in this case, there is a variable degree of ion trapping.

3.10.2 Processes of Renal Drug Excretion

Three renal processes account for renal drug excretion:

i. Glomerular filtration
ii. Active tubular secretion
iii. Passive diffusion across the tubular epithelium

Table12: Transmembrane passage

<table>
<tr><td colspan="4">Principles of transmembrane passage govern renal handling of drugs</td></tr>
<tr><td>Drugs bound to plasma proteins remain in the circulation</td><td>Unbound drugs are contained in the glomerular filtrate</td><td colspan="2">Un-ionised forms of drugs and their metabolites tend to be reabsorbed from tubular fluids</td></tr>
<tr><td colspan="4">Urine pH affects drug reabsorbed and excretion because it determines the ionisation of a weak acid or base</td></tr>
<tr><td colspan="2">Acidification
• Increased reabsorption
• Decreased excretion of weak acids
• Decreased reabsorption of weak basis</td><td colspan="2">Alkalinisation
• Has opposite effects
• Enhanced excretion of acetylsalicylic acid for example</td></tr>
<tr><td colspan="4">Drug elimination rate changes from urinary pH on the:</td></tr>
<tr><td>• Contribution of the renal route to total elimination
• Polarity of the unionised form</td><td>Polarity of the unionised form</td><td colspan="2">Polarity of the unionised form</td></tr>
</table>

i. **Filtration:** Filtration is a passive process driven by pressure difference. Approximately 20% of plasma volume is filtered in one flow through the kidney. Small molecules with a molecular weight of less than 20,000 are readily filtered, including most drugs. Plasma albumin (Mwt: 68,000) cannot cross the membrane. Therefore, most proteins are not filtered nor are drugs that are extensively protein bound.

ii. **Active secretion:** Active secretion is energy dependent and transports substances from the plasma into the tubular urine. It can generate positive concentration gradients.

Aside from specific transport systems, there are two relatively unspecific mechanisms, one for anions and one for cations (acids and bases). This process is saturable. Therefore, there are some possible interactions.

As blood passes through the kidney, the blood is cleared of some of the drug. If renal clearance is greater than the glomerular filtration rate (GFR), there must be active secretion.

Table13: Actively secreted drugs

Acids	**Bases**
• Cephaloridine • Frusemide • Indomethacin • Penicillins • Probenecid • Thiazide diuretics	• Dopamine • Morphine • Pethidine • Quinine • Quaternary • Ammonium salts
Probenecid and penicillins share the same mechanism for acid secretion. Probenecid competes with penicillins – penicillin clearance is reduced.	

Tubular reabsorption

99% of water is reabsorbed. There are specific transport systems but the majority of reabsorption is by passive diffusion through the distal tubular epithelium.

Lipid-soluble drugs are reabsorbed along with water. Only very water-soluble molecules can be efficiently excreted by the kidneys.

Acidic urine – Basic drug ionisation – Reabsorption – excretion.
Renal clearance

As blood passes through the kidney, the blood is cleared of some of the drug. The maximum possible renal clearance is approximately 660 ml/min – all plasma is cleared. If renal clearance is greater than the glomerular filtration rate (GFR), there must be active secretion.

Not filtered OR extensively reabsorbed

The maximum possible renal clearance is approximately 660 ml/min – all plasma is cleared. If the clearance is much less than the GFR, the drug is not filtered or is extensively reabsorbed

3.11 Concept of Clearance

Clearance is: Used to evaluate efficiency of drug removal from the body. A pharmacokinetic measurement of the renal excretion ability. Clearance is almost synonymous with renal clearance or renal plasma clearance. – Each drug has a specific clearance that depends on its filtration characteristics in the kidney. Clearance is the proportionality constant that makes the average steady state drug level equal to the rate of drug administration.

Clearance = Rate of elimination / plasma concentration

Clearance only represents the theoretical volume of blood that is totally cleared of drug per unit time. – It is not an indicator of how much drug is being removed. The amount of drug removed depends on the concentration. Clearance expresses the rate or efficiency of drug removal. Units of flow (mg/h)/ (mg/l) = l/h

Example: Clearance = 1 l/hr. Concentration = 0.5 mg/l
Rate of elimination = Clearance × concentration = 0.5 mg/hr.

Clearance is the apparent volume of plasma completely cleared of drug per unit time.
The rate of elimination is always the same. The value of clearance will differ depending on where you measure the drug:

Rate of elimination = $CL \times C = CLb \times Cb = CLu \times Cu$
Plasma blood plasma water

If you want to measure the volume based on plasma and you want to relate that to clearance, clearance has to be measured with respect to plasma.

3.11.3 Rate of elimination

Volume of reservoir (V) = 1,000 ml
Dose = 10 mg Initial concentration = 10 mg/l
Removal rate (flow rate) (Q) = 100 ml/min

Clearance = Q = 100 ml/min
Fractional rate of removal (K) = 100 ml/min = 0.1 or 10%/min
1,000 ml
The relationship between the amount of drug in the body (A) and the plasma concentration (C) is defined by the volume of distribution (V).

$A = V \times C$

The fractional elimination rate constant (k) is the rate of elimination divided by the total amount of drug in the body
Example: k = Rate of elimination = CL × C = CL
Amount V × C V
CL = k × V

Elimination rate constant

The elimination rate constant can also be expressed as a half-life: t1/2 = ln (2) = K
0.693 V
CL

Table14: Terminal Half-life versus Plasma Clearance (Dog Data)

	Benzyl Penicillin	Gentamicin	Oxytetracycline	Tylosin
Cl (plasma) (ml/kg/min)	3.5	3.1	4	22
t1/2 (min)	30	75	360	54

Half-life changes as a result of changes in elimination

3.11.2Extraction Ratio

Extraction ratio: Rate of elimination = Rate in – Rate out = (Q × CA) – (Q × CV)

Extraction

Extraction ratio (E) = Rate of elimination Rate in = $Q \times (C_A - C_V)$ $Q \times C_A$ $C_A - C_V$ C_A
= Extraction ratio (E) = Rate of elimination = Q × ($C_A - C_V$) = $C_A - C_V$
Rate in $Q \times C_A \times$ (
Extraction ratio and clearance
Rate in $Q \times C_A$ Rate out $Q \times (1 - E) \times C_A$

Rate of elimination = $Q \times (E \times C_A)$
CL = Rate of elimination = $Q (C_A - C_V) = Q \times E$

Entering concentration C_A

Clearance depends on blood flow and extraction ratio

Low and high extraction: The extraction ratio must be between 0 and 1.
$E = Q (C_A – C_V) C_A$

Table 15: Renal extraction Ratio

Low extraction drug	**High extraction drug**
• The eliminating organ is not very efficient at removing the drug. • Clearance is low.	• The drug is efficiently eliminated from the organ. • Clearance is high.
Low clearance drug: E 0	High clearance drug: E ⟹ 1

Table 16: Hepatic extraction ratio

Low extraction	**Medium extraction**	**High extraction**
Diazepam	Quinidine	Alpranolol
Warfarin	Codeine	Propranolol
Tolbutamide	Morphine	Pentazocine
Phenytoin		Lidocaine

3.11.3 Additivity of clearance: Some drugs can be eliminated by more than one organ, for example, hepatic metabolism (liver) and renal excretion (kidneys), such that clearance is additive. In such cases, total clearance is the sum of the component organ clearances.
Rate of elimination (CL X C) = Rate of excretion (CLR X C) + Rate of hepatic metabolism (CL_H XC)

$CL = CL_R + CL_H$

3.12 Pharmacokinetics Changes in Pregnancy and Lactation

3.12.1 Introduction: Physiological Changes in Pregnancy

Immediate Physiological Changes; As the fetus and placenta grow and place increasing demand on the mother, phenomenal alterations in metabolism occur. The most obvious physical changes are weight gain and altered body shape. Weight gain is due to increase in breast tissue, blood and water volume in the form of extra vascular and extra cellular fluid.

Deposition of fat and protein and increased cellular water are added to maternal stores. The average weight gain during pregnancy is 12.5 kg while during normal average increase in non- pregnant women is about 1 kg weight gain is due to protein. Also, plasma albumin levels are decreased and fibrinogen levels are increased. Total body fat increases

during pregnancy. During second half of pregnancy plasma lipids increase but triglycerides, cholesterol and lipoproteins decrease soon after delivery. The ratio of LDL to HDL increases during pregnancy

3.12.2 Absorption: Gastric emptying/small intestine motility are reduced in pregnancy due to elevation of progesterone particularly in the third trimester thus delaying the appearance in the plasma of orally administered drugs & onset of effect of the drug, especially during labor. Absorption from an intramuscular site is likely to be efficient because tissue perfusion is increased due to vasodilatation.

Inhalational drugs may be enhanced due to increased cardiac output and tidal volume, increasing alveolar uptake. For example, dose requirements for volatile anaesthetic agents, such as halothane, are reduced in pregnancy

3.12.3 Distribution: During Pregnancy. a woman's plasma volume increases by 30-50% (up to 8litre of water) and cardiac output and glomerular filtration rate also increase in similar proportion. These factors contribute to lower circulating concentration of some drugs (especially those excreted by kidney) in a pregnant woman and possibly to sub-therapeutic drug levels. Also, there is increase in body fat during pregnancy; which increases the volume of distribution of fat-soluble drugs as a result of haemodilution, plasma albumin (normal 33-55 g/1) declines by some 10 g/1. Thus, there is scope for increased free concentration of drugs that bind to plasma proteins (albumin). e.g. anticonvulsants. Unbound drug is free to distribute, metabolised and excreted out more rapidly by the kidney and liver; and this offset the effect of increased volume of distribution; e.g. the free (and pharmacologically active) concentration of phenytoin is unaltered, although the total plasma concentration is reduced.

3. 12.4 Metabolism: Concurrent use of other common medications during pregnancy such as antacids, iron and vitamins could also bind and inactivate some drugs

3.12.5 Hepatic metabolism increases, but not the blood flow to liver. oestrogen/progesterone induces some enzymes of P-450 system, resulting in a higher rate of metabolism (and hence elimination) of drugs, like Phenytoin. Other isoenzymes are competitively inhibited by progesterone and oestradiol, leading to impaired elimination, for example, theophylline. Drugs that are so rapidly metabolised that their elimination rate depends on their delivery to the liver, i.e. on hepatic blood flow, have unaltered clearance, e.g. pethidine.

3.12.6 Elimination: Renal plasma flow almost doubles: RBF is increased by 60±80% during pregnancy, and GFR rises by 50%, leading to enhanced elimination of drugs that are normally excreted unchanged ± for e.g. penicillin and digoxin. So, there is rapid loss of drugs that are excreted by kidney e.g. amoxycillin, dose of which should be doubled for systemic infections

3.12.7 Placental Transfer of Drugs: The placenta is not a perfect barrier to drugs and chemicals administered to mother.
Thalidomide tragedy, showed that placenta was capable of transferring drugs ingested by mother to fetus, with potential for great harm. On other hand, placental transfer of drugs administered to mother has been used to treat fetal arrhythmias, congestive heart failure, & other conditions.

3.12.-8 Factors affecting placental drug transfer & fetal tissue

The rate of transfer (Rate at which drug crosses placenta & amount of drug reaching the fetus) depends on the chemical properties of the drug such as

i. **Duration of exposure to drug**
ii. **Protein binding:** Only free unbound drug crosses the placenta, during pregnancy maternal plasma albumin decreases while fetal albumin increases. As a result, the concentration of free drug increases which crosses the placenta to reach the fetus
iii. **pH difference**: Fetal pH is slightly more acidic than maternal pH and so weak bases are more likely to cross the placenta.,
iv. **Lipid solubility:** Moderately lipid soluble drugs can easily diffuse across the placental membrane
v. **Molecular weight of the drug:** Drugs with low molecular weight (<500 g/mol) diffuse freely across the placenta. Drugs with a higher molecular weight (between 500-1000 g/mol) cross the placenta less easily, while a few drugs with a high molecular weight (>1000 g/mol) do not cross the placental membrane
vi. Physicochemical properties of drug
vii. Distribution characteristics in different fetal tissues
viii. **Stage of placental & fetal development at time of exposure to the drug: Transplacental:** transfer of drugs increases in the third trimester due to increased maternal and placental blood flow, decreased thickness and increased surface area of the placenta
ix. **Effects of drugs used in combination**: steroid and placental hormones displace drugs from their protein-binding sites.

SELF ASSESSED EXERCISES

i. What is the importance of drug concentration?
ii. What are the advantages and disadvantages of oral drug administration?
iii. Explain the terms “Therapeutic window” and “Therapeutic index”.

4.0 CONCLUSION

In this unit, you learnt about definition terms in pharmacology, and sources of drugs. You have been exposed to one of the major topics in pharmacology; pharmacokinetics (routes of drug administration, kinetics of drug absorption, distribution. Blood-brain-barrier, placental barrier, biotransformation and elimination etc.) and also pharmacokinetic changes in pregnancy and lactations necessary for a public health professional.

5.0 SUMMARY

Basic principles of pharmacology have been discussed. These include Pharmacokinetics, which literally means "What the body does to the drug". It describes the movement of drug as it passes through the body through absorption, distribution, metabolism and excretion. Drug may enter the body in a variety of ways: as an oral liquid, pill, or capsule; as an inhaled vapour or aerosol; absorbed through intact skin or a mucous membrane; injected into muscle, subcutaneous tissue, spinal fluid, or directly into the bloodstream. Pharmacokinetics determine the blood concentration from a prescribed dosing regimen. More often the plasma concentration for analytical purposes. Pharmacokinetic data help us understand: dose and schedule (once a day vs. twice a day, etc.), dose adjustments due to drug interactions and other issues. Many factors affect drug absorption such as particles size, physicochemical properties of the drug, surface area of absorption, pH, and blood supply etc. ort.

Once the drug is in the bloodstream a portion of it may exist as free drug, dissolved in plasma water. Some drugs will be reversibly taken up by red cells and some will be reversibly bound to plasma proteins. For many drugs, the bound forms can account for 95-98% of the total. This is important because it is the free drug which traverses cell membranes and produces the effect. It is also important because protein-bound drug can act as a reservoir which releases drug slowly and thus prolongs its action.

This total volume of distribution determines the equilibrium concentration of drug after a specified dose. The liver metabolises most drugs into inactive or less active compounds which are more readily excreted. These metabolites and some of the parent compounds may be

excreted in the bile and eventually may pass out of the body in the faces. Parent drug and metabolites in the bloodstream may then be excreted: most are filtered by the kidney, where a portion undergoes reabsorption, and the remainder is excreted in the urine. Some drugs are actively secreted into the renal tubule. Another route of excretion is the lung: Drugs like alcohol and the anaesthetic gases are eliminated by this route. Smaller amounts of drugs are eliminated in the sweat, tears and breast milk. Biotransformation may sometimes produce metabolites with a great deal of activity. Occasionally, we administer a parent drug which is inactive (a pro-drug) and only the metabolite has activity.

6.0 TUTOR- MARKED ASSIGNMENT

1) What are different routes of drug administration and write about advantages and disadvantages of parenteral route of administration.
2) Define bio-availability and describe the factors affecting drug absorption.
3) Define the following:
   a) Half-life of a drug
   b) Steady state plasma concentration
   c) Drug - drug interactions

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UNIT 2 TOXICOLOGY AND ADVERSE DRUG REACTIONS

CONTENTS

6.0 Tutor- Marked assignment
7.0 References/Further reading

1.0 INTRODUCTION

Traditionally, the study of poisons was centred around the inherent capacity of a chemical or compound to produce injury. Today, toxicology is more safety driven and modern toxicology uses chemicals as tools to understand molecular/cellular biology. One basic function of toxicology is to assess the likelihood of occurrence of adverse effects (qualitative): Is a chemical or compound safe? This is hazard identification. Also, toxicology studies the nature and mode of action of adverse effects (quantitative). At what concentration is it safe? This is known as dose-response assessment or hazard characterisation

2.0 OBJECTIVES

By the end of this unit, you will are to

- define toxicology, drug interactions and adverse drugs commonly associated terms
- describe the classifications of toxic agents and poisons that can heal
- distinguish adverse drug reactions (ADRs) from adverse drug events
- devise methods for ADR detection, and classify an ADR when it presents
- detect populations most at risk of ADRs.

3.0 MAIN CONTENT

3.1 Definition of Terms

i. **Toxicity:** The word “toxicity” describes the degree to which a substance is poisonous or can cause injury. The toxicity depends on a variety of factors: dose, duration and route of exposure, shape and structure of the chemical itself, and individual human factors.
ii. **Toxic:** This term relates to poisonous or deadly effects on the body by inhalation (breathing), ingestion (eating), or absorption, or by direct contact with a chemical.
iii. **Toxicant:** A toxicant is any chemical that can injure or kill humans, animals, or plants; a poison. The term “toxicant” is used when talking about toxic substances that are produced by or are a by-product of human-made activities. For example, dioxin (2, 3-7, 8-tetrachlorodibenzop-dioxin {TCDD}), produced as a by-product of certain chlorinated chemicals, is a toxicant. On the other hand,

arsenic, a toxic metal, ma**y** **o**ccur as a natural contaminant of groundwater or may contaminate groundwater as a by-product of industrial activities. If the second case is true, such toxic substances are referred to as toxicants, rather than toxins.

iv. **Toxin:** The term "toxin" usually is used when talking about toxic substances produced naturally. A toxin is any poisonous substance of microbial (bacteria or other tiny plants or animals), vegetable, or synthetic chemical origin that reacts with specific cellular components to kill cells, alter growth or development, or kill the organism.

v. **Poisoning:** Definition of a Poison? The study of the adverse effects of a toxicant on living organisms. Any agent capable of producing a deleterious response in a biological system. Living organism: a sachet of water with target sites, storage depots and enzymes. *All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and a remedy. -Paracelsus (1493-1541)*

vi. **Adverse drug reaction** (**ADR):** WHO definesas an adverse drug reaction is "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function." (WHO definition, 2005). This excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors

vii. An **adverse drug reaction** (**ADR**) is an injury caused by taking medication. ADRs may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs.

viii. **An adverse drug event** *is* "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" *(WHO definition, 2005).* In other words, the *reaction* is where the drug does something nasty, and an *event* is something nasty which potentially happens randomly and might be totally unrelated to the drug. The basic requirements for an ADR are that: The reaction is directly related to the drug; the drug was being used correctly and appropriately and the reaction is harmful. Thus, prescribing errors and intentional overdoses do not fall under the definition of an adverse drug reaction.

ix. **Side Effects:** Is define as An unintended effect of a drug occurring at the normal dose related to the pharmacological properties of the drug.

x. **Drug overdose:** Toxic reactions linked to excess dose or impaired excretion, or to both.

xi. **Drug interaction:** Action of a drug on the effectiveness or toxicity of another drug. Reactions that occur only in susceptible subjects

xii. **Drug intolerance:** A low threshold to the normal pharmacological action of a drug
xiii. **Drug idiosyncrasy:** A genetically determined, qualitatively abnormal reaction to a drug related to a metabolic or enzyme deficiency
xiv. **Drug allergy:** An immunologically mediated reaction, characterised by specificity, transferability by antibodies or lymphocytes, and recurrence on re-exposure
xv. **Pseudo allergic reaction**: A reaction with the same clinical manifestations as an allergic reaction (e.g., as a result of histamine release) but lacking immunological specificity
xvi. **Expected Reaction:** The process of assessing the likelihood that the reported adverse reaction is actually due to the suspected medicine using pre-determined criteria such as the WHO causality assessment criteria.
xvii. **Expected Reaction:** A reaction that is consistent with the applicable product information or characteristics of the drug. The reaction can be explained from the mechanism of action of the drug.
xviii. **Unexpected Adverse Reaction:** An adverse reaction, the nature or severity of which is not consistent with the applicable product information or characteristics of the drug.

3.2 Purpose of Toxicology

Toxicology affects us every day. The purpose of toxicology is to provide workers a safe working environment and to ensure consumers' products are safe to use as specified and under foreseeable misuse. Another area of toxicology is the environment or ecotoxicology, which is concerned with the quality of the air, water (surface and ground), soil, and bedrock, and aquatic wildlife (fresh and salt) and terrestrial organisms (flora and fauna). Toxicology provides information to risk managers about the nature and severity of effects on human health and the environment as it relates to specific exposures. Ecotoxicology often drives remediation site clean-ups. There are approximately 6,000,000 known chemicals; approximately 100,000 currently in use worldwide, and 500 new chemicals being added annually.

3.3 the Goal of Toxicology

The goal of toxicology is to contribute to the general knowledge of the harmful actions of chemical substances, to study their mechanisms of action, and to estimate their possible risks to humans on the basis of experimental work on biological test systems. To protect human health, provide information via risk assessments, hazard identification, dose-response assessment, exposure assessment and risk characterization

3.4 History of Toxicology

Toxicology is arguably the **oldest scientific discipline**, as the earliest **humans** had to **recognise** which plants were **safe** to **eat.** Most exposure of humans to chemicals is via naturally occurring compounds consumed from food plants. Humans are exposed to chemicals both inadvertently and deliberately**. Paracelsus**: born Philippus Aureolus Theophrastus Bombastus von Hohenheimis credited as the founder of toxicology. His premise of poisons was that *"Allthings are poison, and nothing is without poison; only the dose permits somethingnot to be poisonous." Simply stated, "The dose makes the poison".*

Many of the Earliest Practitioners of Toxicology Were Women: Lucrezia Borgia (food toxicologist): daughter of Rodrigo Lenzuoli Borgia or Pope Alexander VI, who specialised in faith-based poisoning, was an early Italian who helped develop poisoning into a simple but fine art. It is said that the Borgias selected and laid down rare poisons in their cellars with as much thought as they gave to their vintage wines.
Catherine de Medici of Florence and Queen Consort of France (experimental toxicologist): tested and carefully studied the effects of various toxic concoctions on the poor and sick, noting the onset of action and symptoms that occurred.

Goeie Mie ('Good Mary') of Leiden, The Netherlands (forensic toxicologist): poisoned at least 102 friends (27 died) and relatives between 1867 and 1884, distributing arsenic trioxide in hot milk to her victims after opening life insurance policies in their names.
Catherine Deshayes or "La Voisin" (economic toxicologist): who traded in selling poisons to wives who wished to rid themselves of their husbands, was later burned at the stake.

Other Historical Examples: Stalin: –Politburo allegedly gave him warfarin (a synthetic derivative of Coumarin, found naturally in many plants and used as an anticoagulant medication).
Fidel Castro: CIA, using botulinum-laced pills, made attempts on the life of the Cuban Dictator.

Viktor Yushchenko: Evidence suggests that the Ukrainian President was poisoned with dioxin (the common name for the group of compounds classified as polychlorinated dibenzodioxins) in an attempt to remove him from office as recently as 2006
Study and Documentation of Poisons: 20th Century: Rachel Carson - alarmed public about dangers of pesticides in the environment in her book "Silent Spring". Late in the 1950s, Carson turned her attention to conservation, especially environmental problems that she believed were caused by synthetic pesticides. The result was Silent Spring (1962), which

brought environmental concerns to an unprecedented share of the American people. Although Silent Spring was met with fierce opposition by chemical companies, it spurred a reversal in national pesticides policy, which led to a nationwide ban on DDT and other pesticides, and it inspired a grassroots environmental movement that led to the creation of the U.S. Environmental Protection Agency. Carson was posthumously awarded the Presidential Medal of Freedom by Jimmy Carter.

1900-1200 . - Egyptian documents that had directions for collection, preparation, and administration of more than 800 medicinal and poisonous recipes.

1900-1201 800 B.C. - India - Hindu medicine includes notes on poisons and antidotes**.**

50-100 D. - Greek physicians classified over 600 plant, animal, and mineral poisons.

Swiss physician Paracelsus (1493-1541) credited with being **"the father of modern toxicology."** *"All substances are poisons: there is none which is not a poison. The right dose differentiates a poison from a remedy."*

Italian physician: Ramazzini (1713) published "De Morbis Artificum" (Diseases of Workers) Describing "asthma" in bakers, miners, farmers, gilders, tinsmiths, glass-workers, tanners, millers, grain-sifters, stonecutters, ragmen, runners, riders, porters, and professors. Ramazzini outlined health hazards of the dusts, fumes, or gases that such workers inhaled. The bakers and horse riders described by Ramazzini would today probably be diagnosed as suffering from allergen-induced asthma. The lung diseases suffered by most of the other workers would now be classified as "pneumoconiosis," a group of dust-related chronic diseases.
Paul Ehrlich –developed staining procedures to observe cell and tissues and pioneered the understanding of how toxicants influence living organisms.

From Killers to Healers: Toxicology Evolves, but Poisonings Still Occur

Over the years, there have been several cases of human exposures to chemicals that have led to devastating outcomes and in some instance's death. In 2008, one such case of worldwide poisoning was the exposure of hundreds of thousands of Chinese children to melamine contaminated milk, with ensuing kidney stones, kidney failure, and death in some of the children exposed **(Xin and Stone, 2008, Yang and Batlle, 2008, Chiu, 2008)**. Melamine was found in tainted pet food a year earlier with

hundreds of thousands of dogs and cats being exposed (Dobson et al., 2008).

The government of Nigeria implemented tighter controls on chemical imports after 84 children between the ages of two months and seven years died after consuming a tainted teething syrup, **"My Pikin" (Okuonghae et al., 1992).** Authorities believe diethylene glycol [component of antifreeze] was wrongly labeled as propylene glycol, a chemical generally recognized as safe for use in food and medicine which was smuggled into Nigeria before being purchased by a Lagos-based company, which has since been shut down. To prevent future incidents, The National Agency for Food and Drug Administration and Control (NAFDAC) required all propylene glycol imports from India and China to be certified by the agency's independent analysts in India and China before shipment and to be re-certified upon entry into Nigeria. The first case was discovered on November 3 with symptoms including diarrhea, vomiting, fever, convulsions and an inability to pass urine. Diethylene glycol was used as a cheap replacement for the sweetener glycerin in cough syrup and more than 100 people, mostly children, died in Panama (http://www.cdc.gov/ mmwr/preview/mmwrhtml/mm5848a2.htm). In addition to the United States and Panama, diethylene glycol-tainted toothpaste was found in Australia, the Dominican Republic, Costa Rica, Honduras and Nicaragua (http://www.nytimes.com/2007/06/02/us/02toothpaste.html? _r=0).

In 2009, 121 of 287 children under 14 years of age in Longyan, China had high blood lead levels (http://www.nytimes.com/2009/09/28/world/asia/28china.html). A smelting plant closed after more than 600 children were found to have lead poisoning and, in another case, 800 children living near a zinc and lead smelting plant were found to have high blood lead levels.

In the US, the Food and Drug Administration has a limit of 0.5 μl/dL in products intended for infants and children and has banned the use of lead-soldered food cans. Each year in the United States, 310,000 1- to 5-year-old children are found to have unsafe levels of lead in their blood due to exposure to lead through dust and other sources (https:// www.cdc.gov/nceh/lead/data/). Just recently, Virginia Tech University researchers brought proof of high lead levels in Flint, MI water to public attention in September 2015, performing water tests in more than 250 Flint homes. Lead levels were high enough, up to 38 μl/dL, to warrant urgent government action (https://www.rt.com/usa/327363-flintchildren-blood-lead-water/); however, in a similar problem with Washington, D.C.'s tap water a little over a decade ago, hundreds of homes were found to have stratospheric lead levels of 300 ppb or more (Guidotti et al., 2007).

China has 150 parts per billion (ppb) arsenic limit in foods such as rice. Rice grown in US has an average 260 ppb of arsenic; however, a 100-ppb action level has been proposed for inorganic arsenic in infant rice cereal (http://www.philrice.gov.ph/phl-rice-safe-fromarsenic/).

3.5 Toxicology Sub-Discipline

3.5.1 Environmental Toxicology: Studies chemicals that are contaminants of food, water, soil, or the air. It deals with toxic substances that enter the water ways, such as lakes, streams, rivers and oceans. Most common problems include waterborne bacteria and viruses, waste heat from electrical plants, radioactive wastes, sewage, and industrial pollution.

3.5.2 Occupational (Industrial) Toxicology: studies of protection of workers from toxic substances and makes their work environment safe. Occupational diseases caused by industrial chemicals account for an estimated 50,000 to 70,000 deaths and 350,000 new cases of illness each year in the United States

3.5.3 Regulatory Toxicology: Gathers and evaluates existing toxicological information to establish concentration-based standards of "safe" exposure.

3.5.4 Food Toxicology: Involves delivering a safe and edible supply of food to the consumer

3.5.5 Clinical Toxicology: Is a study that is concerned with diseases and illnesses associated with short term or long-term exposure to toxic chemicals.

3.5.6 Descriptive Toxicology: Is concerned with gathering toxicological information from animal experimentation. These types of experiments are used to establish the chemical dosage that would cause illness and death. The United States Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA), use information from these studies to set regulatory exposure limits.

3.5.7 Forensic Toxicology: Helps to establish cause and effect relationships between exposure to a drug or chemical and the toxic or lethal effects that result.

3.5.8 Analytical Toxicology: Identifies the toxicant through analysis of body fluids, stomach content, excrement, skin, or suspected containers

3.5.9 Mechanistic Toxicology: Makes observations on how toxic substances cause their effects. The effects of exposure can depend on a number of factors, including the size of the molecule, the specific tissue type or cellular components affected, whether the substance is easily dissolved in water or fatty tissues, all of which are important when trying to determine the way a toxic substance causes harm, and whether effects seen in animals can be expected in humans.

3.6 Routes of Drug Toxicity

The common route hard exposure is ocular (Eye), Inhalational (aerosol, Gasses, particles), Ingestion (Food/drinks, upper respiratory tract, hand to mouth), Dermal contact, Breast feeding and Placental see diagram below

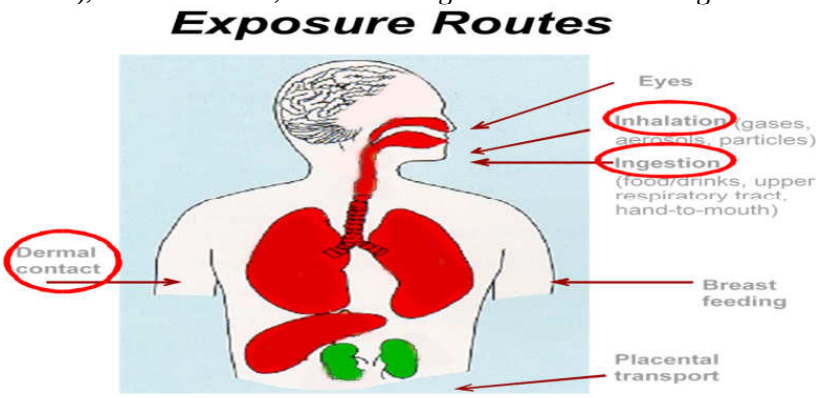

Figure 17: Routes of toxicity exposure. (Liebler. D.C.et al (2005)

The exposure route is generally further described as intake (taken in through a body opening, e.g. as eating, drinking, or inhaling) or uptake (absorption through tissues, e.g. through the skin or eye).

EPA defines exposure as 'contact between an agent and the visible exterior of a person (e.g. skin and openings into the body)'.

The applied dose is the amount of agent at the absorption barrier that is available for absorption. The potential dose is the amount of agent that is ingested, inhaled, or applied to the skin. The applied dose may be less than the potential dose if the agent is only partly bioavailable.

The internal dose or absorbed dose is the amount of an agent that has been absorbed and is available for interaction with biologically significant receptors within the human body. Finally, the delivered dose is the amount of agent available for interaction with any specific organ or cell.

Range of Exposure. For any specific agent or site, there is a range of exposures actually experienced by individuals. Some individuals may

have a high degree of contact for an extended period (e.g. factory workers exposed to an agent on the job). Other individuals may have a lower degree of contact for a shorter period (e.g. individuals using a recreational site downwind of the factory). EPA policy for exposure assessment requires consideration of a range of possible

3.7 Mechanism of Drug Toxicity

All compounds are toxic at high doses and all are safe at very low doses, using the axiom of Paracelsus.3) What we are considering here are not accidental drug overdoses but toxicity and adverse events at doses that are relevant to patients using a medicine. What the context of toxicity will affect how one approaches the matter of circumventing toxicity or developing alternate compounds that will not have this liability. The most commonly encountered problems are with cardiovascular and hepatic toxicity

3.7.1 On -Target: The first context of toxicity is **on-target** (or mechanism-based) toxicity. That is, the toxicity is due to interaction of the drug with the same target that produces the desired pharmacological response. the concept in this mechanism, is based on the biological response that the drug exhibits upon binding to its target is the same one that produces both the efficacious and the toxic effects. All statins produce hypercholesterolemic properties by inhibiting 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase in the liver, i.e. the target.
The adverse effects of statins are also due to inhibition of HMGCoA reductase in muscle and possibly other tissues, i.e. geranylgeranylation of proteins) is inhibited.

3.7.2 Hypersensitivity and immunological Toxicity: The second context of drugtoxicity is **hypersensitivity** and **immune responses**. For instance, allergicreactions to penicillins have been recognised for many years. The concept, is on the basis that drugs (or their metabolites) react with proteins in the body (as haptens) to induce antibodies and immune responses. In this example (penicllins) the chemical is not completely stable and has the potential to bind covalently to proteins and initiate antibody production. See table 1.

Table 17: Contexts of drug toxicity

Type	Example
On -target (mechanism based	Statin
Hypersensitivity and immunological	Penicillins
Off -target	Terfenadine
Biological activation	Acetaminophen
Idiosyncratic	Halofantrine

(Liebler. D.C.et al (2005)

3.7.3 Off target Toxicity: The third context of drug toxicity is off-target toxicity. The issue here is that the drug is not specific in its interactions. Binding to an alternate target is the cause of toxicity. With current knowledge of the complexity of biological regulatory pathways and multi-gene families (e.g. protein kinases), it is not surprising that a drug might not be totally specific. The example in Table 2 is terfenadine, which binds not only to the H_1 receptor (eliciting the desired antihistaminic response) but also to the hERG channel and thus causing arrhythmias. In principle, this liability can be addressed by more screening and development of drug candidates with lower IC_{50} and K_d values, in that a lower dose might avoid the specificity issue.

3.7.4Bioactivation: The fourth context of drug toxicity is **bioactivation**. Many drugs are converted to reactive products (often termed (reactive) "metabolites"). These entities modify the proteins they react with and somehow cause toxicity, although mechanisms have been evasive (*vide infra*). One theory is that important regulatory or other proteins are modified, with loss of function. Another possibility is that the modified proteins induce immune responses, linking with the second context of toxicity. An analysis of drugs at one company, Bristol-Myers Squibb, indicated that "metabolism" was an issue in 28% of cases in which drug candidates had been dropped from development.

Table 2: Mechanistic causes of toxicology attrition. Based on experience from DuPont-Merck and Bristol-Myers Squibb, 1993–2006. Information kindly provided by B. D. Car, Bristol-Myers Squib.

Table 18: Mechanistic causes of toxicology attrition

Mechanistic causes	**% of all advanced molecules[an]**
Biotransformation related	27
Target Based	28
Single or multichannel inhibition	18
Immune mediated	7
All other mechanisms	36

[a]n = 88. Because categories are partially overlapping, the total is > 100%.

3.7.5 Idiosyncratic Reactions; The fifth context of toxicity is idiosyncratic reactions. Idiosyncratic means "individual," and these are rare events ($1/10^3$ to $1/10^4$ individuals), which are not well understood. Such responses are highly problematic in that few (if any) animal models are very predictive. The low incidence makes such adverse events difficult to find even in large clinical trials. However, with widely-used drugs for which millions of prescriptions may be written, even an incidence of $1/10^4$ can yield hundreds of problems.

3.8 Classification of Toxic Agents

3.8.1 Heavy Metals: Metals differ from other toxic substances in that they are neither created nor destroyed by humans. Heavy metals, like lead, cadmium, and mercury, have been harming human health for millennia their use by humans playsan important role in determining their potential for health effects.

Their effect on health could occur through at least two mechanisms: first, by increasing the presence of heavy metals in air, water, soil, and food, and second, by changing the structure of the chemical. For example, chromium III can be converted to or from chromium VI, the more toxic form of the metal.

Heavy metal toxicity can result in reduced mental and central nervous function, lower energy levels, and damage to blood, lungs, kidneys, liver, and other organs.

Some heavy metals like zinc that provide a health benefit in small doses can be toxic at high levels.

3.8.2 Solvents and Vapours: Nearly everyone is exposed to solvents. Occupational exposures can range from the use of "white-out" by administrative personnel, to the use of chemicals by technicians in a nail salon. When a solvent evaporates, the vapours may also pose a threat to the exposed population. Hydrocarbon Solvents: Aliphatic organic solvents are Petroleum distillates, Mineral spirits, and hexanes found in Paints, coating, thinners etc. Aromatic organic solvents such as Toluene, xylene and benzenes are found in adhesives and printing inks. Some solvents are associated with neurotoxicity, reproductive toxicity and carcinogenic effects during short-term high-level exposure and over prolonged periods of low-level exposure.

3.8.3 Radiation and Radioactive Materials: Radiation is the release and propagation of energy in space or through a material medium in the form of waves, the transfer of heat or light by waves of energy, or the stream of particles from a nuclear reactor.

3.8.4 Dioxin/Furans: Dioxin, (or TCDD) was originally discovered as a contaminant in the herbicide Agent Orange. Dioxin is also a by-product of chlorine processing in paper producing industries.

3.8.5 Pesticides: The EPA defines pesticide as any substance or mixture of substances intended to prevent, destroy, repel, or mitigate any pest. Pesticides may also be described as any physical, chemical, or biological agent that will kill an undesirable plant or animal pest.

3.8.6 Plant Toxins: Different portions of a plant may contain different concentrations of chemicals. Some chemicals made by plants can be lethal. For example, taxon, used in chemotherapy to kill cancer cells, is produced by a specie of the yew plant.

3.8.7 Animal Toxins: These toxins can result from venomous or poisonous animal releases. Venomous animals are usually defined as those that are capable of producing a poison in a highly developed gland or group of cells, and can deliver that toxin through biting or stinging. Poisonous animals are generally regarded as those whose tissues, either in part or in their whole, are toxic.

3.9 Poison

3.9.1 Toxicant (Poison): any agent capable of producing a deleterious response in a biological system. Living organism: a sachet of water with target sites, storage depots and enzymes. Poison is a more serious public health problem than generally recognised. Institute of Medicine estimates that more than 4 million poisoning episodes occur annually (IOM, 2004) in 2001 (the most recent year for which data from all sources were available), there were 30,800 poisoning-related deaths in the

United States (based on published figures and specially provided estimates from Lois. Fingerhut at the National Centre for Health Statistics, 2003). This estimate makes poisoning the second leading cause of injury-related death in the United States, behind motor vehicle deaths (N = 42,443) and ahead of gun-related deaths (N = 29,573). (IOM, 2004). Ninety-two (92%) percent of all poisonings happen
at home.

The household products implicated in most poisonings are: cleaning solutions, fuels, medicines, and other materials such as glue and cosmetics. Certain animals secrete a xenobiotic poison called venom, usually injected with a bite or a sting, and others animals harbor infectious bacteria. Some household plants are poisonous to humans and animals.

3.**9.2 Population at Risk:** Not only have the magnitude and cost of the poisoning problem that have been underappreciated, but the diverse nature of poisonings and the populations at risk have changed over time. While poisoning was initially viewed as a problem of young children, it now emerges as a concern across the entire lifespan. Half of all *poison exposures* reported to TESS occur among children years of age; however, only 8 percent of the moderate to major effects from poisonings occur among those in the 5 years and under age group.

Approximately71% of moderate and major exposures occur in those over 19 years of age. Regulatory agencies (EPA, CPSC, DOT) require that certain products and chemicals are tested to determine their potential to cause life-threatening or fatal acute systemic toxicity.

Testing currently involves exposure of rodents by applicable routes and monitoring whether animals die or exhibit any clinical signs of toxicity.

3.9.3 Poisons that Can Heal: The key points of toxicology are: 1) Dose matters (and so does timing); 2) people differ; and 3) things change (Mitchell, 2004). When we explore the concept of dose, there are poisons such as Botulinum Toxin A (0.00001 mg/kg) that can be poisonous, yet this toxin can also heal. **Botulinum toxin A (0.00001 mg/kg) Clostridium** *botulinum* is an anaerobic, gram-positive, spore-former commonly found in soil that produces oval, sub-terminal endospores.

Botulinum toxin A (0.00001 mg/kg) that can be poisonous, yet this toxin can also heal. One of 7 seven strains [ABCDEG] is responsible for approximately 145 cases of poisoning annually and is 40 million times more powerful than cyanide. Because of the widespread occurrence of spores of C. botulinum in the soil and the typical hand to mouth response of infants, C. botulinum spores are often consumed by young children. These spores can germinate in the intestine in infants (approximately 75–100 cases annually; 2nd month of life), causing often-fatal outcomes. This poisoning can be treated with an antitoxin (human Botulinum immunoglobulin) and supportive care. Conversely, Botulinum toxin is a poison that can heal. In its purified form (type A), it was the first bacterial toxin to be used as a medicine. In 1989, the FDA licensed Botulinum for treating two eye conditions characterized by excessive muscle contractions; blepharospasm (tic or twitch of eyelid) and strabismus (eyes not properly aligned). As a medicine,

i. type A toxin can be used to control certain conditions marked by involuntary muscle contractions and can block muscle contractions.
ii. Another beneficial effect of botulinum toxin is its use in cosmetic applications, such as Botox and Botox Cosmetic (Botulinum toxin A).
iii. It is use in the treatment of patients with cervical (neck) dystonia and to reduce the severity of abnormal head position and neck pain associated with cervical (neck) dystonia.
iv. Other applications of Botulinum toxin include severe primary axillary hyperhidrosis (excessive sweating), achalasia (failure of the lower oesophageal sphincter to relax), neuropathies, migraine and other headache disorders, although the evidence is conflicting

in this indication, and overactive bladder and benign prostatic hyperplasia.

Figure 18: Seventeen-Year-Old Patient with Mild Botulism(@ semanticscholar.org).

3.9.4 Thalidomide (Dose matters as does timing): Another example of this concept is thalidomide (100+ mg/kg) and its critical timing of exposure.

Originally developed as a treatment for insomnia and morning sickness in the 1950s, in1960 report of grossly deformed infants in Germany, of cases of phocomelia in pediatric clinics leads to the withdrawal recommended.

Thalidomide is an oral drug that has been shown to be highly active against Myeloma. Many consider thalidomide to be the first new agent with major antimyeloma activity in more than 30 years. Thalidomide has been FDA approved for the treatment of not only myeloma, but also Erythema nodosum leprosum (ENL, treat and prevent skin conditions caused by M. leprae). It also has had limited success in treating a variety of other diseases (Kaposi's sarcoma, primary brain malignancies, chronic graft versus host disease, Bechet's disease, aphthous ulcers, systemic lupus erythematosus (SLE), adult Langerhans cell histiocytosis, rheumatoid arthritis, and Jessner's lymphocytic infiltration of the skin). Thalidomide can inhibit the growth of HIV in test tubes (by selective tumour necrosis factor [TNF] alpha inhibition) and may alleviate symptoms of HIV (Gunzler, 1992, Emer, 2009).

3.9.5 Ricin: Source: castor bean (Ricinus communis). Less toxic orally, 500 ug: human lethal dose if exposure by injection or inhalation (pinhead-sized amount can kill an adult). Eight beans considered toxic for an adult. It causes inhibition of protein synthesis resulting in severe diarrhoea (die of shock). Potential Medicinal Use: Ricin may have therapeutic use in the treatment of cancer, as a so-called "magic bullet" to specifically target and destroy cancer cell. Ricin could be linked to a monoclonal antibody to target malignant cells recognised by the antibody. A promising approach is also to use the non-toxic B subunit as a vehicle for delivering antigens into cells thus greatly increasing their immunogenicity.
Use of ricin as an adjuvant has potential implications for developing mucosal vaccines.

3.9.6 Other: other apparently nontoxic chemical many can be toxic at high doses. Too much of a good thing can be bad (table 1). Also, highly toxic chemicals can be lifesaving when given in appropriate doses. Poisons are not harmful at a sufficiently low dose (Table 2).

Table 19: Showing approximate Lethal Doses of Common Chemicals (calculated for a 160 lb. human from data on rats).

Chemicals	Lethal Dose
Sugar (Sucrose)	3 quarts
Alcohol (ethylalchol	3 quarts
Salt (sodium chloride)	1 quart
Herbicides (2,4 –D)	One half cup
Arsenic (arsenic acids)	1 – 2 teaspoons
Nicotine	One half teaspoon

Table 20: Showing examples of Varying doses of the same substances as non-toxic or beneficial, toxic and lethal *(Adopted from T. Gossel and J. Bricker, Eds).*

Chemicals	Beneficial dose	Toxic Dose	Lethal Dose
Alcohol	0.05%	0.1% (ethanol blood level)	0.5%
Carbon monoxide	<10%	10 – 20% (% Hg. bound)	>60%
Secobarbital	0.1g/dL	0.7g/dL Blood levels)	>1g/dL
Aspirin	0.65g (2 tab)	9.75g (30 tab. acute oral dose)	34g (105 tablets)
Ibuprofen	400mg (2 tab.)	1,400mg (7 tab. acute oral dose)	12000mg (60 tab.)

3.9.6 What makes a Poison?

All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and a remedy. -Paracelsus (1493-1541)

The following factors determine what is poison or not
Dose matters (and so does timing); 2) people differ; and 3) things change (Mitchell,
2004).

Dose Matter: In poison interactions between chemicals and biological systems follow a dose-response relationship.

Toxicity is quantified through the dose-response relationship. Individual change in severity of effect with dose is also called a dose-effect relationship. Population change is the proportion of the population responding with dose (people differ). There are different relationships for different effects, and the shape of the dose response curve gives information about population variability and toxicity of the compound. A key concept in toxicology is the quantitative relationship between the concentration of a xenobiotic (foreign chemical) in the body and the magnitude of its biological effect. The magnitude of the effect is usually a function of the amount of xenobiotic a person is exposed to. In any given population, there will be a range of sensitivities to a xenobiotic. It is extremely useful to know what is the average sensitivity of a population to a xenobiotic and what the average dose required to elicit a toxic response will be. This brings us back to the central tenet of toxicology that the **dose makes the poison and that dose matters.**

People differ: Classic examples of the fact that people differ include allergies to food (e.g., peanuts and shellfish) and to drugs (e.g., penicillin). Severe allergenic reactions are relatively rare, with approximately 120,000 emergency room visits with less than 200 fatalities/year. Eight foods (peanuts, milk, wheat, eggs, shellfish, soybeans, crustaceans, some tree nuts) account for approximately 90% of food allergies (US); whereas, fourteen foods are listed as allergenic in Europe, which are regional and include Mollusca shellfish, lupine, celery root, mustard and sesame seeds and sulfites in addition to those outlined for the US. Even more striking are the differences in the effects of the same chemical on a single individual that may be observed during various stages of life (in utero, neonate, young adult, elderly). For instance, infants have an immature immune system and limited phase II systems (more sulfur conjugation), and reduced kidney function. The elderly may be similar in their sensitivities to the adverse effects of chemicals. There is a difference in sensitivity of new born rats and older rats to DDT. The LD50 of DDT in young male rats is greater than 4, 000 mg/kg; whereas in adult rats at 1-year of age, it is approximately 225 mg/kg.

Acetaminophen (Paracetamol) is metabolised 90% by sulfate or glucuronide conjugation (Phase II). The sulfate pathway predominates in children less than 12 years of age, while adults primarily use the glucuronide pathway. Chloramphenicol (chlornitromycin), an antibiotic for Gram-positive/-negative, [most anaerobic] organisms, is primarily metabolized by glucuronidation and is a poor substrate for sulfotransferases. Therefore, this antibiotic is extremely toxic to neonates (bone marrow) and is responsible for the “Gray baby syndrome” consisting of progressive cyanosis, metabolic acidosis, vasomotor collapse, respiratory difficulty, and death (McIntyre and Choonara, 2004).

Table 21: This is illustrated in the difference in sensitive of new-born rats and older rats to DDT.DDT LD50 in Male rats of various ages

Age	LD50 (mg/kg)
new-born	> 4000
10 days	728
2 weeks	437
1 month	355
2 months	250
4 months	194
1 year	225

Individual differences occur due to a number of factors including

i. Age (foetus, neonate, children, adults, elderly)
ii. Gender (male, female, pregnant female)
iii. Inherent drug metabolism
iv. Life style factors (smoking, alcohol use, previous exposures)
v. Health status including various diseases
vi. Pre-existing or simultaneous exposure to environmental agents, house-hold products, or therapeutic agents.
vii. Individual genetic makeup (polymorphisms)

Things Change: Perfumes were an important part of the court life in Ancient Egypt. Cleopatra's perfume factory was (still is) at the southern end of the Dead Sea. Cleopatra used to drink turpentine (terebinth from Pistacia terebinthus) to make her urine smell of violets. Presumably terpenes within the oil being metabolically converted to ionones, with the volatile organic compounds methanethiol, dimethyl sulfide, dimethyl disulfide, bis (methylthio) methane, dimethyl sulfoxide, and dimethyl sulfone are responsible for the smell. As a chemical pass through the body, it will encounter a number of enzymes that accelerate chemical reactions (intermediary metabolism) that are necessary for growth, maintenance of integrity and continuance of life. Distinctive microenvironments exist at the active sites of each enzyme to assist chemical inter-conversions. It is, therefore, not unexpected that a chemical undergoes chemical alteration(s) as it traverses a living system. What is eliminated from the biological system is not always the same as what entered the system originally. Sometimes the host (i.e., the organism that is exposed to the chemical) plays a critical role in the outcome of toxicity. The process by which this occurs is called biotransformation/metabolism and involves chemical reactions within the organism in which one chemical is changed to another. Chemicals can enter the body and be absorbed by the body by a variety of means such as ingestion, inhalation, and dermal absorption. They are distributed through many bodily compartments and finally

excreted. What happens in between entry and exit, though, plays a key role in toxicity.

Biotransformation usually decreases the ability, and in turn, the likelihood, of a molecule interacting with a biological system. The probability of potential damage is offset or lowered. Usually, but not always, the process makes the molecule more polar (frequently acidic) and thus more water-soluble. As such, the system can more easily remove the molecule via the kidneys (urine) or liver (bile). An example is the enzyme epoxide hydrolase converting ethylene oxide, a chemical with genotoxic and other chronic toxic properties, into the somewhat less toxic ethylene glycol. On occasions, the chemical may be activated and converted into a more dangerous species whereby the body inadvertently poisons itself. For example, chloroform can be converted to phosgene. Phosgene ($COCl_2$), a poisonous gas used as a chemical weapon in World War I, is a highly toxic gas or liquid that is classified as a pulmonary irritant. Exposure to phosgene gas produces delayed-onset noncardiogenic pulmonary oedema. Exposures to 50 ppm may be rapidly fatal [http://emergency.cdc.gov/agent/phosgene/basics/facts.asp].

3.10 Adverse Drug Reaction

In the US, 3 to 7% of all hospitalisations are due to adverse drug reactions. ADRs occur during 10 to 20% of hospitalisations; about 10 to 20% of these ADRs are severe, making ADR 4th to 6th leading cause of death among hospitalised patients. These statistics do not include the number of ADRs that occur in ambulatory and nursing home patients. Although the exact number of ADRs is not certain, ADRs represent a significant public health problem that is, for the most part, 30% to 60% are preventable

A study by the Agency for Healthcare Research and Quality (AHRQ) in 2011, revealed that sedatives and hypnotics were a leading source for adverse drug events seen in the hospital setting. Approximately 2.8% of all ADEs present on admission and 4.4% of ADEs that originated during a hospital stay were caused by a sedative or hypnotic drug. A second study by AHRQ found that in 2011, the most common specifically identified causes of adverse drug events that originated during hospital stays in the U.S. were steroids, antibiotics, opiates/narcotics, and anticoagulants. Patients treated in urban teaching hospitals had higher rates of ADEs involving antibiotics and opiates/narcotics compared to those treated in urban nonteaching hospitals. Those treated in private, non-profit hospitals had higher rates of most ADE causes compared to patients treated in public or private, for-profit hospitals.

In the U.S., females had a higher rate of ADEs involving opiates and narcotics than males in 2011, while male patients had a higher rate of anticoagulant ADEs. Nearly 8 in 1,000 adults aged 65 years or older experienced one of the four most common ADEs (steroids, antibiotics, opiates/narcotics, and anticoagulants) during hospitalisation. A study showed that 48% of patients had an adverse drug reaction to at least one drug, and pharmacist involvement helps to pick up adverse drug reactions.

3.10.1 Adverse Drug Reactionclassification

Adverse drug reactions (ADRs) are global public health problems. In its severe form it may cause hospital admission, morbidity and mortality. Early identification and reporting of suspected ADRs to regulatory authorities such as National Pharmacovigilance centre (NPC) in National Agency for Food Drug and Administration (NAFDAC) Nigeria, is known to be one of the appropriate measures in insure health and safety of public form such as adverse drug reaction of drugs.
There are many classifications of ADR, with most ending at Type A and Type B. But for academic and clinical application, we present a broader classification which would be easier for the public health officer to recognise and identify as follows

Classification according to Onset of event:

i. Acute: - within 60 minutes
ii. Sub-acute: -1 to 24 hours
iii. Latent: - 2 days

CLASSIFICATION – SEVERITY
Severity of reaction: There is no universal scale for describing or measuring the severity of an adverse drug reaction. Assessment is largely subjective. Reactions can be described as

iv. Mild:
v. Moderate:
vi. Severe: disabling or life-threatening,
vii. Lethal (deadly)

i. Mild adverse drug reactions: Mild reactions usually described as bothersome but requires no change in therapy or prolonged hospitalisation. It is of minor significance include:

Opiates causing digestive disturbances (such as nausea, constipation, diarrhea) Headaches, Fatigue, Vague muscle aches, Malaise (a general feeling of illness or discomfort) Antihistamines and changes in sleep patterns. However, such reactions can be very

distressing to people who experience them. As a result, people may be less willing to take their drug as instructed, and the goals of treatment may not be achieved.

ii. Moderate adverse drug reactions:
may require change in therapy (treatment) e.g., modified dosage, addition of a drug, but not necessarily discontinuation of the drug. May required; hospitalisation may be prolonged, or specific treatment may be required.

Examples include, Rashes (especially if they are extensive and persistent), Visual disturbances (especially in people who wear corrective lenses), NSAIDs causing hypertension and oedema. Difficulty with urination (a common effect of many drugs in older men).

Any perceptible change in mood or mental function.
Hormonal contraceptives and venous thrombosis.
Also, reactions that are usually described as mild are considered moderate if the person experiencing them considers them distinctly annoying, distressing, or intolerable.

iii. Severe adverse drug reactions: An ADR is potentially life threatening and requires discontinuation of the drug and specific treatment of the ADRinclude those that may be life threatening such as ACE inhibitors and Angioedema, Phenothiazines and abnormal heart rhythm. Certain types of allergic reactions, that result in persistent or significant disability or hospitalisation, and that cause a birth defect. Severe reactions are relatively rare. People who develop a severe reaction usually must stop using the drug and must be treated. However, doctors must sometimes continue giving high-risk drugs (for example, chemotherapy to people with cancer or immunosuppressant to people undergoing organ transplantation). Doctors use every possible means to control a severe adverse drug reaction.

iv. Lethal adverse drug reactions: Lethal reactions are those in which a drug reaction directly or indirectly caused death. These reactions are typically severe reactions that were not detected in time or did not respond to treatment. Lethal reactions can be the reasons that some drugs are withdrawn from the market such asAcetaminophen over dosage and Liver failure or Anticoagulants and Haemorrhage

Seriousness: The U.S Food and Drug Administration defines a serious adverse event as one when the patient outcome is one of the

following: Death, Life-threatening, Hospitalisation (initial or prolonged), Disability - significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life, Congenital abnormality or Requires intervention to prevent permanent impairment or damage.

Severity is a point on an arbitrary scale of intensity of the adverse event in question. The terms "severe" and "serious" when applied to adverse events are technically very different. They are easily confused but cannot be used interchangeably, requiring care in usage.

A headache is severe, if it causes intense pain. There are scales like "visual analog scale" that help clinicians assess the severity. On the other hand, a headache is not usually serious (but may be in case of subarachnoid haemorrhage, subdural bleed, even a migraine may temporally fit criteria), unless it also satisfies the criteria for seriousness listed above.

3.10.2 Types of Adverse Drug Reactions

Adverse drug reaction is mainly classified into two major types;

i. Type -A [Augmented] and
ii. Type B [Bizarre] effects.
iii. Other classifications also include
iv. Type C (‘C’ for continuous or chronic),
v. Type D (‘D’ for delayed)
vi. Type E (‘E’ for end of use), and
vii. Type F (‘F’ for failure) effects.
viii. Types of adverse drug reactions

Type –A [Augmented]adverse drug reaction:

Refers to predictable dose-dependent responses which are exaggerated pharmacological actions at usual therapeutic doses. This could occur in everyone if enough of the drug is given because they are due to excess of normal, predictable dose-related.

Clinical features: Common, there are in many instances avoidable, extension of pharmacologic effect, often predictable and dose dependent, can be experimentally reproduced, responsible for at least two-thirds of ADRs, constitute approximately 80% of adverse drug reactions, associated with high morbidity and low mortality. Usually known before licensing.

Example

i. Acute Liver failure resulting from acetaminophen overdose
ii. Bupropion: Bupropion is useful for depressed people who also have attention-deficit/hyperactivity disorder or cocaine use disorder and those trying to stop smoking. But overdose can cause Headache, agitation, discontinuation syndrome*, high blood pressure in a few people, and rarely seizures
iii. Lisinopril & postural hypotension,
iv. Insulin & hypoglycemia
v. propranolol and heart block,
vi. anticholinergic and dry mouth
vii. bleeding when using the anticoagulant warfarin

Type B [Bizarre] refers to unpredictable, non-dose dependent, novel responses to a drug occurs only in some people Most times there are unavoidable.

Characteristics: idiosyncratic or immunologic reactions or Drugallergy/hypersensitivity reactions, rare and often unpredictable. Little or no dose relationship occur in predisposed, intolerant patients may explain by rare genetic polymorphism.

Examples;

i. chloramphenicol and aplastic anemia
ii. Fixed drug reaction of sulphonamides.
iii. Anaphylactic reactions with Drugs (e.g. as penicillin), insect stings and animal venoms, Certain foods (particularly eggs, seafood, and nuts) and Latex etc.
iv. Malignant hyperthermia with anaesthesia
v. Idiosyncrasy: Idiosyncrasy due to enzyme abnormality Hemolysis with primaquine if glucose 6-phosphate dehydrogenase (G6PD) enzyme deficiency in any person. If primaquine given - Hemolysis leading to hemolytic anemia due to receptor abnormality e.g. Malignant hyperthermia with general anesthetics (Halothane).
vi. Sudden huge rise in IC calcium concentration, Increase in muscle contraction.
vii. Increase in metabolic activities.
viii. Rise of body temperature

Drug allergy: Drug allergy also known as hypersensitive reaction due to Antigen antibody interactions. 1st dose acts as an antigen, in which antibody is produced against the antigen in the body. With subsequent

dose causes antigen-antibody reaction e.g. Penicillin induced anaphylaxis (Type 1 hypersensitivity reaction)

Types of allergic reactions

i. Type I - immediate, anaphylactic (IgE) e.g., anaphylaxis with penicillins
ii. Type II - cytotoxic antibody (IgG, IgM) e.g., methyldopa and hemolytic anemia
iii. Type III - serum sickness (IgG, IgM) antigen-antibody complex e.g., procainamide-induced lupus
iv. Type IV - delayed hypersensitivity (T cell) e.g., contact dermatitis

Other types of adverse drug reactions

Type C is associated with the long-term use of a drug and is related to cumulative use ('C' for continuous or chronic). It is chronic and of delayed onset. It tends to be both serious and (relatively) common and have profound effect on public health

Characteristics: associated with long-term therapy, involves dose accumulation, often no suggestive time relationship, and connection often difficult to prove, use of drug increases frequency of "spontaneous reporting" and can be Predicted from the chemical structure of drug/metabolite

Examples

i. NSAIDS-induced renal failure (Phenacetin and interstitial nephritis)
ii. Paracetamol – Liver Toxicity
iii. Oral contraceptive induced diabetic microangiopathy
iv. Breast tumors or antimalarial and ocular toxicity.
v. Hypopituitarism- adrenal axis suppression with corticosteroids
vi. Osteoporosis of the jaw with bisphosphonate

Type D refers to a delayed type of reaction ('D' for delayed). May present years after drug was administered. Can be accumulative

Characteristics: Uncommon, usually dose-related and occur sometime after drug use and delayed effects (dose independent).

Example

i. Carcinogenicity (e.g., immunosuppressants)
ii. Teratogenicity (e.g., fetal hydantoin syndrome)

iii. Vaginal cancer in daughters whom mother was treated by diethylstilbestrol or Phenytoin during Pregnancy and Teratogenic effects
iv. bladder cancers following long term cyclophosphamide,
v. gene toxicity of some drugs,
vi. Leucopenia – Limoustine
vii. Carcinoma of the renal pelvis following phenacetin etc.

Type E refers to withdrawal or end of use adverse drug reactions ('E' for end of use).

Characteristics: Uncommon and related to discontinuation that is too abrupt.

Examples

viii. Addisonian crisis (adrenal insufficiency) following steroid withdrawal
ix. opiate withdrawal syndrome
x. rebound convulsions on withdrawal of carbamazepine in non-epileptic patients or Phenytoin - Seizures
xi. myocardial infarction following beta blocker withdrawal

Type F refers to unexpected failure of therapy ('F' for failure).
Characteristics: Often common, -often dose-related, - caused by drug interactions

Examples

i. inadequate dose of oral contraceptive
ii. Concomitant administration with enzyme –inducing drugs.

Table 22: Comparison between Type A and Type B adverse drug reactions

Parameters	**Type A (Augmented response)**	**Type B (Bizarre response)**
Pharmacologically Predictable	Yes	No
Dose dependent	Yes	No
Host factors	Genetic factors may be important	Dependent on host factor
Animal Model	Usually producible in animals	Unknown in animal models
Incidence and morbidity	Common	Uncommon

Mortality	Low	High
Detection	Early in clinical Development	Post – Licensing
Treatment	Adjust (Reduce dose)	Stop (Discontinue Therapy)

3.10.3 Causes of Adverse Drug Reactions

In clinical practice, patients with *Type A reaction* which are usually dose-related and predictable can often be managed by adjusting the dose, substituting a similar but more selective drug or giving additional drugs to antagonise the unwanted effects of the primary agent. In *Type B reactions*, it is usually necessary to withdraw therapy.

Table 23: Causes(a) and Body Systems Commonly Involved in ADR (b)

a) Common Causes of ADRs	**b) Body Systems Commonly Involved**
Antibiotics	Haematologic
Antineoplastic	CNS
Anticoagulants	Dermatologic/Allergic
Cardiovascular drugs	Metabolic
Hypoglycaemic	Gastrointestinal
Antihypertensive	Renal/Genitourinary
NSAID/Analgesics	Respiratory
Diagnostic agents	Sensory
CNS drugs	
ART	
Account for 69% of fatal ADRs	

Body Systems Commonly Involved There are varied complex mechanism involve in adverse drug reactions. From the patient population characteristics like age, sex, population size, genetic constitutions, and tendency to allergy, disease, personality or habit, to Predisposing factors – renal function, liver function, pharmacokinetic and Pharmacodynamics factors etc.

3.10.4 Impact of genetics

Genetic constitution of an individual plays a vital role in ADRs, as every individual responds differently to drugs as a result of their genetic constitutions. This genetic variation can exist as a result of single mutant gene (as in polymorphism or discontinuous variation), or polygenic influences e.g. Drug-induced haemolytic anaemia as a result of G6PD deficiency with drugs like 8-aminoquinolines, antimicrobials and some analgesics.

3.10.5 Factors responsible for Adverse drug reactions (ADR)

i. Age (children and elderly)
ii. Multiple medications
iii. Multiple co-morbid conditions
iv. Inappropriate medication prescribing, use, or monitoring
v. End-organ dysfunction
vi. Altered physiology
vii. Prior history of ADRs
viii. Extent (dose) and duration of exposure
ix. Genetic predisposition

3.10.6 Factors Masking Adverse Drug Reactions

ADR are most times unrecognised due to a number of factors:

i. They may mimic natural disease e.g. phenothiasine - induced hepatitis.
ii. They may appear as an odd or bizarre reaction from an innocent drug like pseudo lymphoma from Phenytoin.
iii. The appearance of the reaction may be delayed like in mucocutaneous syndrome due to practolol, adenocarcinoma of the vagina in children whose mothers received high dose oestrogen during pregnancy or valvular heart disease following fenfluramine administration.
iv. ADR may cause the relapse of a natural disease or evoke a disorder in a naturally susceptible subject e.g. diabetes by thiazides and glaucoma by atropine and
v. It may be masked by the nature and complex clinical situation as in antiarrhythmic drugs with a pro-arrhythmic effect
vi. Environmental factors causing ADRs includes simple pollution e.g. with Halothane in the air of operating theatre, causing abortion in female staff; Penicillin in air of hospital or milk cause drug (hypersensitivity) allergy.

SELF- ASSESSED EXERCISES

i. What are the five contexts of drug toxicity?
ii. Explain the types of drug related hypersensitivity reactions.
iii. Enumerate the causes of drug reactions

4.0 CONCLUSION

In this unit, you have been exposed to the various common define and terminology used toxicology, and adverse drugs reaction. You have learnt describe the purpose of toxicology, subdivision and classifications of toxic

agents including poisons that can heal. Distinguish adverse drug reactions (ADRs) from adverse drug events, classify an ADR when it presents, types of populations most at risk of, ADRs and various factors that can mimic diseases and mask ADR.

5.0 SUMMARY

Toxicology is a field of science that helps us understand the harmful effects that chemicals, substances, or situations, can have on people, animals, and the environment. Some refer to toxicology as the "Science of Safety" because as a field it has evolved from a science focused on studying poisons and adverse effects of chemical exposures, to a science devoted to studying safety.

Most exposure of humans to chemicals is via naturally occurring compounds consumed from food plants.

Toxicology has various sub discipline that made it easy to study and classify. This includes; Environmental Toxicology-Studies chemicals that are contaminants of food, water, soil, or the air. Occupational (Industrial) Toxicology: studies of protection of workers from toxic substances and makes their work environment safe. Regulatory Toxicology: Gathers and evaluates existing toxicological information to establish concentration-based standards of "safe" exposure. Food Toxicology: Involves delivering a safe and edible supply of food to the consumer. Clinical Toxicology: Is a study that is concerned with diseases and illnesses associated with short term or long-term exposure to toxic chemicals. Forensic Toxicology: Helps to establish cause and effect relationships between exposure to a drug or chemical and the toxic or lethal effects that result. Etc.

Toxic agents are classified as Heavy Metals, Solvents and Vapours, Radiation and Radioactive Materials, Dioxin/Furans, Pesticides, Plant Toxins and Animal Toxins

Not all poisons are deleterious, some poisons that can heal, depending on dose (Dose matters (and so does timing)); individual (People differ) differences; and change in times (things change).
WHO definesas an adverse drug reaction as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function? This differentiated from a***n adverse drug event which*** *is* "any untoward medical occurrence that may present during treatment with a pharmaceutical product but *which does not necessarily* have a *causal relationship* with this treatment" *or side effects which is a*n unintended effect of a drug occurring at the normal dose related to the *pharmacological properties of the drug*.ADR

definition excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors.

6.0 TUTOR- MARKED ASSIGNMENT

1. Define toxicology and commonly associated terms
2. Differentiate the sub-disciplines of toxicology
3. Describe the classifications of toxic agents
4. a) What is WHO definition of adverse (ADR) drug reaction, classify ADR according to the onset of events and types of ADR. Giving definitions, clinical characteristics, and at least two drugs and ADR caused under each types of ADR.
   b) Outline five examples each of the following
   i. commonest drug causes of ADR
   ii. commonest system(organ) involved/ susceptible to ADR
   iii. Risk factors of ADR

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UNIT 3 DISCOVERY/DRUG DEVELOPMENTAND PHYTOMEDICINE

CONTENTS

1.0 INTRODUCTION

The pharmaceutical industry is skilled at discovering new chemical entities – millions of novel substances have been produced in the last 50 years. Few of these have the appropriate characteristics to become drugs for use in humans (preclinical studies in animals may reveal an inappropriate pharmacokinetic profile, lack of the desired pharmacological effect, or toxicity), and the industry therefore discards almost all of its discoveries. Compounds that survive preclinical screening may enter the drug development process provided an adequate clinical need exists and the company is confident that it will recoup the costs of development. These costs vary according to the clinical area and the size of the programme, but sums in excess of €250,000,000 are not uncommon. Even for drugs that reach development, success is not guarantee; only 10% of compounds survive clinical assessment, and though the desire of every company is to achieve the success of agents like salbutamol, atenolol and ranitidine, only a few survivors find a significant role in therapeutics.

2. 0 OBJECTIVES

By the end of this unit, you will be able to:

- define terms in drug development and phytomedicine
- recognise the significance of drug development
- identify the pharmacokinetics and pharmacodynamics profiling in drug development
- state the safety and toxicity testing in drug development
- describe the phases involved in clinical trials
- explain the integration of phytomedicine preparation into conventional or official medicine
- identify and describe the standardisation and quality evaluation of herbal drugs
- tell the routes of administration of herbal drugs
- recognise Herb-drug interactions
- explain adulteration and contamination of herbal drugs.

3.0 MAIN CONTENT

3.1 Definition of Terms

i. **Phytomedicine:** Phytomedicine is modern and science based herbal medicine. Phytomedicine, also called Botanical/Plant Medicine. The word ‘phyto’ derives from the Greek work plant; hence it means plant-based medicine. Phytomedicine is rooted in scientific research and therefore not to be confused with homeopathy. The methods used to evaluate plant-based medicines

are similar to those used by orthodox medicine. Yet, an herb contains many active chemicals, unlike conventional drugs, which focuses on specific chemicals. Hence botanical or herbal medicines may combine several actions to support the body's health.

ii. **Phytotherapy (Henri Leclerc):** The branch of herbal medicine that describes the potentials and limitations of herbal drugs in the treatment of human diseases. It should be practiced by physicians trained in herbalism

iii. **Phytotherapists:** qualified Phytotherapists use herbs to treat the diseases the methods used to evaluate plant-based medicines are similar to those used by orthodox medicine, they are safe for many conditions. Phytotherapists conduct individual consultation and then dispense a medicine. It does not use any other therapies like acupuncture; panchkarma etc. pharmacognosy is at the heart of Phytomedicine.

iv. **Phytopharmacy** Preparation of natural drugs. Either in natural forms (teas) or in pharmaceutical preparation.

v. P**hytochemistry**: The study of the chemical constituents in the plants.

vi. **Phytopharmacology**: Natural drugs which have multiple effects must be tested in humans.

3.2 Development

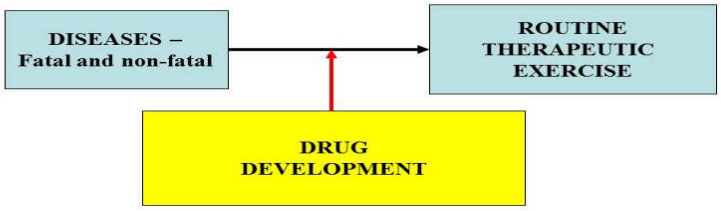
3.2.1 Why are drugs developed?

Drugs are developed so that we can turn fatal or non-fatal diseases into a routine therapeutic exercise (Figure1) or instance, before the development of anti-hypertensive drugs, hypertension was a fatal disease with people dying in a year or two of developing high blood pressure. Now, millions of people with hypertension are successfully managed long term with anti-hypertensive drugs. Drug development is divided into **preclinical** and **clinical** drug development.

The process of drug development includes the activities that take the prospective new drug into the market-place where it becomes available for use by doctors and patients. Development of a new drug is therefore a vast project that lasts many years and involves clinical investigators in specialist department or in departments of clinical pharmacology, as well as experts from different disciplines in the pharmaceutical company.This collaboration is vital for successful drug development, but it is important to recognise that each party has its own agenda and properties. It is not

realistic to develop a drug exclusively in one country; international expertise must be coordinated, taking account of differences in clinical practice and approach around the world. Drug discovery usually exploits advances in knowledge that are available within the research community and it is therefore not surprising to find several companies pursuing similar lines of research. It is often the activities of drug developers that determine which company I first to the Market-place. Companies constantly examine their processes for greater efficiencies, to contain costs and to minimise the duration of drug development. Phase 3 clinical studies (see below) are important determinants of the overall timing because they are perfumed on the critical path, and participating clinicians are likely to feel pressure from the company to complete the trial on schedule. Development times vary between areas of therapeutics, but generally companies expect to develop drugs in 6-7 years (compared with about 12 years two decades ago).

3.2.2 Preclinical Drug Discovery



Preclinical drug discovery is the process before clinical testing of drugs. The first step in preclinical drug development is the discovery or synthesis of a new drug. At least, 10,000 new molecules are discovered/synthesised for each successful new drug introduced. Extensive preclinical safety and efficacy testing of new drugs are required in animals, and this takes an average of 1.5-3 years. There are three mains ways in which new drugs are derived; chemical modification, rational drug design, and random screening.

3.2.3 Serendipity: Serendipity (accidental discovery of something fortunate) may also have a role in drug development.

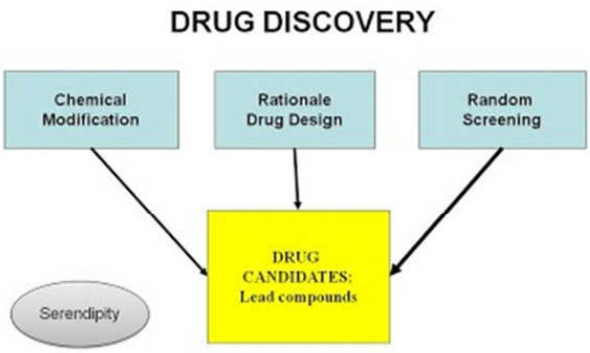


Figure 20: Three methods of drug discovery (Copyright QUT, Sheila Doggrell)

An important group of drugs that were made by chemical modification were the diuretics. However, the initial step was serendipity; an observant physician noticed that sulfanilamide (antibiotic) caused a sodium bicarbonate diuresis the loss of sodium, bicarbonate and water from the kidney. Thus, it was reasoned that a sulphanilamide-like drug could be made that promoted water loss fromthe body. After a string of chemical modification, chlorothiazide was synthesised.

Chlorothiazide increases sodium chloride and water excretion. Further modification of the structure of chlorothiazide led to the discovery of frusemide, which is a very potent diuretic. The thiazide diuretics, such as chlorothiazide, and frusemide are commonly used in the treatment of hypertension and heart failure to promote water loss. The second method for drug discovery is rational drug design, and we will consider a new example of this (zanamivir – Relenza).

Rational drug design usually includes computer design, which is known as in silico. A computer model is made of the site that you want the drug to bind to, and then of the drug with best fit for binding. Then the chemical is synthesised, and then tested pharmacologically to determine, whether the chemicals do as predict.

A drug that was developed in this way is zamanivir (Relenza). Zamanivir can prevent or shorten the flu, which is a virus. Neuramidinase is an enzyme involved in viral replication, and the structure of this enzyme has been determined. The structure shows a pocket, where we may be able to get a drug in to inhibit the enzyme. Zamanivir binds in the pocket to inhibit the activity of Neuramidinase, and consequently, the replication of the flu

virus. A third approach to drug discovery is random screening. This uses high throughput screening managed by robotics. There is random screening for biological activity. The screening can be of banks of previously discovered chemical entities, a large number of natural products, and libraries of peptides and nucleic acids. Random screening led to the discovery of the immunosuppressant cyclosporine.

3.2.4 Pharmacological Profiling

Once a lead compound has been discovered (e.g. a drug with activity at a certain binding site), the compound undergoes pharmacological profiling. A large number of experiments are undertaken, mainly using animals, to determine the pharmacokinetics and pharmacodynamics of the drug. Questions asked include; does the drug do what we expect? Does it do anything else? Is it active after oral administration? The initial profiling usually depends on the pharmacological goal e.g. anti-infective will be tested against infectious organisms. Anti-diabetic drugs will be tested for their ability to lower blood glucose in animal models of diabetes.

3.2.4 Safety and Toxicity

New drugs undergo extensive safety and toxicity testing in animals. This testing was increased after the thalidomide disaster. Thalidomide was developed as a hypnotic (calming) and anti-emetic drug in the 1950s. It was used as a hypnotic and extensively to prevent morning sickness. For severe morning sickness, it was more beneficial than any other drugs available at the time. Limited toxicity testing in rats had suggested it was safe in pregnancy. To women who took thalidomide during pregnancy, 10,000 children were born with phocomelia, which is the absence of arms or legs with hands or feet attached to body trunk. Obviously, when it was shown that thalidomide was the causative agent, it was withdrawn and litigation followed, costing the pharmaceutical company responsible to pay millions in compensation.

What was learnt from the thalidomide disaster? The animal rights movement claimed that the thalidomide disaster showed that the testing of drugs in animals was not predictive of toxicity in humans, and should be abandoned. Toxicity testing should be in humans. There is another interpretation, birth defects are rare in rats. Rats are more likely to reabsorb defective foeti. Closer analysis of toxicity testing of thalidomide showed lower litter numbers, which probably indicated the potential to cause birth defects in humans. More extensive toxicity in animals probably would have prevented the thalidomide tragedy. More extensive toxicity in animals is now undertaken. This preclinical safety and toxicity testing take 2 -5 years, and involves the collection and analysis of lots of data. This testing is closely supervised by an independent Animal Ethics

Committee that works to minimise the number of animals used, and the harm done to animals. Acute toxicity of single doses and chronic toxicity of repeated doses of drugs are often tested on mice. The effects of drugs on reproductive function and teratogenicity (ability to cause birth defects) are tested in a variety of animal species. For drugs that are going to be used long term in chronic illness, the carcinogenic potential has to be tested in animals long-term. Mutagenic potential is undertaken in bacteria

3.3 Clinical Drug Development

3.3. 1 Phases of development

It is convenient to describe clinical drug development in terms of phase. The boundaries between the phases are not rigid, and in some developments phases 2 and 3 are merged. Overlap between phases may occur; for example, pharmacokinetic assessments in patients with hepatic or renal impairment are usually undertaken later in the programme alongside phase 2 or 3. Whether healthy volunteers or patient volunteers are used in phase 1 studies depends on the therapeutic class of the agent. The duration of phase 1 is about 1 year; the duration of phases 2 and 3 together is about 4 years. Submission to regulatory is based on the clinical data obtained from the studies in phases 1, 2 and 3.

3.3.2 Aims and Objectives of clinical drug developments

The aims of clinical development are to determine the following

i. How the recipient handles the potential drug – absorption, distribution, metabolism and excretion (commonly abbreviated to ADME); this may include special populations such as the elderly or those with liver or kidney impairment
ii. How the new agent affects physiological systems relevant to its efficacy or safety – for example, dose-response relationships and the duration of action of a β-adrenoceptor antagonist can be investigated using the agent's effect on heart rate during exercise.
iii. Whether the new agent has efficacy against the target disease and how efficacy relates to the dosing regiment
iv. How the agent is tolerated at different dose and in different groups of patients – every patient must be monitored closely for adverse events and routine screening is conducted to assess whether the new agent adversely affects liver or kidney function or blood constituents
v. The potential for interactions with other drugs

At some stage in the drug development procedure, a drug patent has to be applied for, to protect your discovery from other

companies. Patents are valid for 15-17 years. During the patent, all monies made by that drug are returned to the pharmaceutical company that invested in the development. However as preclinical testing takes on average 1.5 to 5 years, and clinical trialling take 5 to 7 years on average, there may not be much time for the developing company to recoup their investment. After a patent expires, the generic drug can be made by other companies, commonly known as generic companies. The generic companies make drugs but they do not pay towards the development of the drug. After the patent expires, the pharmaceutical company that discovered the drug, no longer receives all the money from that drug.

After successful preclinical testing, a few new drugs enter the next stage, which is clinical trialling. Clinical trials are experiments in humans to evaluate drugs, medical devices, biologics etc. Thus, clinical trials are to evaluate interventions in general. The results of clinical trials are presented to the authorities for assessment. This assessment is carried out by the Federal Drug Administration (FDA) in US, or the National Agency for Food and Drug Administration and Control (NAFDAC) Nigeria or by any countries drug regulatory agency. If the FDA or NAFDAC accept that the drug does better than harm, it is registered for clinical use. The clinical development of drugs does not stop at registration, as there is ongoing preclinical and clinical assessment. It is presently considered that it costs A$1.2 billion for a single, successful new drug.

Only about 10% of compounds that enter clinical trial are approved/registered for sale. Clinical trials are under stringent law enforced guidelines. These guidelines include ethics, which is assessed by human ethics committee, and patient consent. For patient consent, they must be fully informed in lay language of exactly what is happening in the trial. Clinical trials of drugs are often funded by pharmaceutical company with independent investigators. Without this funding, there would be little development of new drugs. There is some government funding available for clinical trials of complementary and alternative medicines in the US, which allow these medicines to be properly evaluated. Clinical trials are not quick, as they take 7-9 years.

3.4 Ethics in Clinical Trials

The atrocities of the Nazis on concentration camp inmates, such as cutting people and seeing how long they bled for, were investigated after World War II in Nuremberg Tribunal. The tribunal developed the Nuremberg Code, which started the modern era of ethics. There are 4 main principles of modern ethics (Figure 1).

i. **Non-maleficence:** non-maleficence, means to do no harm.

ii. **Beneficence:** The second aspect, is the reverse of this, it is beneficence, which is to do good. Combining non-maleficence and beneficence means that clinical trials have to maximise benefits and minimise harm to the patient.

iii. **Justice:** The third aspect of ethics in clinical trials is justice, which means that the benefits of research should be distributed fairly, not just to the rich and powerful.

iv. **Respect for person:** Respect for person has three parts, Firstly, individuals be regarded as **autonomous agents**, and their opinions and choices respected, regardless of how daft or illogical they are. The second part is **veracity**, the truth must be told to participants. Participants have to be able to understand the clinical trial, and the benefits and risks, and these are provided in a Plain Language Statement, prior to consent being asked for. Finally, **confidentiality**, the participants name, details etc. are to be kept confidential.

Ethics are policed by IRBs, Institutional Research Boards, which are also known as Ethics committee. This process involves peer review of proposed research. Peer review is independent review of the proposed clinical trial to determine whether the trial is appropriate. Universities often have ethics committees both for peer reviewing animal experiments and human experiments. For instance, QUT has a Human Research Ethics committee, an Animal Ethics committee and a Biosafety committee.

3.5 Clinical Trial Design

There are a number of factors that make a good clinical trial design. There should be similarity of the control group, who do not receive the drug, with the group receiving the intervention (drug). Otherwise any difference between the control and intervention group, may be due to other differences between the groups, other than due to the drug intervention. One way of achieving similarity between groups is the random assignment of patients to control and intervention group. In initial clinical trials, the control group was untreated whereas the treated group were given the drug. This is almost guaranteed to show a beneficial effect with the drug, as people like to believe the drug is going to do them good. To avoid this,

the control group are given an inert replica of the drug, which is known as the **placebo**. Placebos are very good for you! The placebo response (which means "I shall please") is 40% of relief of pain in labour, and up to 60% in relieving depression. This is the key reason for not accepting anecdotal evidence, and requiring placebo-controlled clinical trials.

Another danger in clinical trials is observer bias. The observer of the patients will want the patient to get better and will be looking for signs of benefit with the drug, which may or may not be present. To avoid this problem, blinding is used. There are two types of blinding. In single blinded clinical trials, only the study participants are blinded, not the investigator, and this happens when it is considered important that the investigator knows which participant has the active drug. In double-blinded clinical trials, neither the participants nor the investigator knows who is taking the active drug. The best design for a clinical trial is the randomised, double-blind, placebo-controlled trial. Such a trial has the highest likelihood of revealing the truth about the effects of a drug. The randomised, double-blind, placebo-controlled trial has a very simple design (Figure 22).

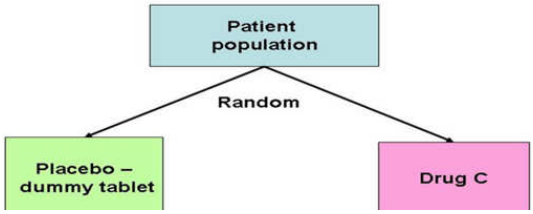


Figure 21: Randomized, double-blind, placebo-controlled trial (Copyright QUT, Sheila Doggrell)

In a randomized, double-blind, placebo-controlled trial, the selected patient population is randomised to either the placebo (dummy tablet) or the drug, and the health of the participants is monitored.

3.5.1 Phases of Clinical Trials

In drug development, it mandated that new drugs have to go through 4 Phases with each phase having different requirements. Each drug has to successful pass Phase I before moving onto Phase II, and so on (Figure…). Clinical trialing usually starts with small numbers of participants and is mainly to test safety, and is often in health volunteers (Figure 4.5). Only when some safety has been established, does testing

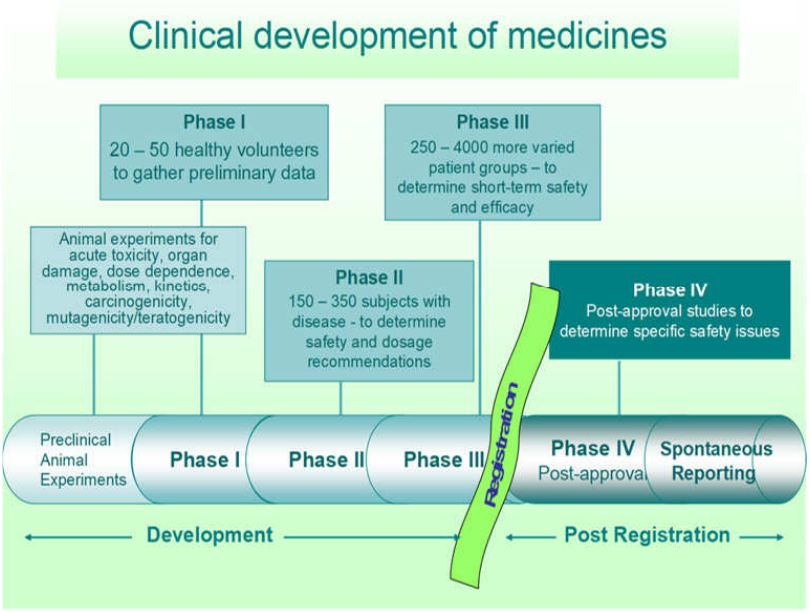


Figure 22: The Phases of clinical trials (Copyright QUT, Sheila Doggrell)

Phase I clinical trials are often performed in University Hospitals using experts in clinical pharmacology. They are open with both subject and observer knowing what is happening. Phase I clinical trials use small numbers (20-80) of healthy volunteers. The exception to this is when testing toxic drugs for cancer and HIV. As these would be toxic to healthy volunteers, the Phase I testing of cancer and HIV drugs is in patients. The dose tested in Phase I will be a small fraction of that shown to cause toxicity in animals. The main reason for the trial is to establish safety, and the trial will measure toxicity and, possibly, efficacy. In Phase I, provided an assay is available to measure the drug, blood samples may be taken to measure the pharmacokinetics of the drug. If a drug shows unacceptable toxicity, the clinical trial will stop after Phase I.

Phase II clinical trials are also often performed in University Hospitals using experts. They are single-blinded i.e. they use placebo/dummy tablets to prevent the subject knowing which is active drug, but the physician does know which is the active drug. Phase II trials may have a comparison with standard treatment. If there is a standard drug available for a certain condition, it has to be established that the new drug is better than the standard drug before it can be registered. Phase II trials are in 10-200 patients with the disease the drug is indicated for. The Phase II trial

is to establish the efficacy and toxicity of the drugs. This information is needed for more extensive Phase III trialing. If a drug does not show efficacy in Phase II trial, it will not go forward to Phase III.

Phase III clinical trials are usually performed in the setting the drug will eventually be used in. Thus, if a drug is to be used in hospital, it will be tested in hospital, whereas if a drug is used in general practice, it will be tested in general practice. The investigators are usually specialists in the disease being treated. Phase III trials are double-blinded; neither the observer nor the subject knows which is active drug. A third person holds the code identifying the drug, which is not broken until the trial is completed. Phase III trials enrol large numbers of patients, and are expensive. Phase III clinical trials establish efficacy and toxicity.

Positive results in Phase III lead to applications for registration to market the drug to the Therapeutics Goods Administration (TGA).

Phase IV clinical trial is also known as post-marketing surveillance. Even though Phase III trials enrol large numbers of patients, this may not be large enough to detect any rare or long-term adverse effects, and this is done in Phase IV. Phase IV is under the actual conditions the drug will be used. It is monitoring safety in large numbers of patients and over longer periods of time than previous Phase. Phase IV clinical trials, especially the monitoring of adverse effects, involves, all health professionals, not just investigators.

3.5.2 Laminations of Clinical drug development

A typical clinical drug development may provide information on 5000 patients. This appears to be an impressive body of information, but some of these patients will have been exposed to the comparator treatments rather that to the agent under trial. Furthermore, many patients given the new agent may have been given non-therapeutic doses or may have been treated for short periods only. Programmes involving drugs that will be given chronically usually include at least 100 patients treated for at least 1 year; this is an important ‘safety platform’ but has limitations, particularly in detecting adverse event with an incidence of less than 1%. Post-marketing surveillance is therefore important and clinicians should report adverse events seen in clinical practice (see page 25).

There are also limitations in the assessment of efficacy. Chronic degenerative disease is a challenging therapeutic target but the improvement may be limited by pathology that is largely irreversible. Modest efficacy may be the consequence, and effects that are statistically significant in large trials may be difficult to extrapolate to individual patients; it may be necessary to debate the clinical significance, for

example, a 5% increase in peak flow rate or a 10% increase in a quality-of-life measure. Evaluation of dose-response, which is a long-standing area of weakness in drug development, becomes even more difficult when changes in the end-points are small. Also, clinical trials tend to be conducted in well-defined at controlled settings. How well result of a clinical programme predicts the real world of clinical practice is a matter of concern to regulatory authorities and clinicians.

Practice points

i. Clinical evaluation of new drug is a collaborative process involving clinical pharmacological industry
ii. Clinical development of a new drug is divided into phases 1-4
iii. Even after a through clinical trial programme, experience with a new drug is limited and much remains to be discovered in clinical practice
iv. Reporting of adverse events is the responsibility of all clinicians

3.5.3 How to Appraise a Clinical Trail

Readers of the medical regularly encounter descriptions of clinical trials forming the basis for recommendations about medical practice. The ability to practice. The ability to appraise these reports critically is essential if they are to be given appropriate weight. Only a limited appraised can be conducted from a published most important supporting document is the protocol. It is worth trying to obtain a copy for trails of special interest – protocols of important trials are increasingly being published.

The overall purpose of a clinical trial may be exploratory or confirmatory:

i. Confirmatory trials are intended to provide a definitive answer to a question based on earlier indicative research (e.g. the efficacy of a new medicinal product in its intended manner of use).
ii. Exploratory trails are intended to suggest ideas for later confirmation.

This contribution focuses on confirmatory trials because these are the trails which primarily influence practice. Confirmatory trials are usually controlled and randomised to achieve the high degree of scientific rigour necessary to ensure the validity of their conclusions.

The three aspects of a clinical trial that most affect its interpretation are design, conduct and analysis. The most important aspect is design, because serious flaws I design are generally irretrievable.

3.6 Statistical Design

3.6.1 Parallel-group and cross-over trails– in most clinical trials, patients are randomised to one of two or more treatment arms, which are subsequently compared (parallel-group). This is the most robust design and minimal assumptions underlie its use. The second most commonly used design is the cross-over trail, which requires fewer subjects, but at the expense of additional assumptions for valid use. Cross-over trails should be used only in stable disease, and carry-over trails should be used only in stable disease, and carry-over of treatment effects from one period to the next should be avoided. The cross-over design is standard in bioequivalence studies and some other early-phase studies, but outside these applications its use should always be carefully justified.

3.6.2 Randomisation and masking – the most reliable control group is randomised and double-masked (double-blind). Details should be provided of the means by which randomisation was achieved and its security maintained. In double-masked trails, numbered supplies of drug can be given to individual trial lists pre-packed according to a properly generated random scheme. Alternatively, a telephone randomisation system may be used; this is particularly advantageous. when masking is impossible – the entry criteria can be checked when the call is made and if these are satisfactory the patient is irrevocably entered into the trail. Other randomisation methods (e.g. sealed envelopes) should be regarded with scepticism and confirmation of diligent and secure operation with scepticism and confirmation of diligent and secure operation should be sought. If code-breaks are supplied for emergencies, they should be tamperproof and individualised.

If the trial is not double-masked (single-masked or open), the other steps taken to avoid bias should be described and their success evaluated; for example, it may be possible to use independent refers who are ignorant of treatment to take the key measurements.

3.6.3 Primary outcome: the aim of the trail should lead to the choice of a key measurement as the primary outcome in the protocol, and this outcome should be the main focus of attention in the report. This ensures that the main test of statistical significance undertaken at the end of the trail is not affected by multiplicity (figure 2). Post hac selection of the outcome that achieves the highest level of significance is a biasing procedure. Sometimes, however, insistence on a unique choice of outcome presents difficulties. This situation can be dealt with by statistical means; the method chosen should be described clearly.

3.6.4 Power calculation: an ell-designed trial should include sufficient patients to make achieving the trail aim likely. The basis for this number

is usually found in the power calculation, which should be written into the protocol and also reported in the publication.

The prospective power calculation is a valuable source of information for the appraiser when doubts arise. It identifies the planed primary outcome, the treatment comparison of greatest interest and the size of difference that the study was intended to detect. These factors should correspond to those used during analysis and interpretation.

Once the trail is complete retrospective power calculations are of little value because the precision achieved can be illustrated better in other ways (confidence intervals).

3.7 Phytomedicine

3.7.1 Introduction and Historical Background

Phytomedicine or the use of herbal medicine with therapeutic properties have played a significant role throughout history. Although its usage greatly diminished during the dawn of the scientific era, there is a revival of interest in its potential by late 20th century, especially in the development of new drugs.

The history of herbal medicine can be traced back to thousands of years in both Western and Eastern tradition. It came into existence since the advent of human civilisation. Sheng-Nongs Herbal Book, one of the earliest sources of folk knowledge on the use of herbs in China, dated back to 3000 B.C. and included knowledge of 365 plants, animals and minerals useful as medication. It encompasses the details of almost 365 plants, animals, and minerals that find a place in medication. Our Earth houses approximately 420,000 species of plants; however, there is a lack of appropriate knowledge about them and their varied uses. There are three major areas, namely, food (foodstuffs), medicine (folk and traditional medicines), and research (phytochemical analysis), that predominantly find an immense use of herbal preparations and products and hence can be explored further. Although the industrial revolution and the development of organic chemistry resulted in a preference for synthetic products, World Health Organisation (WHO) reports that between 70% and 95% of citizens in a majority of developing countries still rely on traditional medicine as their primary source of medication. The role of herbal medicine started to decline after the 1960s as vast quantities of resources and money were used to promote synthetic medication. Besides this, advances in the human genome, increase knowledge of the structure and function of proteins and the notion that synthetic drugs are safer with fewer side effects (which does not necessarily be true) also contributed to the rise in the popularity of synthetic drugs. However, these advancements have several major

constraints. The large number of possible new drug targets has already outgrown the number of existing compounds that could potentially serve as drug candidates and the field of chemistry has limitation when it comes to synthesising new drug structures.

In the last decade, herbal medicine has seen some form of revival, advancing at a greater pace in community acceptance of their therapeutics effects. This field is bringing forward new lead drug discoveries as well as safe and efficacious plant-based medicines. In turn, this leads to growing number of sales of commercialised medicinal herbs and most importantly, growing number of pharmaceutical companies that involve in the research and development of plants as a source for modern medicine. What chemists have been desperately seeking, Mother Nature has already plenty of stock. Phytomedicine, in amalgamation with various other health-care fields, have indeed revolutionised and strengthened the foundation of the existing health-care system and occupies a major stake in the industry. Reports gathered from all over the world indicate there are around 35,000 species of plants that are currently being used in herbal therapies/recipes. Although according to research data available only 20% of the total undergoes the stage of phytochemical analysis while 10% reach the biological screening stage. The remaining still needs some amount of exploration making use of modern technologies. The future of medicinal plant–derived drugs therefore seems to have tremendous scope for discovering some new and novel therapeutic strategies and products (Khan, 2015). Herbal medicine can be categorized into phytotherapy, over-the-counter herbal and traditional herbalism. There is an increase of interest in the pharmaceutical industry to develop new medications from plants. Phytomedicine research has employed high-throughput screening methods and the increasingly popular “reverse pharmacology” methods.

There is some documentation on a wide range of plants used in sub-Saharan Africa to treat ailments (Okigbo 2006; Verzar 1987), but there has been little in the way of systematic appraisal of their benefits in randomised controlled trials.

In Nigeria, one of these phytomedicines is collectively known as Niprisan® (also known as Nicosan®), a freeze-dried extract of Piper guineenses seeds, Pterocarpus osun stem, Eugenia caryophyllum fruit and Sorghum bicolor leaves. Niprisan® has been investigated in vitro and in animal studies (Adzu 2001; Awodogan 1996; Iyamu 2002). Others are Ciklavit® (Cajanus cajan seed extract as base) and Zanthoxylum (Fagara) zanthyloides, which are also being researched (Imaga 2013). There may well be other potential phytomedicines available for people with SCD, but their safety and efficacies will have to be scientifically evaluate

3.7.2 Characteristics of Herbal Drugs

i. The pharmacologically active compounds in herbal drugs are present in lower concentrations than the conventional tablets and capsules. This fact generally means that risks associated with crude herbal drugs are minimal with moderate use. Many herbal drugs have been safely used for centuries.
ii. They contain a wide variety of different compounds, some pharmacologically active (2ry metabolites) and some not (such as cellulose, starches and sugars).
iii. Herbs contain mixture of components that may have synergistic or antagonistic effects e.g. Rhubarb (anthraquinone & tannin).
iv. Plants may also contain active and toxic compounds such as pyrrolizidine alkaloids which are converted in the liver into hepatotoxic and carcinogenic metabolites.
v. Herbal medicines are less expensive i.e. cheaper than conventional medicines. In fact, the WHO is encouraging developing countries to develop their own herbal formula, from local herbs within each country.

3.7.3 Uses of Phytomedicines

Common Parts Use: Specific parts of plants species aerial parts rhizome leaf root flower bark fruit, stems are accordingly store properly. Predominant terrain, north direction, are usually use. Extraction of phytochemicals mainly use alcohol to extract the plant's active constituents from dry or fresh plants alcoholic extracts are prepared by maceration and/or percolation most phytomedicines are prescribed as alcoholic tinctures, taken twice daily with a dose of 15 ml each time.
The role of phytomedicines is unique because the appropriate drugs stimulate or strengthen the body's own functions and immune system, hence support the body to restore itself to health.

Phytomedicine consultation assessment of the person as a whole detailed medical history, lifestyle, diet and other causes are considered rather than focusing on disease or symptoms required investigations.

Table 24: Showing Conventional medicineversus Herbal medicine or Phytomedicine

Conventional medicine	Herbal medicine or Phytomedicine
Uses of pure chemicals in the treatment of disease, regardless of their origin, whether of plant, animal, micro-organism, synthetic or semi-synthetic, organic or inorganic nature.	Uses plants or their crude products for the treatment of diseases. It may include also animal, fungi or bacteria
Is simple often with single indication	Is complex promoted for several divergent uses
contains one active principle in high concentration	contains several active principles in low concentrations

Table 25: Table Plants as Identified by traditional use, types of Toxic and Physical Symptoms Some commonly used herbal supplements.

ant (Family)	Traditional Use	Area of Plant Collection	Part Used; Extraction Solvent	Physical Signs of Toxicity (Animal Model)
Acanthus montanus (Acanthaceae)	Pain, female infertility,and threatened abortion	Cameroon	Leaves; water	Kidneys revealed crystals resulting in glomeruloscler osis
Annona senegalensis (Annonaceae)	Sleeping sickness, malaria,anthelmintic, etc	Nigeria	Liver sections showed degenerati necrosis of the hepatocytes	Liver degeneration and necrosis of the hepatocytes
Anacardium occidentale (Anacardiaceae)	Diabetes and hypertension	Cameroon	Leaves; methanol	anorexia and weight gain, and syncopal observed (mice). liver and kidney injury
Butyrospermum paradoxum (Sapotaceae)	Trypanosomiasis and several human & animal diseases	Nigeria	Stem bark; ethanol	Anorexia, dehydration, depression,

				prostration, coma, and death. and the kidney, hepatomegaly.
Chrysophyllum albidum (Sapotaceae)	cancers and cancer-related problems	Nigeria	Root bark. 80% ethanol	Fairly toxic to brine shrimps
Corrigiola telephiifolia (Caryophyllaceae)	Dermatological diseases, flu, ulcer, cough, jaundice, anaesthesia diuretic, and parturient women	Morocco	Roots; ethanol: water (75:25)	Decrease in the relative body weight
Cylicodiscus gabunensis (Mimosaceae)	GIT disorder, rheumatism, filariasis, and headache	Cameroon	Stem bark; ethyl acetate	Decrease in relative weight of the spleen. Toxic effect on liver, kidneys and lungs (rats)
Entada abyssinica (Fabaceae)	Coughs, diarrhoea, fever, gonorrhoea, prevent miscarriage, rheumatic	Tanzania	Stem bark; 80% ethanol	At doses 2000 mg/kg body wt., the mice exhibited increased respiratory rate and scruffy hair. Mice died at the dose of 3000 mg/kg body wt.
Erythrina senegalensis (Fabaceae)	Malaria, hepatitis jaundice, gastrointestinal disorders, ame sterility, pains, onchocerchosis, and headache	Cameron	Stem bark; water	Reduction in locomotion, exploration, aggressiveness, touch, sensibility, and pain sensibility (mice)
Ficus exasperata (Moraceae)	Cardiac arrhythmias, asthma, enhance expulsion of placenta, etc	Nigeria	Leaves;	Water
000Garcinia kola (Guttiferae)	Bronchitis, URTI, colic, head or chest,	Nigeria	Root; 80% ethanol	Toxic to brine shrimps

	liver disorders, and as a chewing stick, purgative,antimicrobial			
Glinus lotoides (Molluginaceae)	Anthelmintic and tapeworm infestation	Ethiopia	Seeds; 60% methanol	No physical sign of toxicity was observed (rats)
Hydnora johannis Becca. (Hydnoraceae)	Diarrhoea, cholera, and swelling tonsillitis.	Sudan	Roots; ethanol	Toxic effect on liver, kidney, and spleen (Wistar rats)
Senecio latifolius (Asteraceae)	Wounds, burns, and abortion	South Africa	Leaves; water	A dose-related toxicity of hepatocytes, with apoptosis, and necrosis was observed (rats)
Leonotis leonurus (Lamiaceae)	Epilepsy, coughs, influenza, bronchitis,diabetes, snakebites, and muscular cramps	Nigeria	Shoots; water	Decreased respiratory rate and motor activity, loss of righting reflex, ataxia and death (rats). Marked hyperplasia of pulmonary arteries; glomerulonephritis; necrosis, and mild hemosiderosis in the liver.
Pteleopsis hylodendron (Combretaceae)	Measles, dropsy, chickenpox, STD, female sterility, liver and kidney disorders	Cameroon	Stem bark; methanol	Growth retardation, inflammation and vascular congestion in the liver and kidneys (rats)

i. Ginkgo (Ginkgo biloba) standardised extract improves awareness, judgment, and social function in people with Alzheimer's
ii. St. John's wort (Hypericum perforatum) antidepressant effects

iii. Saw palmetto (Serenoa repens) for the treatment of benign prostatic hyperplasia (BPH) improvement in urinary symptoms and flow compared to finasteride (Proscar), a pharmaceutical drug used in BPH.
iv. Valerian (Valeriana officinalis) a sleep-inducing agent, (no hangover feeling the next day)
v. Echinacea (Echinacea purpurea) and other Echinacea species) may improve the body's natural immunity.

Table 26: Examples of Phytomedicine: A few very well-known IN Orthodox Medicines

Anti-cancer drug Taxol	Taxusbrevifolia	1971
Strychnine	Strychhnos	1817
Emetine	Ipecacuanha	1817
Caffeine	Coffee shrub	1821
Atropine	Belladonna	1833
Qininine	from cinchona bark	1820
Salicin Also known as Aspirin)	willow bark	1838
Morphine	opium poppy	1923
Benzylpenicillin		1928
Tamiflu	shikimic Anis seed acid	

3.7.3 Herbal preparations

i. Botanical: Macroscopically – shape, external, marking, microscopically quality, quantity, scanning electron microscopy (SEC) studies, powder study.
ii. Physical: Moisture constituents, extract values, Ash values Fluores.
iii. Chemicals: Qualitative, quantitative using Chromatography – HPTLC, GLC, HPLC, DNA Finger printing etc.
iv. Biological: such as Microbial contamination, Toxicological and Pharmacological.
v. Other specific activities: Antagonistic.
vi. Orgnoleptic: colour, odour, taste, texture and fracture

Methods of purification include washing, decoloration, sifting, boiling, elutriation, rubbing, lixiviation, dipping, percolation, sublimation, maceration, bachnag, dialysis, and despumation.

Preparations: Active ingredients of plants can be first tasted – sweet, sour, salty, pungent, bitter and astringent. Treatment is nothing but restoration of deranged body potency – cold and hot elements – anatomically and physiologically unique and specific taste after digestion

– actions sweet, sour and pungent. A phytopharmaceutical preparation or herbal medicine is any manufactured medicine obtained exclusively from plants, either in the crude state or as pharmaceutical formulation.

3.7.5 Standardisation and quality evaluation of herbal drugs

Several methods of standardisation may determine the number of herbs used. One is the ratio of raw materials to solvent. However different specimens of even the same plant species may vary in chemical content. For this reason, thin layer chromatography is sometimes used by growers to assess the content of their products before use. Another method is standardisation on a signal chemical.

3.7.6 Routes of administration: There are many forms in which herbs can be administered, the most common of which is in the form of liquids, tinctures topical, herbal wines, essential oils tisanes oils, balms, decoctions, creams, lotions, macerate poultice, vinegar syrups, compressions extract and inhalations.

i. **Liquid that** is drunk by the patient either an herbal tea or a (possibly diluted) plant extract.
ii. **Herbal teas**, or tisanes, are the resultant liquid of extracting herbs into water, though they are made in a few different ways. Infusions are hot water extracts of herbs, such as chamomile or mint, through steeping.
iii. **Decoctions** are the long-term boiled extracts, usually of harder substances like roots or bark.
iv. **Maceration i**s the cold infusion of plants with high mucilage-content, such as sage or thyme. To make macerates, plants are chopped and added to cold water. They are then left to stand for 7 to 12 hours (depending on herb used). For most macerates, 10 hours is used.
v. **Tinctures** are alcoholic extracts of herbs, which are generally stronger than herbal teas. Tinctures are usually obtained by combining 100% pure ethanol (or a mixture of 100% ethanol with water) with the herb. A completed tincture has an ethanol percentage of at least 25% (sometimes up to 90%). Non-alcoholic tinctures can be made with glycerine but it is believed to be less absorbed by the body than alcohol-based tinctures and has a shorter shelf life.
vi. **Herbal wine** and elixirs are alcoholic extract of herbs, usually with an ethanol percentage of 12–38%. [32]. Extracts include liquid extracts, dry extracts, and nebulises. Liquid extracts are liquids with a lower ethanol percentage than tinctures. They are usually made by vacuum distilling tinctures. Dry extracts are extracts of

plant material that are evaporated into a dry mass. They can then be further refined to a capsule or tablet.

vii. **Topical** Many herbs are applied topically to the skin in a variety of forms. Essential oil extracts can be applied to the skin, usually diluted in a carrier oil. Many essential oils can burn the skin or are simply too high dose used straight; diluting them in olive oil or another food grade oil such as almond oil can allow these to be used safely as a topical. Salves, oils, balms, creams and lotions are other forms of topical delivery mechanisms. Most topical applications are oil extractions of herbs. Taking a food grade oil and soaking herbs in it for anywhere from weeks to months allows certain phytochemicals to be extracted into the oil. This oil can then be made into salves, creams, lotions, or simply used as an oil for topical application. Many massage oils, antibacterial salves, and wound healing compounds are made this way.

viii. **Inhalation**, as in aromatherapy, can be used as a treatment.

3.7.7 Safety Issues in the use of Phytomedicines

Although many consumers believe that herbal medicines are safe because they are "natural", herbal medicines and synthetic drugs may interact, causing toxicity to the patient. Herbal remedies can also be dangerously contaminated, and herbal medicines without established efficacy, may unknowingly be used to replace medicines that do have corroborated efficacy. For example*; Datura stramonium* has been used in Ayurveda for various treatments, but contains alkaloids, such as atropine and scopolamine, which may cause severe toxicity. Examples of herbs where a high degree of confidence of a risk long term adverse effects can be asserted include ginseng, which is unpopular among herbalists for this reason, the endangered herb goldenseal, milk thistle, senna, against which herbalists generally advise and rarely use, aloe vera juice, buckthorn bark and berry, cascara sagrada bark, saw palmetto, valerian, kava, which is banned in the European Union, St. John's wort, Khat, Betel nut, the restricted herb Ephedra, and Guarana.

Therefore, some safety issues in the use Phytomedicines can be from;

i. **Adverse Effects:** There is also concern with respect to the numerous well-established interactions of herbs and drugs. In consultation with a physician, usage of herbal remedies should be clarified, as some herbal remedies have the potential to cause adverse drug interactions when used in combination with various prescription and over-the-counter pharmaceuticals, just as a patient

should inform an herbalist of their consumption of orthodox prescription and other medication.

ii. Effect on Blood Pressure: dangerously low blood pressure may result from the combination of an herbal remedy that lowers blood pressure together with prescription medicine that has the same effect. Some herbs may amplify the effects of anticoagulants.

iii. Examples of herbal treatments with likely cause-effect relationships with adverse events include aconite, which is often a legally restricted herb, ayurvedic remedies, broom, chaparral, Chinese herb mixtures, comfrey, herbs containing certain flavonoids, germander, guar gum, liquorice root, and pennyroyal.

iv. **Drug Interactions:** Certain herbs as well as common fruits interfere with cytochrome P450, an enzyme critical to much drug metabolism.

v. **Undisclosed Additives:** a 2018 study, FDA identified active pharmaceutical additives in over 700 of analysed dietary supplements sold as "herbal", "natural" or "traditional". The undisclosed additives included "unapproved antidepressants and designer steroids", as well as prescription drugs, such as sildenafil or sibutramine. False adulteration, inappropriate formulation, or lack of

vi. understanding of plant and drug interactions have led to adverse reactions that are sometimes life threatening or lethal.

vii. **Labelling accuracy:** A 2013 study found that one-third of herbal supplements sampled contained no trace of the herb listed on the label. The study found products adulterated with contaminants or fillers not listed on the label, including potential allergens such as soy, wheat, or black walnut. One bottle labelled as St. John's Wort was found to actually contain Alexandrian senna, a laxative.

viii. **Lack of Registration:** Researchers found in 2014 that almost 20 per cent of herbal remedies surveyed were not registered with the Therapeutic Goods Administration, despite this being a condition for their sale. They also found that nearly 60 per cent of products surveyed had ingredients that did not match what was on the label. Out of 121 products, only 15 had ingredients that matched their TGA listing and packaging.

In 2015, the New York Attorney General issued cease and desist letters to four major U.S. retailers (GNC, Target, Walgreens, and Walmart) who were accused of selling herbal supplements that were mislabelled and potentially dangerous. Twenty-four products were tested by DNA barcoding as part of the investigation, with all but five containing DNA that did not match the product labels.

3.7.8 Challenges

There are at least five major limitations in the development of herbal medicine: the reproducibility of biological activity of herbal extracts;

i. Its toxicity and adverse effects;
ii. Its adulteration and contamination;
iii. Herb drug interactions issues; and
iv. Standardisation issues.

Brief description of each of these limitations.

i. **Reproducibility of biological activity of herbal medicine**: One of the most problematic issues faced by the field of Phytomedicine is the high failure rate to reproduce the biological activity of individual herbal extracts after the success of initial screening process. Over 40% of plant extracts found actually lack this reproducibility31. Although this failure in re-sampled and re-extracted batches points towards the variation of biochemical profiles of plants harvested at different times and locations, as well the existence of unique variation in the same type of plant, put challenge to scientific confidence on the efficacy. Nonetheless, sometimes in our pursuit to isolate an active compound from a particular plant, we might inadvertently exclude phytocompounds with relevant pharmacological activities.

ii. **Toxicity and adverse effects of herbal medicine**: There is a predominant myth in society that medicinal herbs or plants are much safer than conventional pharmaceuticals due to its "natural" origin. This cannot be further than the truth! Like all other medicines, there is a specific dosage threshold for each herbal medicine to be efficacious as well as to be toxic. There have been reports in the literature 32, 33 that many herbal medicine preparations are potentially toxic and some are even carcinogenic. For example, aristolochic acid derived from Aristolochia spp. is associated with the development of nephropathy and urothelial cancer. The toxic effect of herbal medicines may be due to

(i) existence of phytotoxins in some unadulterated herbal medicines;
(ii) (ii) mistakes in botanical identification;
(iii) (iii) unsuitable combinations of plants; and
(iv) (iv) usage of plants that interfere with conventional pharmacotherapy.

Adulteration and contamination of herbal medicine: Herbal medicine may become adulterated and contaminated in countries that are lax in their purity control regulation. This may cause significant medical problems, especially in children. A recent cross-sectional study among 13,504 adults

in the USA showed that women using herbal supplements (including Ayurvedic or traditional Chinese medicine herbs, St. John's Wort, and "other" herbs) had blood lead levels that were 10% higher than women non-users, although these increased levels were not seen among men.

Herb drug interactions issues: Not surprisingly, the pharmacokinetic profile of administered conventional pharmaceuticals can be changed by the usage of herbal medicine. These interactions may potentiate or antagonise the absorption and metabolism of drugs, as well as cause adverse effects like allergy. However, it is worthy of note that herbal medicine has the lowest level (7.6%) of reported adverse effects compared to other modes of complementary and alternative medicine.

Herbal medicine standardisation issues: Herbal medicine rarely meet the standard of standardisation, which is partially due to the scarcity of scientific information about the acting pharmacological principles of the extracted phytocompounds and the fact that the plants are not cultivated under controlled condition. The significant variability in content and quality of commercialised herbal products are the result of variability in the content and concentration of phytocompounds within the extract as well as the different extraction and processing techniques employed by different producers.

Aside from the limitations discussed above, among the problems faced from plant-based drug development is the issue of eco-sustainability. Taxol, an anti-tumour agent, is isolated from the bark of Taxus brevofolia and Taxus bacata 43. In order to produce 2.5kg of Taxol, 27,000 tons of bark is required, equivalent to 12,000 trees. We can imagine that if there was no alternative to the natural phytocompound extraction method, then the mass production of Taxol would cause the extinction of these unique tree species. Hopefully, the problem of low yield will be outdated with the advancement in combinatorial organic chemistry, with the creation of semi-synthetic analogues and better method of extraction and purification that will result in higher yield.

3.7.9 The Future of Herbal Medicine

What does the future hold in store for herbal medicine? Socio-cultural and economic problems, lack of well-planned and integrated strategies, as well as poor access to scientific information must be dealt with in order to fully utilise the available resources for the modern concept of drug development. It is important to encourage more ethnobotanical studies among indigenous people before their way of life or they themselves disappear. Besides this, the problem of patents, intellectual property and rights of the native population where the phytomedicine knowledge originated should be addressed adequately. This native population is often

found to be in need of better care, but they do not usually benefit from sharing their knowledge to the rest of the so-called "modern world". It is curious to note that drug companies generate more than USD 100 million each year from the sale of drugs from natural compounds, without returning profits to the countries where the compounds were found. Protecting and compensating local groups for their indigenous knowledge as well as providing access to modern medicine should be seen as a reasonable expectation from the conventional pharmaceutical or herbal medicine companies that stand to benefit greatly from this "collaboration". Meanwhile, it is unfortunate that current herbal medicine companies are still mainly small businesses and as a result, products sold are of inferior quality and frequently mixed with contaminants and sometimes toxin. Professional links must be forged between these businesses, the government, large pharmaceutical companies, academic institution and the local community to continue the expansion and development of herbal medicine in the right direction. This will promote the rational and responsible exploitation of biodiversity as a source of chemical compounds that can be used for developing new drugs. For example, the International Cooperative Biodiversity Group (ICBG) programme, which is currently based in Peru, has been established to form interdisciplinary collaboration between universities, research institutions, government and pharmaceutical companies. In China, Yunnan Institute of Tropical Botany (YITB) has collaborated with Yamanouchi Pharmaceutical of Japan, resulting in the development of seven patents from 1988 to 19911. Similar programs should be encouraged worldwide.

Besides this, the improvement of drugs found in nature is now possible by organic chemistry, gene amplification and recombinant procedures, high-throughput screening, gene chip technology, or chemo systemic. Through these methods, now there are new local anaesthetics derived from cocaine without its original dangerous effects and there is also chloroquine that is less toxic than quinine.

SELF- ASSESSED EXERCISES

i. List the methods of purifying herbal preparations.
ii. Discuss the safety issues that can arise from the use of phytomedicines.

4.0 CONCLUSION

In this unit, you have learnt key words in drug development, preclinical drug discovery, pharmacological profiling, safety and toxicity, clinical trials, ethics in clinical trials, clinical trial design, Phases in clinical trials, Therapeutics Goods Administration, Pharmaceutical Benefits Scheme. You have also learnt what is phytomedicine or the use of herbal medicine

with therapeutic properties and its significant role throughout history, the various methods of preparations, indications and types of some example medicinal plants in sub-Saharan Africa including Nigeria.

5.0 SUMMARY

The process of drug development includes the activities that take the prospective new drug into the market-place where it becomes available for use by doctors and patients.

Drug discovery usually exploits advances in knowledge that are available within the research community and it is therefore not surprising to find several companies pursuing similar lines of research. Development times vary between areas of therapeutics, but generally companies expect to develop drugs in 6-7 years (compared with about 12 years two decades ago).

Preclinical drug discovery is the process before clinical testing of drugs. The first step in preclinical drug development is the discovery or synthesis of a new drug. At least, 10,000 new molecules are discovered/synthesized for each successful new drug introduced. Extensive preclinical safety and efficacy testing of new drugs are required in animals, and this takes an average of 1.5-3 years. There are three main ways in which new drugs are derived; chemical modification, rational drug design, and random screening. Many a times Serendipity (accidental discovery of something fortunate) may also have a role in drug development.

Once a lead compound has been discovered (e.g. a drug with activity at a certain binding site), the compound undergoes pharmacological profiling. A large number of experiments are undertaken, mainly using animals, to determine the pharmacokinetics and pharmacodynamics of the drug.

New drugs undergo extensive safety and toxicity testing in animals. This preclinical safety and toxicity testing take 2 -5 years, and involves the collection and analysis of lots of data.

It is convenient to describe clinical drug development in terms of phase. The boundaries between the phases are not rigid, and in some developments phases 2 and 3 are merged. Overlap between phases may occur. The duration of phase 1 is about 1 year; the duration of phases 2 and 3 together is about 4 years. Submission to regulatory is based on the clinical data obtained from the studies in phases 1, 2 and 3.

Only about 10% of compounds that enter clinical trial are approved/registered for sale. Clinical trials are under stringent law enforced guidelines.

Phytomedicine or the use of herbal medicine with therapeutic properties has played a significant role throughout history. Phytomedicine, in amalgamation with various other health-care fields, has revolutionized and strengthened the foundation of the existing health-care system and occupies a major stake in the industry.

In Nigeria, one of these phytomedicines is collectively known as Niprisan® (also known as Nicosan®), a freeze-dried extract of Piper guineenses seeds, Pterocarpus osun stem, Eugenia caryophyllum fruit and Sorghum bicolor leaves. Niprisan® has been investigated in vitro and in animal studies. Others are Ciklavit® (Cajanus cajan seed extract as base) and Zanthoxylum (Fagara) zanthyloides, which are also being researched. There may well be other potential phytomedicines available for people in Nigeria. The sustain used of herbal medicine over the years is based on the believe of the following characteristics of herbal medicines That; 1-The pharmacologically active compounds and this fact generally means that risks associated with crude herbal drugs are minimal with moderate use. 2-They contain a wide variety of different compounds, some pharmacologically active (2ry metabolites) and some not (such as cellulose, starches and sugars).3-Herbs contain mixture of components that may have synergistic or antagonistic effects e.g. Rhubarb (anthraquinone & tannin). 4-Plants may also contain active and toxic compounds such as pyrrolizidine alkaloids which are converted in the liver into hepatotoxic and carcinogenic metabolites. And 5- Herbal medicines are less expensive i.e. cheaper than conventional medicines. Common Parts Use: Specific parts of plants species aerial parts, rhizome, leaf root flower, bark, fruit and stems are accordingly store properly.

6.0 TUTOR- MARKED ASSIGNMENT

1. What is Phytomedicine and what are their main differences with traditional (orthodox medicine)?
2. Classify some African medicinal plants, their uses, indications and adverse effects
3. What are the main challenges of using Phytomedicines

7.0 REFERENCE/FURTHER READING

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MODULE 2 APPLIED PHARMACOLOGY IN PUBLIC HEALTH

Unit1 Principles of Drug Action (Pharmacodynamics)
Unit2 Mode of Action of Antimicrobial and Chemotherapeutics Drugs
Unit3 Mode of Drug Action in Diseases

UNIT1 PRINCIPLES OF DRUG ACTION (PHARMACODYNAMICS)

CONTENTS

1.0 NTRODUCTION

The measurement of the effects of drugs on humans (or, in basic pharmacology, an organ system) is termed Pharmacodynamics refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects. The effect of a drug present at the site of action is determined by that drug's binding with a receptor. Receptors may be present on neurons in the central nervous system (i.e., opiate receptors) to depress pain sensation, on cardiac muscle to affect the intensity of contraction, or even within bacteria to disrupt maintenance of the bacterial cell wall. For most drugs, the concentration at the site of the receptor determines the intensity of a drug's effect. However, other factors affect drug response as well. Density of receptors on the cell surface, the mechanism by which a signal is transmitted into the cell by second messengers (substances within the cell), or regulatory factors that control gene translation and protein production may influence drug effect.

In the simplest examples of drug effect, there is a relationship between the concentration of drug at the receptor site and the pharmacologic effect, this lecture series is designed to facilitate the learning of key principles and concepts regarding the basic pharmacodynamics principles of drugs, drug receptors and interactions at these receptors. This knowledge will be critical in the understanding of the various drugs and drug classes to be discussed throughout this course. Understand drug safety and effectiveness like factors affecting drug action in man. More specifically this information will be used to facilitate the understanding of the receptors in the autonomic nervous system and the drugs that interact at these receptors.

2.0 OBJECTIVES

By the end of this unit, you will be able to:

- list different types of receptors at which drugs can act
- identify concept of affinity and those factors that cause a drug to bind to a receptor
- state concept of intrinsic activity
- differentiate between full and partial agonists
- give the definitions of potency and efficacy
- apply the information regarding drugs that can be obtained from the log-dose response curve
- explain the properties of a competitive antagonist and how it differs from an irreversible receptor agonist.

3.0 MAIN CONTENT

3.1 Definition of Terms

i. **Pharmacodynamics.** This term encompasses both mechanism of action and endpoint (e.g. heart rate, blood pressure).
ii. In Greek Pharmacon = Drug Dynamics = Action/Power It covers all the aspects relating to "What a drug does to the body" Mechanism of action.
iii. **Action:** How and where the effect is produced is called as Action.
iv. **Effect:** The type of response producing by drug

3.2 Drug Action in Man

The action of drugs on the human body and the mechanism of interaction between drugs and human to produce effects is described.

3.3 Site of Drug Action

The receptors sites where a drug acts to initiate a group of functions is that drugs site of action. This a can either:

i. Extra cellular
ii. Cellular
iii. Intracellular

a. Types of Drug Action (Type of Responses): -

iv. Stimulation
v. Inhibition/Depression
vi. Replacement

vii. Irritation
viii. Cytotoxic

3.5 Mechanism of Drug Action in Man

The types of an effect produce by a drug is called mode of action of that drug. For example, Morphine, by depressing the function of the cerebral cortex, hypothalamus and medullar centre, it depresses pain perception (analgesia), Heavy sedation (Narcosis), and depressing cough centre (antitussive effect). Initially it stimulates, then depressing the vomiting centre and depressing respiration.

3.5.1 Drug action via Receptors

Definition: Receptors are macromolecules involved in chemical signalling between and within cells; they may be located on the cell surface membrane or within the cytoplasm. Operationally receptor denote any cellular macromolecules to which a drug binds to initiate the response to it, but itself has no other function, e.g. Muscarinic (M type) and Nicotinic (N type) receptors? of Cholinergic system. Most are proteins, some receptor sites are intracellular (e.g. steroid) cytoplasm
or in the nucleus. The drug-receptor interaction leads to a molecular change in the receptor, which triggers a chain of events leading to a response. Receptors tend to be highly specific, interacting with a limited number of structurally related molecules. For some drugs, the receptor is nonspecific in terms of cell function (e.g. an alkylating agent that cross-binds molecule within DNA).

Other ways, in which drug acts on receptors includes: Agonist, Antagonists and partial antagonists.

3.5.2 Drug action via indirect alteration of the effect of an endogenous agonist

I. Physiological
ii. Increase endogenous release
iii. Inhibition of endogenous re-uptake
iv. Inhibition of endogenous metabolism
V. Prevention of endogenous release

3.5.3 Drug activation via the inhibition of transport processes

3.5.4 Drug action via enzyme inhibition.

3.5.5 Drug action via enzyme activity activation.

3.5.6 Miscellaneous drug action

i. Chelating
ii. Osmotic diuresis
iii. Volatile general anaesthetics
vi. Replacement drugs

3.5.7 Receptor Functions

Two essential functions (see diagram below), Reorganisation of specific ligand molecule (Ligand binding domain) and Transduction of signal into response(Effector domain).

3.5.8 Reorganisation functions (signal into response)

Two Domains:

i. Ligand binding domain (coupling proteins)
ii. Effectors Domain – undergoes functional conformational change

Action": Initial combination of the drug with its receptors resulting in a conformational change (agonist) in the later, or prevention of conformational change (antagonist).

"Effect": It is the ultimate change in biological function brought about as a consequence of drug action, through a series of intermediate steps (transducers).

3.5.9The Transducer mechanism: Most transmembrane signalling is accomplished by a small number of different molecular mechanisms (transducer mechanisms). Large number of receptors share these handful of transducer mechanisms to generate an integrated and amplified response.

There Mainly 4 (four) major categories:

i. G-protein coupled receptors (GPCR)
ii. Receptors with intrinsic ion channel
iii. Enzyme linked receptors
iv. Transcription factors (receptors for gene expression)

Table 27: Receptor and coupling mechanisms

S/NO	Receptor type	Location	Coupling mechanism	Examples
1.	Receptor controlled - ion channels	Membrane	Entry/exit of ions - Depolarization or hyperpolarization	Nicotinic, acetylcholine γ-aminobutyric acid, Glutamate
2.	Ligand Gated - G – Protein receptors	Membrane	Receptor protein associated with a G-protein which may: Activate messenger Adenylate cyclase – cAMP Phospholipase C–inositol triphosphate, diacylglycerol Activate an ion channel	Muscarinic/acetylcholine**,** β-adrenergic Dopaminergic Serotoninergic Opiate
3.	Receptor-controlled enzymes	Membrane	Initiate protein phosphorylation (e.g. tyrosine kinase, guanylate cyclase)	Insulin Atrial natriuretic peptide
4	Intracellular receptors, Gene	Intracellular	Stimulate mRNA synthesis in the cell nucleus, leading to protein synthesis	steroid hormones, Thyroid hormones, vitamin D

Drug +Receptor - Drug receptor complex = Response

Drug receptor interaction: -

i. **Selectivity: -** Degree of complimentary correlation between drug and receptor. Ex: - Adrenaline Selectivity for α, ß Receptor

ii. **Affinity: -** Ability of drug to get bound to the receptor.
iii. **Intrinsic activity (IA) or Efficacy**: - Ability of drug to produce a pharmacological response after making the drug receptor complex

3. 6 Receptor Families

Four types of receptors families are Ligand-gated ion channels (inotropic receptors), G-protein coupled receptor (Metabotropic receptors), Enzymatic receptors (tyrosine kinase), and receptor regulating gene expression (transcription factors/ Steroids). The interaction of a ligand with a receptor protein induces a conformational change that eventually initiates an intracellular signal.

3.6.1Ligand-activated ion channels (a signal transduction mechanism)**:** Ion gated receptors: - Localised on cell membrane and coupled directly to an ion channel acetylcholine interacting with a nicotinic receptor that is a nonspecific Na1/K1 transmembrane ion channel. Interaction of a molecule of acetylcholine with each subunit of the channel produces a conformational change that permits the passage of Na1 and K1. Other channels that are targets for various drugs include specific Ca21 and K1 channels.

3.6.2G-protein coupled receptors: G-protein–coupled receptors compose the largest class of receptors. All the receptors have seven transmembrane segments, three intracellular loops, and an intracellular carboxyl-terminal tail. The biologic activity of the receptors is mediated via interaction with a number of G (GTP binding) proteins. Bound to inner face of plasma membrane (2nd messenger)

Varieties of G-protein

i. $G\alpha_2$ s-coupled receptors a β-adrenoceptor, which when activated by ligand binding (e.g., epinephrine) exchanges GDP for GTP. This facilitates the migration of Gαs (Gαstimulatory) and its interaction with adenylyl cyclase (AC). Gαs-bound AC catalyses the production of cyclic AMP (cAMP) from adenosine triphosphate (ATP); cAMP activates protein kinase A, which subsequently acts to phosphorylate and activate a number of effector proteins. The βγ dimer may also activate some effectors. Hydrolysis of the guanosine triphosphate (GTP) bound to the Gα to guanosine triphosphate (GDP) terminates the signal.
ii. **$G\alpha_1$ (G-inhibitory)-coupled receptors**. Ligand binding (e.g., somatisation) to $G\alpha_1$ (Gαinhibitory)-coupled receptors similarly exchanges GTP for GDP, but Gαi inhibits AC, leading to reduced cAMP production.

iii. **Gq (and G_{11})-coupled receptors**. Gq (and G_{11}) interact with ligand (e.g., serotonin)-activated receptors and increase the activity of phospholipase C (PLC). PLC cleaves the membrane phospholipid phosphatidylinositol 4, 5-bisphosphate (PIP2) to diacylglycerol (DAG) and inositol 1, 4, 5-triphosphate (IP3). DAG activates protein kinase C, which can subsequently phosphorylate and activate a number of cellular proteins; IP3 causes the release of Ca21 from the endoplasmic reticulum into the cytoplasm, where it can activate many cellular processes.

iv. **Go**: Neurotransmitters in brain, Not yet clear

G-protein effector systems

- Adenylase cyclase: cAMP system
- Phospholipase –C: Inositol phosphate system
- Ion channels

Ion channel regulation; G-protein coupled receptors can control the functioning of ion channel by not involving any second messenger; e.g.: - In cardiac muscles.

3.6 Enzymatic receptors:

Receptor-activated tyrosine kinases. Many growth-related signals (e.g., insulin) are mediated via membrane receptors that possess intrinsic tyrosine kinase. Ligand binding causes conformational changes in the receptor; some receptor tyrosine kinases are monomers that dimerize upon ligand binding. The liganded receptors then auto - phosphorylate tyrosine residues, which recruit cytoplasmic proteins to the plasma membrane where they are also tyrosine phosphorylated and activated. Receptor regulating: gene expression (transcription factors) unfolds the receptor and expose normally masked DNA binding site Increase RNA polymerase activity.

i. **Intracellular nuclear receptors**. Ligands (e.g., cortisol) for nuclear receptors are lipophilic and can diffuse rapidly through the plasma membrane. In the absence of ligand, nuclear receptors are inactive because of their interaction with chaperone proteins such as heat-shock proteins like HSP-90. Binding of ligand promotes structural changes in the receptor that facilitate dissociation of chaperones, entry of receptors into the nucleus, hetero- or homodimerization of receptors, and high-affinity interaction with the DNA of target genes. DNA-bound nuclear receptors are able to recruit a diverse number of proteins called coactivators, which subsequently act to increase transcription of the target gene.

ii. **Alteration of the activity of enzymes** by activation or inhibition of the enzyme's catalytic activity.
iii. **Antimetabolite action** in which the drug, acting as a non-functional analogy of a naturally occurring metabolite, interferes with normal metabolism.
iv. **Nonspecific chemical or physical interactions** such as those caused by antacids, osmotic agents, and chelators.

3.6.4 Receptor regulation theory

Receptors are in dynamic state. The affinity of the response to drugs is not fixed. It alters according to situation.

3.6.5 Up regulation of receptors: In topically active systems, prolonged deprivation of agonist (by denervation or antagonist) results in super sensitivity of the receptor as well as to effector system to the agonist. Sudden discontinuation of Propranolol, Clonidine etc. after prolong use, produce withdrawal symptoms. Rise Blood Pressure, induce of angina. Unmasking of receptors or proliferation or accentuation of signal amplification.

3.6.6Receptor down regulation: Continued exposure to an agonist or intense receptor stimulation causes desensitisation or refractoriness: receptor become less sensitive to the agonist, e.g. beta adrenergic agonist and levodopa causes:

i. Masking or internalisation of the receptors
ii. Decreased synthesis or increased destruction of the receptors (down regulation). Tyrosine kinase receptors.

3.6.7Ligand gated G-protein coupled Enzymatic Nuclear Location Membrane Intracellular Effector Ion Channel, Ion Channel or enzyme Gene coupling Direct G-protein Direct via DNA, example: Nicotinic, Muscarinic, Insulin Steroid and hormone.

3.6.8G-protein coupled receptors: Membrane bound, which are coupled to effector system through GTP binding proteins called as G-proteins bound to inner face of plasma membrane (2nd messenger)

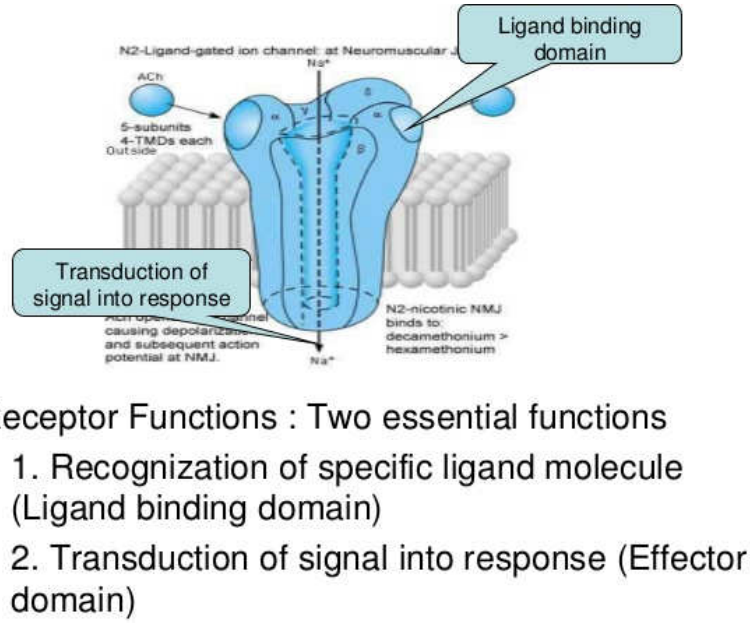

Figure23: Receptor Function

3.7 Function of Receptors

i. To Regulate signals from outside the cell to inside the effector cell – signals not permeable to cell membrane.
ii. To amplify the signal.
iii. To integrate various intracellular and extracellular signals
iv. To adapt to short term and long-term changes and maintain homeostasis.

3.8 Agonists and Antagonists

3.8.1 Agonists: are drugs that activate a receptor producing response. An agonist can be defined as a ligand, the binding of which to a receptor protein produces a conformational change necessary to initiate a signal that is coupled to a biological response. When all available receptors are occupied, a maximal response in produced. Example of such receptor systems include:

i. adrenergic (agonist – salbutamol, antagonist – atenolol)
ii. dopaminergic (agonist – dopamine, antagonist – haloperidol)
iii. cholinergic (agonist – bethanechol, antagonist – atropine)

Agonist: Both the high affinity as well as intrinsic activity (IA=1). ***These drugs trigger the maximal biological response or mimic effect of the endogenous substance***. e.g.: - Methacholine is a cholinomimetics drug which mimics the effect of Ach on cholinergic receptors.

Types of agonism:

i. **Summation: -** Two drugs eliciting same response, but with different mechanism and their combined effect is equal to their summation. (1+1=2) Aspirin inhibit Prostaglandin = analgesic +, Codeine stimulate Opioids receptor = Analgesic+ + +.

ii. **Additive:** combined effect of two drugs acting by same mechanism Aspirin PG Analgesic+ Analgesic+. Together analgesic effect is + +.

iii. **Synergism (Supra additive): -** (1+1=3) the combined effect of two drug effect is higher than either individual effect e.g. Sulfamethoxazole+ Trimethoprim, Levodopa + Carbidopa.

iv. **Partial agonist**: Some ligands have properties intermediate between agonist and antagonists and are known as 'partial agonist'. Example: Pindolol, Pentazocine.
They are unable to produce a maximal signalling effect even when all available receptors are occupied. However, partial agonists also block receptor sites that could potentially be occupied by the full agonist and this competition for receptors means that, in some circumstances, partial agonists may also appear to be the full agonist when they bind to a receptor and are known as 'inverse agonists.

V. **Inverse agonist:** These have full affinity towards the receptor but intrinsic activity is zero to -1 i.e., produces effect is just opposite to that of agonist. e.g.: - ß-Carboline is inverse agonist for Benzodiazepines receptors

3.8.2 An antagonist: is a ligand that binds to a receptor but (that block receptor does not produce the conformational change that initiates an intracellular signal. Occupation of the receptors by an antagonist prevents the binding of any other ligand and so 'antagonises' the biological response to the agonist.

Antagonism: Effect of two drugs is less than sum of the effects of the individual drugs.

i. Chemical antagonism e.g.: -heparin (-ve) protamine +ve, Chelating agents
ii. Physiological /Functional antagonism
iii. Pharmacokinetic antagonism
iv. Pharmacological antagonism (Competitive (Reversible)/Non-competitive (Irreversible)

Pharmacokinetic antagonism

One drug affects the absorption, metabolism or excretion of other drug and reduce

their effect. e.g. Warfarin in presence of phenobarbitone, warfarin metabolism is increased, its effect is reduced.

Pharmacological antagonism
Pharmacodynamic antagonism between two drugs acting at same receptors. Two important mechanisms according to which these antagonist, Reversible antagonism (Competitive antagonism) and Irreversible Antagonism (Non)

Reversible antagonism (Competitive antagonism): These inhibitions are commonly observed with antagonists that bind reversibly to the same receptor site as that of an agonist. These type inhibitions can be overcome increasing the concentration of agonist e.g. Atropine is a competitive antagonist of Ach.

Irreversible Antagonism: It occurs when the antagonist dissociates very slow or not at all from the receptors result that no change when the agonist applied. Antagonist effect cannot be overcome even after increasing the concentration of agonism.

For a drug to produce a physiologic effect it must first bind to a receptor. Two factors, related to the chemical nature of a drug, determine the interaction of drugs with receptors and hence the effect a drug will have on physiologic processes.

Affinity is a measure of the tightness with which a drug binds to the receptor.

Intrinsic activity is a measure of the ability of a drug that is bound to the receptor to generate an activating stimulus and produce a change in cellular activity.

Both agonists and antagonists can bind to a receptor. However, only agonist molecules can activate the receptor.

Partial agonists can occupy receptors but cannot elicit a maximal response. Such drugs have an intrinsic activity of 1 (Fig. 1.3; drug C). antagonists bind to the receptor but do not initiate a response; that is, they block the action of an agonist or endogenous substance that works through the receptor.

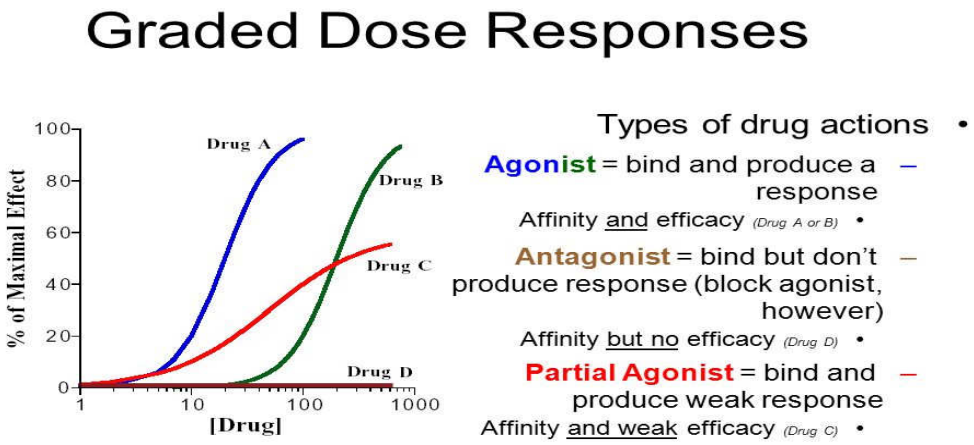

Figure 24: Graded dose–response curves for two agonists (A and B) and a partial agonist (C).(@ Pharmacodynamics (RousselPharmacology\ memorangapp.com).

i. **Competitive antagonists** combine with the same site on the receptor but their binding does not activate the receptor (i.e., their intrinsic activity 5 0) so they have no efficacy per se but may cause a pharmacological response in some cases by inhibiting the actions of endogenous substances or other drugs. Competitive antagonists may be reversible or irreversible. Reversible, or equilibrium, competitive antagonists are not covalently bound, shift the dose–response curve for the agonist to the right, and increase the ED50; that is, more agonist is required to elicit a response in the presence of the antagonist (Fig. 1.4). Because higher doses of agonist can overcome the inhibition, the maximal response can still be obtained.

ii. **Non-competitive antagonists** bind to the receptor at a site other than the agonist binding site (Fig. 1.5) and either prevent the agonist from binding correctly or prevent it from activating the receptor. Consequently, the effective amount of receptor is reduced. Receptors unoccupied by antagonist retain the same affinity for agonist, and the ED50 is unchanged.

3.9 Graded Dose–Response Curve

This expresses an individual's response to increasing doses of a given drug. The magnitude of a pharmacologic response is proportional to the number of receptors with which a drug effectively interacts (Fig. 2). The graded dose–response curve includes the following parameters:

i.Magnitude of response is graded; that is, it continuously increases with the dose up to the maximal capacity of the system, and it is

often depicted as a function of the logarithm of the dose administered (to see the relationship over a wide range of doses).

ii. ED50 is the dose that produces the half-maximal response; the threshold dose is that which produces the first noticeable effect.

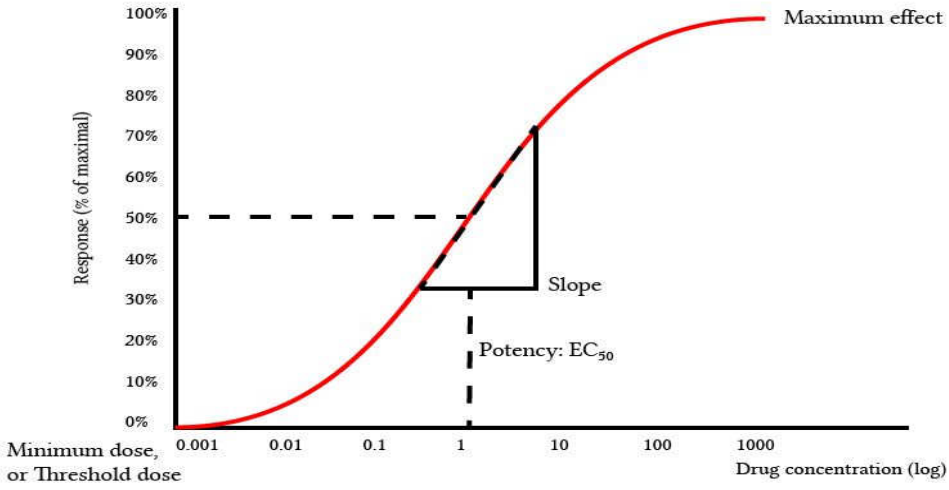

Figure 255: Graded dose -response(@ Pharmacodynamics (Roussel Pharmacology .memorangapp.com).

Intrinsic activity is the ability of a drug once bound to activate the receptor. A. Agonists are drugs capable of binding to, and activating, a receptor. (1) Full agonists occupy receptors to cause maximal activation; intrinsic activity.

3.9.1 Dose-Response Relationship

Drug administered – 2 components of dose- response – Dose-plasma concentration – Plasma concentration (dose)-response relationship E is expressed as Emax X [D] Kd + [D] E is observed effect of drug dose [D], Emax = maximum response, KD = dissociation constant of drug receptor complex at which half maximal response is produced E max

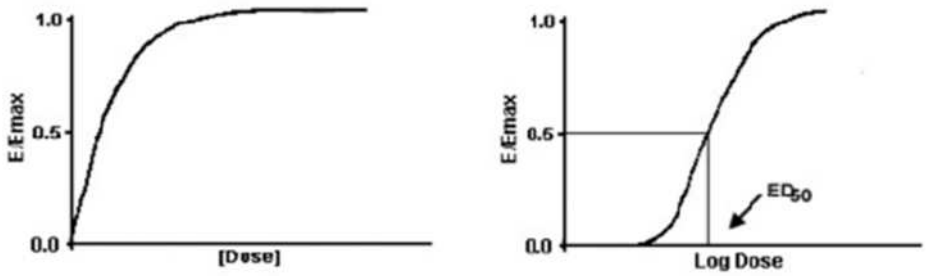

Figure 26: The dose which 50% of the maximal effect is observed is referred to as the ED50. ***((@*** Pharmacodynamics (Roussel

Pharmacology .memorangapp.com).
Dose-Response Curve, Log-dose %response, %response 100% - 50% - 100% - 50% - E = Emax X [D] Kd + [D]

3.9.2 Dose-response curve: Clinical Applications

When the relation between drug dose (X-axis) and drug response (Y-axis) is plotted on a linear scale, the resulting curve is usually hyperbolic. Clinical responses that might be plotted in this way include change in heart rate, blood pressure, gastric pH or blood glucose. Non-clinical (biochemical) responses can also be plotted in this way including enzyme activity, accumulation of an intracellular second messenger, membrane potential, secretion of a hormone, or contraction of a muscle.
If the drug dose is plotted on a base 10 logarithmic scale, this produces a sigmoidal dose-response curve. This representation is more useful because it expands the dose scale in the region where drug response is changing rapidly and compresses the scale at higher doses where large changes have little effect on response. Note that, in reality, it is ligand concentration (and resulting receptor occupation) that affects response - the term 'dose-response curve' assumes that the drug dose and ligand concentration are closely linked

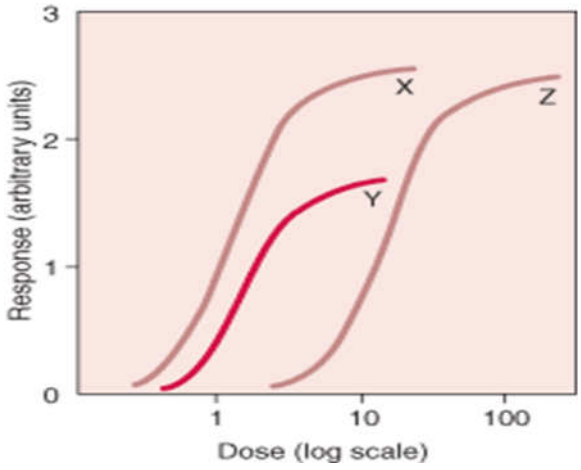

Figure 27*: Treatment comparison of dose response relationship(@* Pharmacodynamics (Roussel Pharmacology .memorangapp.com).

Drug X has greater biologic activity per dosing equivalent and is thus more potent than drug Y or Z. Drugs X and Z have equal efficacy, indicated by their maximal attainable response (ceiling effect). Drug Y is more potent than drug Z, but its maximal efficacy is lower.

3.9.3 Dose-Response Curve - Advantages:

i. Stimuli can be graded by Fractional change in stimulus intensity
ii. A wide range of drug doses can easily be displayed on a graph

iii. Potency and efficacy can be compared
iv. Comparison of study of agonists and antagonists become easier

3.10 Potency and Efficacy

3.10.1 Potency of a drug is the relative measure of the amount of a drug required to produce a specified level of response (e.g., 50%) compared with other drugs that produce the same effect via the same receptor mechanism. The potency of a drug is determined by the affinity of a drug for its receptor and the amount of administered drug that reaches thereceptor.

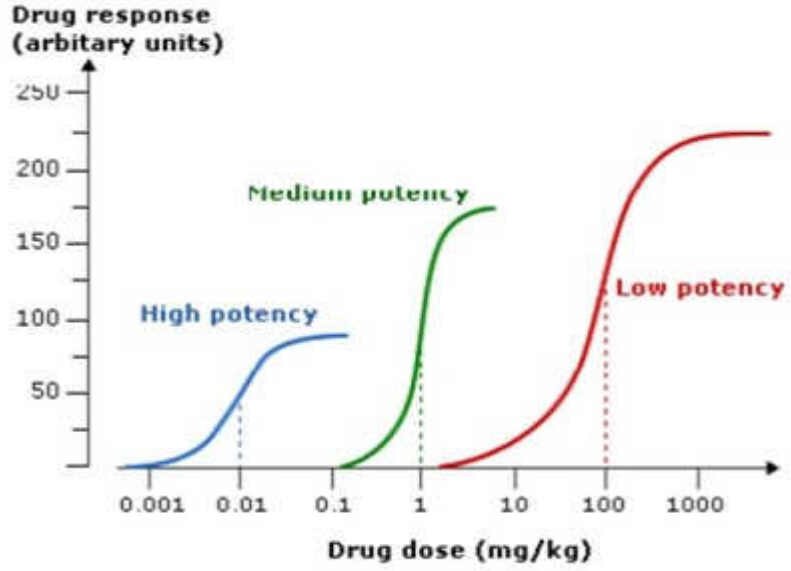

Figure28: Dose response curves for drugs with high, medium and low potency acting on the same target. Note that the drug with the highest potency has the lowest efficacy and vice versa. (@Pharmacodynamics | Pharmacology ...pharmacologyeducation.org).

3.10.2 Efficacy

Efficacy is the term used to describe the extent to which a drug can produce a response when all available receptors or binding sites are occupied (i.e. Emax on the dose–response curve). When comparing drugs acting at the same receptor, a full agonist will have the greatest efficacy and can produce the maximum response of which the receptor is capable. A partial agonist at the same receptor, by definition, will have a lower efficacy, even when all receptor sites are occupied. The concept of efficacy is not restricted to comparing the effects of drugs that act at the same receptor. The term therapeutic efficacy is used to describe the comparison of drugs that produce the same therapeutic effects on a biological system but do so via different pharmacological mechanisms (e.g. loop and thiazide diuretics, proton pump inhibitors and H2-antagonists). Potency is a term used to describe the amount of a drug

required for a given response. More potent drugs produce biological effects at lower doses (or concentrations), which means that they have a lower ED50 (Fig)

The potency of a drug is related to its affinity for the receptor (i.e. how readily the drug-receptor complex is formed). Less potent drugs can have an efficacy similar to that of a more potent one; the difference in potency can be readily overcome by giving the less potent drug in higher doses. This is illustrated by the varying recommended dose ranges of drugs acting at the same drug target (e.g. H2 antagonists, ACE inhibitors).

When choosing between drugs with a similar beneficial effect (e.g. analgesia) from a group of similar drugs it might seem logical to choose the one with the greatest therapeutic efficacy. However, in some cases the most efficacious drug may be less favourable because the same mechanism of action that leads to clinical benefits may also be responsible for causing dose-limiting adverse-effects (e.g. opioids, β1-adrenoceptor blocking drugs). When the same action leads to both beneficial and adverse effects, the latter can be minimised by carefully increasing (titrating) the dose. However, some drugs have a steeper dose–response curve, which makes it more difficult to titrate to the dose that is effective but avoids adverse effects.

The potency of a drug is rarely a reason for choosing one out of a collection of drugs with similar beneficial therapeutic effects. This is because any differences in potency can be overcome simply by giving higher doses. Although differences in relative potency can be overcome by altered dosage, it should be remembered that most of the adverse effects of drugs are also dose-related. Potency may be relevant if these occur by a mechanism other than the receptor–ligand interaction that mediates the beneficial effect (because only the more potent drug will be active at concentrations that avoid unwanted adverse effects).

For these reasons greater potency or efficacy does not necessarily mean that one drug is preferable to another. When judging the relative merits of drugs for a patient, prescribers should also consider other important factors, such as the overall adverse effect profile, therapeutic index, ease of administration for the patient, duration of effect (i.e. the number of doses needed each day) and cost.

Dose: It is the required amount of drug in weight, volumes, moles or IU to provide a desired effect. In clinical it is called as Therapeutic dose; in experimental purpose it is called as effective dose.

The therapeutic dose varies from person to person. For example,

Single dose of;

1. Piperazine (4-5g) is sufficient to eradicate round worm.
2. Single IM dose of 250mg of ceftriaxone to treat gonorrohoea.

Daily dose: It is the quantity of a drug to be administered in 24hr, all at once or equally divided dose. For example;

1.10mg of cetirizine (all at once) is sufficient to relive allergic reactions.
2. Erythromycin is 1g per day to be given in 4 equally divided dose (i.e.250mg every 6 hr.).

Total dose: It is the maximum quantity of the drug that is needed to complete course of the therapy e.g. procaine penicillin in early syphilis is 6 million units, given as 0.6 million units per day for 10days.

Loading dose: - It is the large dose of drug to be given initially to provide the effective plasma concentration rapidly. The drugs having high Vd of distribution. Chloroquine in Malaria – 600 mg Stat 300mg after 8 hours 300 mg after 2 day

Maintenance dose: Loading dose normally followed by maintenance dose. Needed to maintain the steady state plasma concentration attained after giving the loading dose.

MAXIMAL DRUG RESPONSES AND SPARE RECEPTORS

3.11Therapeutic window

Therapeutic window: Optimal therapeutic range of plasma concentrations at which most of the patients experience the desired effect. It is also called Therapeutic range. It is the gap between Sub optimal drug level and Toxic drug level.

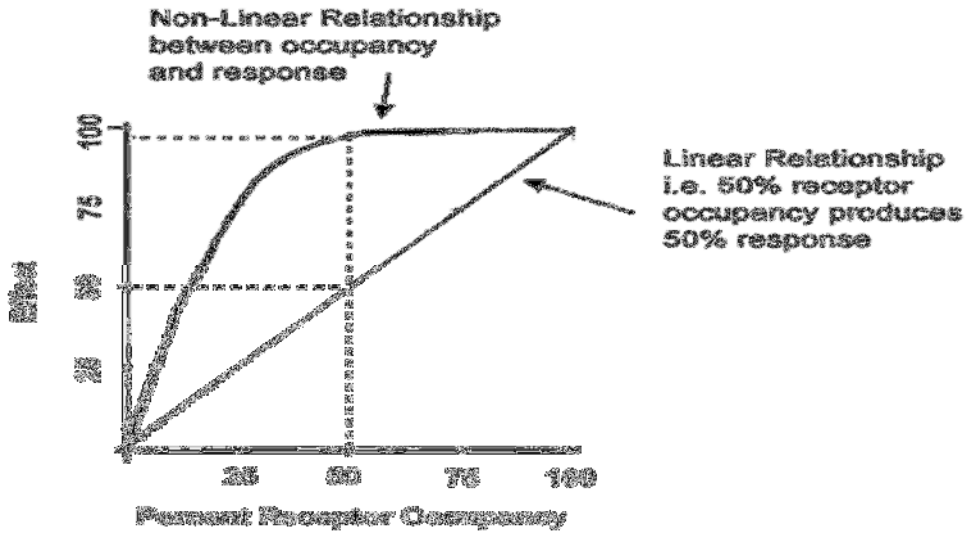

Figure 29: Dose-response relationships are a common way to portray data in both basic and clinical science (@ CONTENT uky.edu).

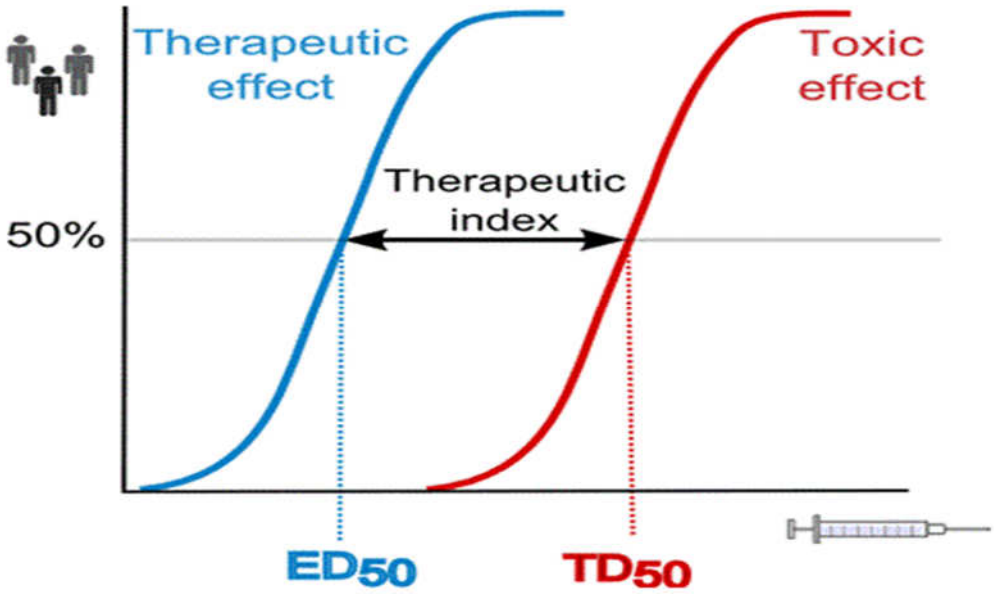

Figure30: Therapeutic window(@ pharmacologyeducation.org) [TUSOM .tmedweb.tulane.edu).

3.11.1 Therapeutic index: Margin of safety

Depend upon factor of dose producing desirable effect and dose eliciting toxic effect.

Therapeutic Index = TD50 or LD50
ED50

TI - should be more than one

Table 28: Example of drugs with narrow therapeutic Window

Drug	Therapeutic Range
Cyclosporine	100-400ng/ml
Carbamazepine	4-10µg/ml
Digoxin	0.8-2ng/ml
Lithium	0.8-1.4 mEq/L
Phenytoin	10-20µg/ml
Quinidine	2-6µg/ml

3.12 Factors Modifying the Effects of Drugs In Man

Individuals differ both in the degree and the character of the response that a drug may elicit. The aeration in response to the same dose of a drug between different patients and even in the same patient on different occasions.

One or more of the following categories of differences among individuals are responsible for the variations in drug response: Individuals differ in pharmacokinetic handling of drug, Variation in number or state of receptors, coupling proteins or other components of response and Variation in neurogenic/ hormonal tone or concentrations of specific constituents.

These factors modify drug action either

i. **Quantitatively:** The plasma concentration and / or the drug action is increased or decreased or
ii. **Qualitatively**: The type of response is altered, e.g. drug allergy and idiosyncrasy.

The various factors are:

i. **Body weight/size:** It influences the concentration of drug attained at the site of action. The average adult dose refers to individuals of medium built. For exceptionally obese or lean individuals and for children dose may be calculated on body weight basis

Individual dose = $\frac{\text{BW (Kg)}}{70}$ X adult Average dose

Individual dose = $\frac{\text{BSA (m2)}}{1.7}$ X adult Average dose

BSA= $\frac{\text{BW (Kg)}^{0.425} \times \text{Height (cm)}^{0.725}}{0.007184}$

ii.**Age**: Infants and Children: The dose of drug for children is often calculated from the adult dose

Child dose = $\frac{\text{Age}}{12+\text{Age}}$ X adult dose ……. (Young' formula)

Child dose = $\frac{\text{Age x adult dose}}{20}$ ..... (Dilling' formula).

However, infants and children have important physiological differences
Higher proportion of water
Lower plasma protein levels
More available drug

iii.Immature liver/kidneys

Liver often metabolises more slowly
Kidneys may excrete more slowly

iv.Age: Elders: In the elderly

renal function progressively declines (intact nephron loss) and drug doses have to be reduced in Chronic disease states, decreased plasma protein binding, Slower metabolism, Slower excretion, Dietary deficiencies, Use of multiple medications and Lack of compliance

v.Sex: Females have smaller body size, and so require doses of drugs on the lower side of the dose range. They should not be given uterine stimulants during menstruation, quinine during pregnancy and sedatives during lactation.

vi.**Pregnancy:** Profound physiological changes which may affect drug responses:
GI motility reduced –delayed absorption of orally administered drugs
Plasma and ECF volume expand
Albumin level falls
Renal blood flow increases markedly
Hepatic microsomal enzyme induction

vii.**Food:** Delays gastric emptying, delays absorption (ampicillin) and Calcium in milk interferes with absorption of tetracycline and iron by chelation.
Protein malnutrition may result in
Loss of BW
Reduced hepatic metabolising capacity
Hypoproteinaemia

viii. **Species and race:** Rabbits resistant to atropine
Rat & mice are resistant to digitalis
In humans: blacks require higher Mongols require lower concentrations of atropine and ephedrine to dilate their pupil

ix. **Route of drug administration:**
I.V route dose smaller than oral route - Magnesium sulfate:
Orally –purgative
Parenterally –sedative
Locally –reduces inflammation.

x. **Biorhythm:** (Chronopharmacolgy)
Hypnotics –taken at night
Corticosteroid –taken at a single morning dose

xi. **Psychological state:** Efficacy of drugs can be affected by patients' beliefs, attitudes and expectations ′ particularly applicable to centrally acting drugs ′ in some patients' inert drugs - (placebo) may produce beneficial effects equivalent to the drug, and may induce sleep in insomnia.

xii. **Presence of diseases/pathological states:** Drug may aggravate underlying pathology
Hepatic disease may slow drug metabolism
Renal disease may slow drug elimination
Acid/base abnormalities may change drug absorption or elimination
Severe shock with vasoconstriction delays absorption of drugs from S.C. or i.m
Drug metabolism in hyperthyroidism is enhanced where as in hypothyroidism, it is diminished.

xiii. **Cumulation:** Any drug will cumulate in the body if rate of administration is more than the rate of elimination e.g.: digitalis, heavy metals etc.

xiv. **Genetic factors:**
Lack of specific enzymes
Lower metabolic rate
- Acetylation
- Plasma cholinesterase (Atypical pseudo cholinesterase)
- G-6PD Glucuronide conjugation

xv. **Tolerance:** It means requirement of a higher dose of the drug to produce an effect, which is ordinarily produced by normal therapeutic dose of the drug. Usually seen with alcohol, morphine,

barbiturates, CNS active drugs. Drug tolerance may be: Natural, Acquired, Cross tolerance, Tachyphylaxis (ephedrine, tyramine, nicotine) or Drug resistance

Reverse tolerance: Same amount of drug produces increase pharmacological response. Cocaine, amphetamine, rats- increase motor activity

Acquired tolerances: Occurs due to repeated use of drug under 3 processes Pharmacokinetic tolerances, Pharmacodynamics tolerance and Acute tolerance

Pharmacokinetic tolerances: Repetitive administration causes decrease absorption or increase metabolism e.g. Alcohol decrease Absorption of Barbiturates increases its own metabolism

Pharmacodynamics tolerance

i. Down regulation of receptors
ii. Impairment in signal transduction
iii. Example: Morphine, caffeine, nicotine.

Acute tolerance: Tachyphylaxis: Acute development of tolerance after a rapid and repeated administration of a drug in shorter intervals Example; Ephedrine, tyramine. Monday disease. - Nitro glycerine taken on Monday, by Tuesday workers get headache, after they get tolerances. After holiday (Sunday) they get again headache.

Cross tolerances: Cross tolerance among drugs belonging to same category. Morphine, Heroin and Narcotic etc.

3.13 Other Effects of Drugs in Man: By interactions in many ways:

Alterations in receptors responsiveness

In the short term, most receptor-mediated responses are altered by changing the local concentration of agonist around the receptors. It is now recognised that, in the longer term, it is possible for changes to occur in the response of the tissue to a given concentration of agonist which can be attributed to altered receptor function. These changes (loosely termed ‘up-regulation’ and ‘down-regulation’) may involve alterations in receptor numbers on the cell surface or in the coupling of receptor occupation to the intracellular response. Down-regulations is usually seen in response to chronic receptor over stimulation as a result of long-term administration of a drug (exogenous agonist) or in a disease process (endogenous

agonist). In some cases, this can occur quickly, leading to the phenomenon of tachyphylaxis, in which repeated administration of a drug is associated with rapidly diminishing efficacy. Adaptive down-regulations is a potential disadvantage of developing partial agonist drugs for therapeutic use-the full receptor occupancy required for a response makes down – regulation more likely.

In Parkinson's disease, the term on-off phenomenon is used to describe the rapid swing form mobility to immobility that occurs some hours after administration of L-dopa. It has been attributed to down-regulation of dopaminergic receptors in the brain following prolonged treatment with L-dopa. Which renders the extrapyramidal pathways usually sensitive to the falling concentrations of dopamine.

In patients will pheochromocytoma with high endogenous catecholamine concentrations, receptor numbers are down-regulated, leading to a relative insensitivity to catecholamine.

In automatic neuropathy, receptor up-regulation renders the cardiovascular system hypersensitive and exaggerated responses to catecholamine may occur.

3.14 Assaying Receptor Binding

Assays for receptors are designed to detect binding sites, not all of which are coupled to a signal. Most assays use radiolabelled ligand and measure the amount of radioactivity bound to cell membranes, whole cells or tissue sections fixed to a microscope slide. Nonspecific binding can be assessed by displacing the radiolabelled ligand by addition of large quantities of unlabelled ligand. This procedure exploits a fundamental property of receptor binding – that it is saturable, unlike nonspecific binding. Mathematical manipulation of the data allows the number of receptors and their affinities to be calculated; however, these calculations are often inaccurate when high-affinity and low-affinity binding sites are present, and is preferable to use a reiterative computer programmer to analyses the raw data.

In receptor autoradiography, images are obtained by exposing section of radiographic film after incubation and washing steps. Various image analysis programs allow Colour-coded pictures to be obtained after subtraction of the nonspecific image form the total binding. Another example of receptor up-regulation is the use of 3-bydroxy-3-methylglutaryl coenzyme A inhibitor to lower plasma cholesterol concentrations. These drugs inhibit the rate-limiting enzyme in the synthesis of cholesterol in hepatocytes, promoting increase and expression of receptors for low-density lipoprotein (LDL) particles. As a

consequence, the rate of uptake of cholesterol-laden LDL particles from the circulations is increase and the plasma cholesterol concentration is reduced. Sometimes, receptor responses are regulated by changes in the coupling of receptor occupation of intracellular signalling. Chronic β-adrenoceptor blockade potentialities the response of the adenylate cyclase-cAMP system and consequently up-regulates the response to other receptors that are linked to it.

3.14.1 Selectivity

Receptors are usually subtyped on the basis of their selectivity for agonist selectivity is determined by the ratio of EC_{50} at the two receptor subtypes. In the case of β-adrenoceptor, the concentration of noradrenaline (norepinephrine) required to cause Broncho dilatation (β_2) is ten times higher than that required to cause tachycardia (β_1); therefore, the selectivity of noradrenaline (norepinephrine) for β_1-receptors with respect to β_2-receptors is 10.

Antagonist selectivity is measured as the relative shift of the agonist dose-response curves achieved by a single dose of antagonists infecting responses mediated through the two receptors. For example, if the non-selective β-adrenoceptor agonist isoprenaline was used in the situation above, the concentration of atenolol achieved in the bloodstream after administration of a 50mg dose would shift the dose-response curve at the bronchus by only 10% of that at the heart, giving selectivity for β_1-receptors of 10. Thus, a ten times greater concentration of atenolol is required to produce a shift in the agonist response curve for the lung equal to that for the heart.

It must be remembered that selectivity for a receptor subtype is only a relative concept and does not equate with specificity. Drugs with selectivity for one receptor subtypes can produce a maximum effect at other subtypes if enough is given. This is particularly important if the beneficial effects are activated by one receptor subtypes and the unwanted effects by another; for example, atenolol is considered a β_1-selective adreno receptor antagonist but has some effects but has some effects at β_2-receptors, and is therefore absolutely contraindicated in asthmatic patients in whom any reduction in β_2-mediated bronchodilator may be dangerous. Selectivity is useful in clinical practice only when the ratio of the impact of the drug at the two receptor sites is 100 or more. When selectivity is lower, it is difficult to predict drug doses that will exploit the difference in subtype's activity. Selectivity is most likely to be achieved at the lowest effective dose.

3.14.2 Practice points

Many drugs are used clinically at the top of their dose-response curve; thus, increasing the drug dose does not increase the response and may only expose the patient to a greater risk of side-effects – it may be possible to reduce a drug dose to prevent unwanted side-effects without a significant reduction in the response.

-Drugs that are partial agonists produce significant of a full agonist; in the presence of full agonist, the same drug used at the same dose may produce the opposite response because it competes for receptor binding with the more effective agonist.

i.-Receptor-medicated responses can adapt to chronic exposure to agonists or antagonists by down-regulation or up-regulations or receptor function

ii.-Selectivity of an agonist or antagonist between two receptors subtypes is only 'relative' and is manifest

3.11 Therapeutic window

Therapeutic window: Optimal therapeutic range of plasma concentrations at which most of the patients experience the desired effect. It is also called Therapeutic range. It is the gap between Sub optimal drug level and Toxic drug level in a narrow concentration range above which the drug is active at both receptors.

3.15 Drug Monitoring

Therapeutic drug monitoring is defined as the use of assay procedures for determination of drug concentrations in plasma, and the interpretation and application of the resulting concentration data to develop safe and effective drug regimens. If performed properly, this process allows for the achievement of therapeutic concentrations of a drug more rapidly and safely than can be attained with empiric dose changes. Together with observations of the drug's clinical effects, it should provide the safest approach to optimal drug therapy. The usefulness of plasma drug concentration data is based on the concept that pharmacologic response is closely related to drug concentration at the site of action. For certain drugs, studies in patients have provided information on the plasma concentration range that is safe and effective in treating specific diseases—the therapeutic range (Figure 1-7). Within this therapeutic range, the desired effects of the drug are observed. Below it, there is greater probability that the therapeutic benefits are not realized; above it, toxic effects may occur. No absolute boundaries divide sub-therapeutic, therapeutic, and toxic drug concentrations. A grey area usually exists for most drugs in which these

concentrations overlap due to variability in individual patient response. Numerous pharmacokinetic characteristics of a drug may result in variability in the plasma concentration achieved with a given dose when administered to various patients (Figure 1-8). This inter-patient variability is primarily attributed to one or more of the following:

i. Variations in drug absorption
ii. Variations in drug distribution
iii. Differences in an individual's ability to metabolize and eliminate the drug (e.g., genetics)
iv. Disease states (renal or hepatic insufficiency) or physiologic states (e.g., extremes of age, obesity) that alter drug absorption, distribution, or elimination
v. Drug interactions

Therapeutic monitoring using drug concentration data is valuable when:

i. A good correlation exists between the pharmacologic response and plasma concentration. Over at least a limited concentration range, the intensity of pharmacologic effects should increase with plasma concentration. This relationship allows us to predict pharmacologic effects with changing plasma drug concentrations (Figure 1-9).
ii. Wide inter-subject variation in plasma drug concentrations results from a given dose.
iii. The drug has a narrow therapeutic index (i.e., the therapeutic concentration is close to the toxic concentration).
iv. The drug's desired pharmacologic effects cannot be assessed readily by other simple means (e.g., blood pressure measurement for antihypertensive).

The value of therapeutic drug monitoring is limited in situations in which:

i. There is no well-defined therapeutic plasma concentration range.
ii. The formation of pharmacologically active metabolites of a drug complicates the application of plasma drug concentration data to clinical effect unless metabolite concentrations are also considered.
iii. Toxic effects may occur at unexpectedly low drug concentrations as well as at high concentrations.
iv. There are no significant consequences associated with too high or too low levels.

4.0 CONCLUSION

In this unit, you have learnt the description of the principles governing drug actions in humans and the principles of receptor theory, identifying different types of drug targets and their relevant use. The difference between potency and efficacy, drug agonist and antagonist and factors modifying drug action in man.

5.0 SUMMARY

Pharmacodynamics refers to the relationship between drug concentration at the site of action and the resulting effect, including the time course and intensity of therapeutic and adverse effects. The effect of a drug present at the site of action is determined by that drug's binding with a receptor. This can occur either extracellular, cellular or intracellular.

The expression of an individual's response to increasing doses of a given drug is known as graded dose response. The relative measure of the amount of a drug required to produce a specified level of response (e.g., 50%) compared with other drugs that produce the same effect via the same receptor mechanism is **called Potency of a drug**. The potency of a drug is determined by the affinity of a drug for its receptor and the amount of administered drug that reaches the site of action, whereas **efficacy** of a drug is the term used to describe the extent to which a drug can produce a response when all available receptors or binding sites are occupied (i.e. Emax on the dose–response curve).

Optimal therapeutic range of plasma concentrations at which most of the patients experience the desired effect is also called Therapeutic range (**Therapeutic window**). It is the gap between Sub optimal drug level and Toxic drug level.

Many factors can modify the effects of drugs in man. Individuals differ both in the degree and the character of the response that a drug may elicit. Therapeutic drug monitoring which is defined as the use of assay procedures for determination of drug concentrations in plasma. The interpretation and application of the resulting concentration data to develop safe and effective drug regimens.

SELF ASSESSED EXERCISES

i. List the various types of G- proteins.
ii. Discuss the concept of receptor regulatory theory in relation to drug interaction.

6.0 TUTOR- MARKED ASSIGNMENT

1. Main sites of drug actions (receptors, enzymes... etc.)
2. Elaborate, with examples, on your understanding of the following terms with respect to drug action (pharmacodynamics):

(a) Competitive vs. non-competitive antagonism
(b) Receptor selectivity vs. specificity
(c) Inhibition of carrier molecules

3. From your pharmacodynamics and drug-receptor interactions define: Efficacy, potency, therapeutic index, graded dose response, quantal dose-response, and spare receptors. Give examples and graphical representation whenever possible.
4. Briefly discuss the following pharmacological concepts, using examples where appropriate:

(a) Receptor down regulation
(b) Therapeutic index

5. Write about the factors modifying drug action.

7.0 REFERENCES/FURTHER READING

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UNIT 2 MODE OF ACTION OF ANTIMICROBIAL DRUGS

CONTENTS

1.0 INTRODUCTION

Antimicrobial compounds include antibacterial, antiviral, antifungal and antiprotozoal agents. Antimicrobial Chemotherapy Control or the destruction of microorganisms that reside within the bodies of humans & other animals is of tremendous importance. This unit introduces the principles of chemotherapy & discusses the ideal characteristics for successful chemotherapeutic agents. The course unit also presents characteristics of some commonly used antibacterial, antifungal, and antiviral drugs and mechanism of antimicrobial resistance and rational use of antibiotics.

2.0 OBJECTIVES

By the end of this unit, you will be able to:

- define terms use in antimicrobial chemotherapy
- state types and sources of antimicrobial chemotherapy
- identify the basic Mechanisms of action of antimicrobial
- explain the mechanisms of antimicrobial resistance
- give the strategies for Avoiding Resistance
- describe the rational use of antimicrobial chemotherapy

3.0 MAIN CONTENT

3.1 Definition of Terms

i. **Antimicrobial Drugs: The** word antimicrobial was derived from the Greek words anti (against), mikros (little) and bios (life) and refers to all agents that act against microbial organisms. This is not synonymous with antibiotics, a similar term derived from the Greek word anti (against) and biotikos (concerning life). An ANTIMICROBIAL is any substance of natural, semisynthetic or synthetic origin that kills or inhibits the growth of microorganisms but causes little or no damage to the host.

ii. **Antibiotics**: By definition, the word "antibiotic" refers to substances produced by microorganisms that act against another microorganism. An antibiotic is a low molecular substance produced by a microorganism that at a low concentration inhibits or kills other microorganisms.

iii. **Antibiotic Resistance: Antibiotic** Resistance is defined as micro-organisms that are not inhibited by usually achievable systemic concentration of an antimicrobial agent with normal dosage schedule and / or fall in the minimum inhibitory concentration (MIC)range. Antibiotic Resistance (DR) = MIC / MCC > Toxic Plasma Concentration

3.1 ANTIMICROBIALS

Different types of "antimicrobials" include all agents/drugs that act against all types of microorganisms:

i. Bacteria (Antibacterial) drugs
ii. Fungi (Antifungal) drugs
iii. Protozoa (Antiprotozoan) drugs
iv. Antihelminthic drugs
v. Viruses (antiviral) drugs.

3.1.1 **Sources of Antimicrobial Drugs:** Most modern antibiotics come from species of microorganisms that live in the soil. To commercially produce antibiotic:

vi. Select strain and grow in broth
vii. When maximum antibiotic concentration reached, extract from medium
viii. Purify
ix. Chemical alter to make it more stable

3.1.2 Features of Antimicrobial Drugs

i. **Selective Toxicity: Cause** greater harm to microorganisms than to host

ii. **Chemotherapeutic index:** lowest dose toxic to patient divided by dose typically used for therapy

iii. **Activity Against Bacteria:** Antimicrobial medications vary with respect to the range of microorganisms they kill or inhibit

iv. **Bacteriostatic:** inhibit growth of microorganisms; inhibit or delay bacterial growth and replication *(static drugs stop multiplication; body's immune system clears).* Examples of such include tetracyclines, Sulfonamides, and macrolides.

v. **Bactericidal:** Kill microorganisms hence preferred in immunocompromised patients e.g. of bactericidal drugs include aminoglycosides, cephalosporins, penicillins, and quinolones.

vi. **Spectrum of Activity**

Narrow-spectrum: Some kill only limited range. Narrow-spectrum antimicrobial Aminoglycosides and Sulfonamides are only effective against aerobic organisms, while nitroimidazoles are generally only effective for anaerobes.

Broad-spectrum: While others kill wide range of microorganisms. Broad-spectrum antimicrobial is active against both Gram-positive and Gram-negative organisms. Examples include: tetracyclines, phenicols, fluoroquinolones, "third-generation" and "fourth-generation" cephalosporins.

vii. **Effects of Combining Drugs:** Combinations are sometimes used to fight infections

Synergistic: action of one drug enhances the activity of another or *vice versa*. **Antagonistic:** activity of one drug interferes with the action of another.

viii. **Adverse Effects**

Allergic Reactions: some people develop hypersensitivities to antimicrobials

Toxic Effects: some antimicrobials are toxic at high concentrations or cause adverse effects

ix. **Suppression of normal flora**: when normal flora killed, other pathogens may be able to grow to high numbers

x. **Resistance to Antimicrobials:** Some microorganisms inherently resistant to effects of a particular drug. Other previously sensitive microorganisms can develop resistance through spontaneous mutations or acquisition of new genes (more later).

xi. **Concentration dependent:** Maximum kills depends on concentration achieved

- High doses as shorter infusions or lesser frequency are better
- Has post antibiotic effect Time dependent

- Maximum kills depending on time achieved
- Optimal doses as longer infusions or at higher frequency
- No post antibiotic effect. Minimum bactericidal concentration

3.3 Antibacterial Drugs

i. **Inhibit cell wall synthesis:** A drug that targets cell walls can therefore selectively kill or inhibit bacterial organisms. Examples: penicillin, cephalosporins, bacitracin and vancomycin**.**

ii. **Injury to plasma/Cell membrane:** Cell membranes are important barriers that segregate and regulate the intra- and extracellular flow of substances. A disruption or damage to this structure could result in leakage of important solutes essential for the cell's survival. Examples: polymixin B and colistin.

iii. **Inhibit protein synthesis:** Enzymes and cellular structures are primarily made of proteins. Several types of antibacterial agents target bacterial protein synthesis by binding to either the 30S or 50S subunits of the intracellular ribosomes. Examples: Aminoglycosides, macrolides, lincosamides, streptogramins, chloramphenicol and tetracyclines.

iv. **Inhibit nucleic acid synthesis:** Some antibiotics work by binding to components involved in the process of DNA or RNA synthesis, which causes interference of the normal cellular processes which will ultimately compromise bacterial multiplication and survival. Examples: quinolones, metronidazole, and rifampin.

v. **Inhibit synthesis of essential metabolites:** Other antibiotics act on selected cellular processes essential for the survival of the bacterial pathogens. For example, both Sulfonamides and trimethoprim disrupt the folic acid pathway, which is a necessary step for bacteria to produce precursors important for DNA synthesis. - Sulfonamides target and bind to dihydropteroate synthase, - trimethophrim inhibit dihydrofolate reductase; both of these enzymes are essential for the production of folic acid, a vitamin synthesised by bacteria, but not humans.

3. 3.1Antituberculosis (TB) drugs

Tuberculosis (TB) is an air-borne infectious disease caused by bacteria, which primarily affects the lungs. Infection with Mycobacterium tuberculosis begins when a susceptible person inhales airborne droplet nuclei containing viable organisms. Tubercle bacilli that reach the alveoli are ingested by alveolar macrophages. Infection follows if the inoculum escapes alveolar macrophage microbicidal activity.

Mycobacterium tuberculosis, the organism that causes tuberculosis infection and disease, infects an estimated 20 – 43% of the world's population with 3 million people worldwide die each year from the disease

TB is both preventable and curable.

Multi-drug resistant (MDR) TB is TB that is resistant to any of the first-line drugs, specifically Rifampicin and Isoniazid.

Tuberculosis

The World Health Organisation (WHO) declared TB a global emergency in 1993 and it remains one of the world's major causes of illness and death. Tuberculosis is one of the world's most widespread and deadly illnesses. More than 90% of new TB cases and deaths occur in developing countries.

Nigeria ranks 10th among the 22 high-burden TB countries in the world. WHO estimates that 210,000 new cases of all forms of TB occurred in the country in 2010, equivalent to 133/100,000 population? There were an estimated 320,000 prevalent cases of TB in 2010, equivalent to 199/100,000 cases.

Tuberculosis occurs disproportionately among disadvantaged populations such as the malnourished, homeless, and those living in overcrowded and sub – standard housing.

TB poses significant challenges to developing economies as it primarily affects people during their most productive years.

The proportion of TB patients tested for HIV was 79% in 2010, with a 25% TB-HIV co-infection rate. 59% of these patients were started on cotrimoxazole (CPT) prophylaxis and 1.8% provided with isoniazid (IPT) prophylaxis.

The proportion of TB/HIV co-infected patients on anti-retro viral (ARV) therapy was 33% in 2010.

The proportion of HIV cases that developed TB was 4% in 2010 and 3% in 2011.

Once infection is established, lymphatic and haematogenous dissemination of tuberculosis typically occurs before the development of an effective immune response. This stage of infection, primary tuberculosis is usually clinically and radiologically silent.
In most persons with intact cell – mediated immunity, T cells and macrophages surround the organisms in granulomas that limit their

multiplication and spread. The infection is contained but not eradicated, since viable organisms may lie dormant within granulomas for years to decades.

Tuberculosis
Symptoms and Signs: Malaise, Anorexia, Weight loss, Fever, Night sweats, Chronic cough, blood with sputum and Rarely, dyspnea.

3.3.2Mycobacterial Drugs

Mycobacteria are intrinsically resistant to most antibiotics. They grow slowly compared with other bacteria, antibiotics that are most active against growing cells are relatively ineffective. so, that's why we use combination of drugs. Mycobacterial cells can also be dormant and thus completely resistant to many drugs or killed only very slowly.
The lipid rich mycobacterial cell wall is impermeable to many agents (e.g. drugs).

Mycobacterial species are intracellular pathogens, and organisms residing within macrophages are inaccessible to drugs that penetrate these cells poorly.

Combinations of two or more drugs are required to overcome these obstacles and to prevent emergence of resistance during the course of therapy.

The response of mycobacterial infections to chemotherapy is slow, and treatment must be administered for months to years, depending on which drugs are used.

First-line drugs:

i. Rifampin,
ii. Isoniazid (INH),
iii. Pyrazinamide,
iv. Ethambutol, and
v. Streptomycin

These drugs are the first-line agents for the treatment of tuberculosis.
Isoniazid and Rifampin are the two most active drugs.

i. ISONIAZID (INH)

Isoniazid is the most active drug for the treatment of tuberculosis caused by susceptible strains. It is small (MW137) and freely soluble in water, with structural similarity to pyridoxine = (Vit.B6)
It is bactericidal for actively growing tubercle bacilli. It is less effective against atypical mycobacterial species.

Mechanism of Action: INH, a prodrug is activated by KatG enzyme, a mycobacterial catalase peroxidase enzyme. It penetrates into macrophages and is active against both extra- and intracellular organisms.

The activated form of isoniazid forms a covalent complex with an acyl carrier protein (AcpM) and KasA, a ß-ketoacyl carrier protein synthetase, which blocks mycolic acid (Mycolic acid, essential component of cell wall) synthesis and kills the cell.

USES: All infections caused tuberculosis, along with other antitubercular drug.

Dosage: 5mg/kg/day, usually up to 300mg/day per oral adults, or 900mg twice/week. INH is the primary drug used to treat latent TB, caseous disease, tuberculous meningitis, Pyridoxine 10 -20mg od will also be needed to prevent peripheral neuropathy

Adverse Reactions of INH: The incidence and severity of untoward reactions related to dosage and duration of administration.
Direct toxicity - Isoniazid induced hepatitis (most common major toxic effect). The risk of hepatitis is higher in alcoholics, pregnancy and postpartum period.

Peripheral neuropathy in 10-20% of patients given dosages greater than 5mg/kg/day but infrequently seen with the standard 300mg adult dose. It is more likely to occur in slow acetylators and patients with malnutrition, alcoholism, diabetes and AIDS. Neuropathy is due to relative deficiency of pyridoxine.

CNS toxicity, which is less common includes. Optic neuritis or atrophy, Various mental disturbances (memory loss, psychosis), dizziness, ataxia and seizures.

Immunologic reactions - Fever, Skin rashes and drug induced systemic erythematous.

Miscellaneous adverse effects - Provocation of pyridoxine deficiency anaemia, tinnitus and gastrointestinal discomfort.

Drug interactions- isoniazid can reduce the metabolism of **phenytoin**.

i.RIFAMPIN

Rifampin is a semisynthetic derivative of rifamycin, an antibiotic produced by *Streptomyces Mediterranean.* It is active in vitro against gram positive and gram-negative cocci, some enteric bacteria, mycobacteria and chlamydia.

Mechanism of Action

Rifampin acts by binds to the**β subunit of bacterial DNA–dependent RNA polymerase** and thereby **inhibits RNA synthesis in bacteria** but not mammalian cells. Human RNA polymerase does not bind torifampin and is not inhibited by it. Rifampin is bactericidal for mycobacteria. It readily penetrates most tissues and phagocytic cells.

Resistance results from any one of several possible point mutations in rpoB, the gene for the β subunit of RNA polymerase. These mutations result in reduced binding of rifampin to RNA polymerase.

USES: It can kill organisms that are poorly accessible to many other drugs, such as intracellular organisms and those sequestered in abscesses and lung cavities.

Mycobacterial infections: Rifampin 10mg/kg/day (usually600mg/day), orally must be administered with isoniazid or other ant tuberculosis drugs to patients with active tuberculosis to prevent emergence of drug resistant mycobacteria.

Atypical mycobacterial infections and Leprosy. In these two conditions rifampin 600mg daily or twice weekly for 6 months is effective in combination with other agents.

As alternative of isoniazid in prophylaxis of latent tuberculosis 600mg/day as a single agent for 4 months, in patients with isoniazid-resistance or rifampin-susceptible bacilli.

In exposure to a case of active tuberculosis caused by an isoniazid resistant, rifampin susceptible strain.

To eliminate meningococcal carriage,600mg, twice daily, for 2 days.
To eradicate staphylococcal carriage with combination to another agent.
Osteomyelitis and prosthetic valve endocarditis caused by staphylococci in combination therapy with another agent.

Adverse effects: Rifampin imparts a harmless ***Pink to frank red (blood – like)*** colour to urine, sweat, tears and contact lenses.

Less common adverse effects include ***facial flushing, itching, rashes or eye*** irritations can occur 2 -3 hours after a dose.

Cholestatic jaundice

Flu –like syndrome at high doses characterised by fever, chills, myalgias, anaemias, thrombocytopenia and acute tubular necrosis

Hepatitis: Liver damage and death

Nephritis: Acute renal failure

Drug interactions: Rifampin strongly induces most cytochrome p450 isoforms (3A4,2C9,2D6,2C19,1A2).Anticoagulants, cyclosporine, anticonvulsants, contraceptives, methadone, protease inhibitors, non-nucleoside reverse transcriptase inhibitors. Administration of rifampin results in significantly lower serum levels of these drugs.

NB

HIV patients, Women on contraceptives and warfarin requiring rifampicin, alternative treatment should be sort

ii. **Ethambutol**

Mechanism of action: It is bacteriostatic to mycobacteria by an unknown mechanism. However, it is believed to inhibit mycobacterial arabinosyl transferases. Arabinosyl transferases are involved in the polymerization reaction of arabinoglycan, an essential component of the mycobacterial cell wall.

Its action on the bacterial cell wall integrity may be related to its action as a chelating agent, by inactivation of bacterial zinc and copper.

Resistance to ethambutol is due to mutations resulting in overexpression of emb gene products or within the emb B structural gene. This resistance to ethambutol emerges rapidly when used alone, therefore it is always given with other antitubercular agents.

Uses:Tuberculosis: Ethambutol hydrochloride 15-25mg/kg/d is usually given as a single daily dose in combination with isoniazid or rifampin.

Adverse effects: Retrobulbar (optic) neuritis resulting in loss of visual acuity and ocular scotoma or Colour (red green colour blindness).

Usually occur at doses of 25mg/kg/day continued for several months.

Precaution & contraindication: Periodic visual acuity testing is desirable if the 25mg/kg/day dosage is used. It is relatively contraindicated in children too young to permit assessment of visual acuity and red green colour discrimination.

iii. Pyrazinamide (PZA)

Pyrazinamide (PZA) is a relative of nicotinamide, stable and slightly soluble in water.

It is inactive at neutral PH, But at PH 5.5 it inhibits tubercle bacilli, and some other mycobacteria at concentrations of approximately 20mcg/ml.

Mechanism of Action: The drug target and mechanism of action are unknown. The drug is taken up by macrophages and exerts its activity against mycobacteria residing within the acidic environment of lysosomes. Pyrazinamide is converted to pyrazinoic acid, the active form of the drug, by microbial pyrazinamide, which is encoded by pncA.

Resistance may be due to impaired uptake of pyrazinamide or mutations in pncA that impair conversion of pyrazinamide to its active form.

Uses: Pyrazinamide is an important front-line drug used in conjunction with isoniazid & rifampin in short course (i.e. 6 months) regimens as a sterilizing agentactive against residual intracellular organisms that may cause relapse.

Adverse Effects: Hepatotoxicity (in 1-5% of patients-major adverse effect).

Hyperuricemia (it may provoke acute gouty arthritis).

Nausea, vomiting, & drug fever.

iv.Streptomycin

Streptomycin was isolated from a strain of *Streptomyces griseus.*

Mechanism of action: Like all aminoglycosides, streptomycin irreversibly inhibits bacterial protein synthesis. Protein synthesis is inhibited in at least three ways; interference with the initiation complex of peptide formation, misreading of mRNA, which causes incorporation of incorrect amino acids into the peptide, resulting in a non-functional or toxic protein and breakup of polysomes into non-functional monosomes.

Streptomycin penetrates into cells poorly and is active mainly against extracellular tubercle bacilli. Streptomycin crosses the blood brain barrier and achieves therapeutic concentrations with inflamed meninges.

Mechanism of resistance:

- Production of a transferase enzyme or enzymes inactivates the aminoglycosides by acetylation, adenylation or phosphorylation (major action).
- Impaired entry of drug into the cell.
- The receptor protein on the 30s ribosomal subunit may be deleted or altered as a result of mutation.

Uses: Tuberculosis: Streptomycin is used when an injectable drug is needed, principally in individuals with severe, possibly life-threatening forms of tuberculosis e.g., meningitis and disseminated disease.

Adverse Effects: Ototoxicity and Nephrotoxicity are common. Toxicity is dose related and the risk is increased in elderly

Alternative Second-Line Drugs for Tuberculosis

v. **ETHIONAMIDE**

Ethionamide is chemically related to isoniazid. It is poorly water soluble and available only in oral form.

Mechanism of action: Ethionamide blocks synthesis of mycolic acids in susceptible organisms.

Adverse effects: Intense gastric irritation, Neurologic symptoms and Hepatotoxicity. Neurologic symptoms may be alleviated by pyridoxine.

vi. **CAPREOMYCIN**

Capreomycin is an antibiotic from streptomyces capreolus

Mechanism of action: It is a peptide protein synthesis inhibitor. Capreomycin is an important agent for the treatment of drug resistant tuberculosis.
Strains of M tuberculosis that are resistant to streptomycin or amikacin usually susceptible to capreomycin

Adverse drug reactions: Nephrotoxicity, Ototoxicity – tinnitus, deafness, vestibular disturbance may occur and Local pain & sterile abscesses due to injection.

i. CYCLOSERINE

ii. **Cycloserine** is an antibiotic produced by streptomyces orchidaceous, a structural analogy of D- alanine.

iii. **Mechanism of action:** It inhibits the incorporation of D- alanine into peptidoglycan pentapeptide by inhibiting alanine racemase, which converts L-alanine to D- alanine, and D- alanyl-D –alanine ligase (finally inhibits mycobacterial cell wall synthesis).

iv. **Uses:** Cycloserine used exclusively to treat tuberculosis caused by mycobacterium tuberculosis resistant to first line agents

v. **Adverse effects:** CNS dysfunction, including depression and psychotic reactions (Peripheral neuropathy, Seizures, and Tremors etc.).
Pyridoxine 150mg/day should be given with Cycloserine because this ameliorates neurologic toxicity.

vi. **Amino salicylic acid (PAS):** Amino salicylic acid is a folate synthesis antagonist that is active almost exclusively against mycobacterium tuberculosis. It is structurally similar to p-aminobenzoic acid (PABA) and the Sulfonamides.

vii. **Adverse effects:**Peptic ulcer and gastric Hemorrhage. Hypersensitivity reactions (manifested by fever, joint pain, hepatosplenomegaly, hepatitis, granulocytopenia, adenopathy) often occur after 3-8 weeks of amino salicylic acid therapy.

viii. **Fluoroquinolones:** (Ciprofloxacin, Levofloxacin, Gemifloxacin, moxifloxacin) can inhibit strains M tuberculosis. The eye are also active against atypical mycobacteria.
Moxifloxacin is the most active against M tuberculosis.
Fluoroquinolones are an important addition to the drugs available for tuberculosis, especially for strains that are resistant to first line agents.

ix. **Mechanism of action:** They inhibit bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA Gyrase) and topoisomerase IV.
Inhibition of DNA Gyrase prevents the relaxation of positively supercoiled DNA that is required for normal transcription and replication. Inhibition of topoisomerase IV interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division.

Adverse effects: Nausea, vomiting, diarrhoea (most common), Headache, dizziness, insomnia, skin rash, photosensitivity, Damage growing cartilage and cause an arthropathy and Tendinitis, tendon rupture.

vii. **Kanamycin & Amikacin:** Kanamycin has been used for the treatment of tuberculosis caused by streptomycin – resistant strains, but the availability of less toxic alternatives (e.g. capreomycin and amikacin) has rendered it obsolete.

Amikacin's role in the treatment of tuberculosis has increased with the increasing incidence and prevalence of multidrug resistant tuberculosis.

Prevalence of amikacin resistant strains is low and most multidrug –resistant strains remain amikacin susceptible. Amikacin is also active against atypical mycobacteria.

USES: Amikacin is indicated for the treatment of tuberculosis suspected or known to be caused by streptomycin resistant or multi drug resistant strains.

viii. **LINEZOLID:** Linezolid has been used in combination with other second and third line drugs to treat patients with tuberculosis caused by multi drug resistant strains.

Uses: used as a drug of last resort for infection caused by multi drug resistant strains that are also resistant to several other first and second line agents.

Adverse effects: Bone marrow depression, Irreversible peripheral and optic, neuropathy reported with prolonged use of drug

ix. **RIFABUTIN**

Rifabutin is derived from rifamycin and is related to rifampin. It has significant activity against mycobacterium tuberculosis, M avium- intracellular and mycobacterium fortuitum

Uses: Rifabutin is effective in prevention and treatment of disseminated atypical mycobacterial infection in AIDS.

As preventive therapy of tuberculosis.
It is a hepatic enzyme inducer of cytochrome P450 enzymes.

Adverse effects: insomnia, skin -

x. Rifapentine

Rifapentine is an analog of rifampin.It is active against both M tuberculosis and M avium

Mechanism of action: It is a bacterial RNA polymerase inhibitor. Rifapentine and its active metabolite, 25 deacetyl rifapentine have an elimination half-life of 13 hours.

uses: It is indicated for treatment of tuberculosis caused by rifampin-susceptible strains during the continuation phase only (i.e. after the 2 months of therapy and ideally after conversion of sputum cultures to negative).

3.3.3 Anti-leprosy drugs

Leprosy is a chronic infectious disease caused by the acid – fast rod Mycobacterium leprae. The mode of transmission probably is respiratory and involves prolonged exposure in childhood.

Symptoms and Signs:

onset is insidious, Lesions involve the cooler body tissues: skin, superficial nerves, nose,pharynx, larynx, eyes, and testicles.
Skin lesions may occur as pale, anaesthetic macular lesions 1 – 10 cm in diameter. Discrete erythematous, infiltrated nodules 1- 5 cm in diameter; or a diffuse skin infiltration. Neurologic disturbances are manifested by nerve infiltration and thickening, with resultant anaesthesia, neuritis and paranaesthesia. Bilateral ulnar neuropathy is highly suggestive. In untreated cases, can result in disfigurement due to the skin infiltration and nerve involvement may be extreme, leading to trophic ulcers, bone resorption, and loss of digits.

DRUGS USED IN LEPROSY:

i. DAPSONE& OTHER SULFONES: Are used effectively in the long-termtreatment of leprosy.

Mechanism of action: Dapsone like the Sulfonamides, inhibits folate synthesis (PABA antagonist). It is bacteriostatic
Resistance can emerge in large populations of M leprae, e.g. in lepromatous leprosy, if very low doses are given. Combination of dapsone, rifampin and clofazimine is recommended for initial therapy.

uses: Leprosy: Tuberculoid leprosy (combine with rifampin), Lepromatous leprosy (combine with rifampin and clofazimine) and Prevention and treatment of pneumocystis jiroveci pneumonia in AIDS patients.

Adverse effects: Haemolysis (in patients having G6PD deficiency), Methemoglobinemia, GI intolerance, Fever, Pruritus and various rashes.

Erythema nodosum leprosum develops during dapsone therapy of lepromatous leprosy. Suppressed by corticosteroids or thalidomide

ii. CLOFAZIMINE

Clofazimine is a phenazine dye that can be used as an alternative to dapsone.

Mechanism of action: Unknown, but may involve DNA binding and & inhibits template function. Its redox properties may lead to generation of cytotoxic oxygen radicals that are also toxic to the bacteria. It is bactericidal.

Adverse effects: Skin discoloration ranging from red brown to nearly black (major adverse effect), Gastrointestinal intolerance occurs occasionally (eosinophilic enteritis).

3.4 Antifungal Drugs

Fungal infections are more difficult to treat than bacterial infections, because the greater similarity between fungi and host limits the ability of a drug to have a selective point of attack; furthermore, many fungi have detoxification systems that inactivate drugs

3.4.1 Superficial mycoses: are infections of superficial tissues and can oftenbetreated by topical application of antifungal drugs such as Miconazole, Nystatin, and griseofulvin, thereby minimising systemic side effects

3.4.2 Systemic mycoses: are more difficult to treat and can be fatal; however, amphotericin B and flucytosine have been used with limited success; amphotericin B is highly toxic and must be used with care; flucytosine must be converted by the fungus to an active form, and animal cells are incapable of this; some selectivity is possible, but severe side effects have been observed with both drugs.

3.4.3 Drug resistant fungal strains: Drug resistant fungal strains are alsobeginning to emerge.

3.5 Antiviral Drugs

Selectivity has been a problem because viruses use the metabolic machinery of the host. Antiviral drugs target specific steps of life cycle, especially enzymes that function in the life cycle (e.g. amantadine, vidarabine, acyclovir, and azidothymidine). Human interferon is used to treat some viral infection

3.5.1 Introduction

Rational drug design approaches now dominate the drug discovery process. HIV infection and AIDS represent one of the first diseases for which the discovery of drugs was performed entirely via a rational drug design approach.

3.5.2 HIV life cycle

i. Free Virus
ii. Binding and Fusion: Virus binds cell at two receptor sites
iii. Infection: Virus penetrates cell. Contents emptied into cell.
iv. Reverse transcriptase: single stranded viral RNA is converted into double stranded DNA by the reverse transcriptase enzyme
v. Integration: viral DNA is combined with the cells own DNA by integration enzyme
vi. Transcription: when the infected cell divides, the viral DNA is "read" and long chains of proteins are made.
vii. Assembly: Sets of viral protein chains come together.
viii. Budding: immature virus pushes out of the cell, taking some cell membrane with it.
ix. Immature virus breaks free of the infected cell
x. Maturation: Protein chains in the new viral particles are sort by the protease enzyme into individual proteins that combine to make a working virus.

3.6 Classification of Antiretroviral Agents

i. **Nucleoside/Nucleotide ReverseTranscriptase Inhibitors (NRTI's)-** Zidovudine (AZT, ZDV), Didanosine (ddI), Stavudine (d4T), Lamivudine (3TC), Abacavir (ABC), Tenofovir (TDF), Emtricitabine (FTC)
ii. **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) -** Nevirapine (NVP), Delavirdine (DLV, Efavirenz (EFV), Etravirine (ETR), and Rilpivirine (Edurant)

iii. **Protease Inhibitors (PIs) -** Saquinavir- (SQV-HGC), Ritonavir- (RTV), Indinavir - (IDV), Nelfinavir - (NFV), Saquinavir- (SQV-SGC), Amprenavir - (APV), Lopinavir/ritonavir - (KAL), Ritonavir (RTV), Atazanavir - (ATV), Fosamprenavir - (fos-APV), Tipranavir - (TPV) and Darunavir - (DRV)
iv. **Integrase Inhibitors -** Raltegravir (RAL), Dolutegravir (DTG)
v. **Fusion Inhibitors -** Enfuvirtide (T-20, Fuzeon)
vi. **Chemokine Receptor Antagonists -** Maraviroc (MVC, Selzentry)

3.6.1 Mechanism Action of Antiretroviral Therapy (Art)

The mechanism of action of ART is best understand through their chemical classifications. They act at different stages of the viral life cycle best on the nature of their amino acid basis.

The Nucleoside Groups - Also called Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs). These are divided into

Pyrimidines-Thymidine: Zidovudine (AZT) and Stavudine (d4T), Cytosine: Lamivudine (3TC) and Emtricitabine (FTC)
Purines - Guanosine: Abacavir (ABC),
Adenosine: Didanosine (ddI), Tenofovir (TDF)

NRT are known as the Nukes, Nucleoside analogues or sometimes called ‘backbone of combination therapy. The first group of antiretroviral drugs are the Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs). These were the first type of drug available to treat HIV infection in 1987. NRTIs interfere with the action of an HIV protein called reverse transcriptase, which the virus needs to make new copies of itself. Nucleoside Analogs are analog of thymidine, cytosine, adenine, or guanine, activated intracellularly by phosphorylation by cellular kinases inside lymphocytes. The triphosphate form acts by competitive inhibition of HIV-1 reverse transcriptase. Incorporation into HIV DNA results in chain termination.

All except tenofovir (TDF), does NOT need to be tri-phosphorylated only di-phosphorylated to active compound. After incorporation of the NRTI, viral DNA synthesis will be terminated. They prevent the addition of the natural nucleosides into the DNA strand. This halts the production of new virions.

NRTI’s mainly undergo renal excretion EXCEPT, Zidovudine (AZT) undergoes glucuronidation and Abacavir metabolised by alcohol dehydrogenase.

3.6.2 Drug specific mode of action and adverse effects

All has tendency to cause Lactic acidosis with hepatic steatosis however, it's a rare but serious complication of NRTI therapy. Signs/Symptoms: Abdominal distention, abdominal pain, nausea, vomiting, diarrhoea, weight loss, difficulty breathing, generalised weakness and myalgias.
Risk Factors: Stavudine and Didanosine use during pregnancy, Female gender, Obesity and Prolonged use of NRTIs.

i. **Zidovudine (AZT/ZDV): Adverse effects**

Chronic AZT therapy may cause ***nail hyper-pigmentation, myopathy, hepatic toxicity (with or without steatosis) and lactic acidosis.***

Anaemia - (anaemia, neutropenia, thrombocytopenia), may develop as early as four weeks in about 7% of patients with advanced HIV/AIDS possibly due to toxic effects of AZT on erythroid stem cells.
This effect is characterised by depletion of bone marrow red cell precursors, elevated serum erythropoietin levels, and normal serum folate and vitamin B12 levels.

Do not commence Patient on ZDV if Hb < 8.0 g/dL (PCV <24%)
GI intolerance (hypersalivation, nausea, anorexia, fatigue and abdominal discomfort).

Other toxicities include: Nausea, insomnia and headache effects, convulsions and encephalopathy

ii. **Didanosine: (ddI)**

Didanosine is a synthetic analog of deoxyadenosine. Food decreases absorption: Take at least 30 minutes before meal, or 2 hrs. after meal or administered on an empty stomach!

Adverse Effects: Transient / minor Events, Primarily GI-related (Abdominal cramps and Diarrhoea). EC caps < chewable tabs
Serious Events: ***Pancreatitis*** - effect is worse when combined with hydroxyurea, Painful Neuropathy, Lactic acidosis and Hepatic steatosis.

Avoid use of ddI + d4T à additive toxicities!

iii. Stavudine: (d4T)

It is a thymidine analog, originally development was 4-10 mg/kg, but this was stopped due to *liver toxicity* in phase I. 1 mg/kg eventually approved…hence weight-based dosing.

Has antagonistic effects when combined with zidovudine (AZT). Major dose limiting effects are peripheral neuropathy. Chronic toxicity became significant over time; the drug has been virtually abandoned since 2010 in Nigeria treatment programme.

Other side effects include; Lipodystrophy - Peripheral fat atrophy, and ascending motor weakness resembling Guillain-Barre syndrome may occur. Neuropathy - Numbness, tingling sensation and pain in the feet sensations worst in the lower than upper limb, usually resolves on stopping the drug. It is more common in patients with advanced HIV/AIDS, Lactic acidosis (potentially fatal), Hepatic steatosis - Lactic acidosis with hepatic steatosis; is worse when d4T is used in combination with ddI. Minor toxicities: Moderate transaminase elevation, headache, nausea, and skin rash also seen are Insomnia, anxiety, panic attacks, Monitoring/ management. Periodic serum triglycerides should be monitored; suspicion of lactic acidosis – measure serum lactate and/or anion gap and serum bicarbonate; When there are signs of mitochondrial toxicity, stavudine should be substituted.

iv.Lamivudine (3TC):

It is a cytosine analog Improves. Reduces viral fitness and is an Important nucleoside analog in HBV treatment

Almost didn't get developed because of low resistance threshold. Now the #1 selling anti-HIV drug in the world. First approved combination therapy – Combivir. Resistance common – M184 mutation. Has benefit noted when continued in presence of M184 associated with less fit virus and 0.5 log decrease from baseline VL

Side effects Very safe; occasional side effects are **– headache and insomnia.** Serious toxicities are rare, and generally well tolerated. Extensive long-term use in patients with chronic hepatitis B (100 mg daily). Primary toxicities: Pancreatitis, liver toxicity, Mild peripheral neuropathy. Minor toxicities: Skin rash, headache.

v.**Emtricitabine:** It is a fluorinated lamivudine (analog), Structurally similar to lamivudine. It is Important nucleoside analogue for HBV treatment.

Adverse effects: Hyper pigmentation of palm and soles Lactic acidosis and hepatitis.

vi.**Zalcitabine: (ddC):** It is a cytosine analog – has antiviral activity against zidovudine sensitive and resistance strains.
Adverse effects: Pancreatitis and Peripheral neuropathy.

vii. **Tenofovir (TDF):** Nucleotide analog, Good tolerability, acute and chronic. ***Very active against Hepatitis B.***

Adverse effects: TDF causes **renal** failure - Renal Tubular Necrosis, Hypophosphatemia, Hepatitis B exacerbation, Fanconi's syndrome (rare). Other effects may not be serious and may lessen or disappear with continued use of TDF. include abdominal discomfort, diarrhoea, dizziness, intestinal gas, headache, and rash.
Avoid in patients with borderline renal dysfunction. Renal dosing necessary.
Risk factors: Existing renal disease, hypertension, Advanced HIV disease (AIDS), Concomitant protease inhibitor use and Concomitant nephrotoxic agents

viii. **Abacavir:** It is a Guanosine analog

Abacavir adverse effects: Hypersensitivity: Reported rates 3-8% (true incidence lower) Genetic predisposition HLA B*5701 allele in 94.4% confirmed cases. Not common in African populations. Onset: 90% within 1st 6 weeks; median: 9 days. Présentation : Fever, rash (diffuse), malaise, headache, chills, nonspecific GI symptoms (abdominal pain, N/V/D), respiratory symptoms (dyspnea, tachypnea, pharyngitis).
Stop abacavir! If confirmed, do NOT rechallenge!

Non- Nucleotide Reverse Transcriptase Inhibitors (NNRTIs)
Available NNRTIs in the Nigeria**: Nevirapine, Efavirenz, Delavirdine and Etravirine (TMC-125)**

Mechanism of Action: NNRTIs causes non-competitive inhibition with the viral reverse transcriptase enzyme RT (near catalytic site) but have a different mechanism of action compared to NRTIs. They Do NOT require intracellular phosphorylation (unlike NRTIs), but instead bind directly to the reverse transcriptase enzyme Viral RNA double stranded DNA. The result RNA unable to undergo transcription to DNA therefore replication cycle
cannot continue

NNRTI Adverse Effects

Nevirapine: The most common side effect with Viramune is skin rash that occurs among 17% of patients. The majority of severe rashes occur within the first four weeks of therapy. A 14 day "lead-in" dose of one 200 mg tablet daily is used for adults, in combination therapy. This decrease the rate of rash. The dose can then be increased to 1 tablet bid (if no rash, hepatitis, or other serious adverse effect)

Severe, life-threatening hepatotoxicity; Often associated with rash.
Greatest risk in women with CD4 >250 (12-fold greater risk). Increased risk for men with CD4 > 400 (3-fold greater risk) and greatest risk during 1st 6 weeks (continued risk through 18 weeks)
Hepatotoxicity more common in women with pre-treatment $CD4^+$ cell counts > 250 cells/mm^3, men with $CD4^+$ cell counts > 400 cells/mm^3 and patients co-infected with hepatitis B or C.
Monitor LFTs minimally at baseline, 2 weeks, monthly for the 1st 3 months in all patients

ii. **Efavirenz: M**any patients taking efavirenz can experience nervous system symptoms (for example, dizziness, vivid dreams, decreased concentration, and insomnia) which are generally mild to moderate and resolve after 2 to 4 weeks.

Rash is also a potential but uncommon side effect Rash (1.7%), increased transaminase levels should be used with caution in patients who have a history of psychiatric illness due to side effects including vivid (sometimes disturbing) dreams, insomnia, somnolence, difficulty concentrating, dizziness, amnesia, confusion or agitation. Some concern that efavirenz can trigger cravings in patients with a history of substance abuse. Mental health and/or substance abuse supports should be available. Should be taken before bedtime to avoid daytime difficulties

PROTEASE INHIBITORS (PIS)

Mechanism of Action: Protease enzyme is responsible for cleaving (cutting up) larger polyproteins into structural proteins and reverse transcriptase enzyme. Protease is needed to form a fully mature, functional virus that is able to replicate and produce more virus. Protease inhibitors prevent this enzyme from doing its job in the later steps of the viral life cycle. **Hence PIs, Inhibit HIV-1 protease, p**revents cleavage of Gag-Pol poly-proteins individual structural and enzymatic proteins necessary for the formation of mature virions are NOT produced. **Net**

Result: Immature, non-infectious virions are released.

Protease inhibitors provide a beneficial Drug Interaction: Ritonavir INHIBITS cytochrome p450 metabolism in liver and gut when co-administered with other PI, result increased absorption (bioavailability) and Decreased metabolism in liver.

Class adverse effects: Hyperglycemia, lipodystrophy, hyperlipidaemia (less with atazanavir), increased transaminases.

PIs Containing Sulfa Moieties (Darunavir, Fosamprenavir and Tipranavir)

– Above agents are not contraindicated with sulfa allergy
– History of sulfa allergy did not correlate with rash in studies and patients with history of sulfa allergy were not excluded
– Use with caution

• **Metabolic Complications of PIs**

– **Glucose intolerance:** Rare diabetes, diabetic ketoacidosis
– **Lipodystrophy:** Central obesity, "buffalo hump", peripheral fat wasting
– **Hyperlipidaemia:** Hypertriglyceridemia and/or hypercholesterolemia
– **Osteonecrosis, osteopenia, osteoporosis**
– **Lipoatrophy**
– **Facial Wasting**

3.6.3 New ARV Targets Against HIV: Fusion Inhibitor

Enfuvirtide (T-20, Fuzeon®): Approved March 2003
Mechanism of Action

Inhibits entry of HIV into the CD4 cell. T-20 binds to glycoprotein gp41 (a protein on the viral membrane). This binding prevents a change in the shape of the membrane protein and prevents fusion of the virus and the CD4 cell membrane

Enfuvirtide, unfortunately, is only active when injected subcutaneously
This aspect (in addition to its high cost) severely limits it use in the correctional setting

Adverse effects:

- injection site Rxn, hypersensitivity (rare)
- resistance: changes in gp41 (cell surface protein)

3.5.7 Integrase Inhibitors

Raltegravir (Isentress™)

Atazanavir must be boosted with ritonavir if used in combination with tenofovir

Tipranavir - Approved June 2005
Darunavir - Approved June 2006
MK-0518 (Raltegravir) - Investigational integrase inhibitor available via EAP

Maraviroc - Investigational CCR5 inhibitor available via EAP

– Approved August 6th, 2007

Tipranavir

– AEs: Hepatotoxicity-monitor LFTs, closely, rash (8-14%) of patients, diarrhoea, nausea, vomiting, rare cases of intracranial haemorrhage
– Caution with sulfa allergy

Darunavir

• Patient Counselling Points
– Take with food
– AEs: Rash (7%), abdominal pain, constipation, headache
– Caution with sulfa allergy

3.6.4 ARV Drug Interactions

"The modification of the effect of one drug by the prior or concomitant administration of another."

PIs and NNRTIs

Primarily metabolised by the cytochrome P450 3A4 (CYP3A4) enzyme system., hence inhibit or induce the CYP450 enzyme system
Clinically Significant Drug Interactions – Due to Effect on Antiretrovirals

i. Rifampin, Phenytoin, phenobarbital, carbamazepine: Decrease PI and NNRTI levels?
ii. Ketoconazole: Increase in NVP concentrations by 30% and Decrease in ketoconazole concentrations by 40-60%.
iii. **St. Joh**n's Wort: Concern with other herbal products
    a. Clinically Significant Drug Interactions – Concern for the Co-Administered Drug
iv. Warfarin: Often PIs decrease potency of warfarin – HIGHER warfarin doses needed

3.7 Overview of Cancer Chemotherapeutic Agents

3.7.1 Introduction

Cancers account for 20-25% of deaths in clinical practices. In the US, cancer is the 2nd cause of death highest cause of death due to cardiac disease. Result from alteration of DNA within the cells.

Human body contains 5x1013 cells. Tumour becomes clinically detectable when there is a mass of 109 cells (1g). About 109 new cells are manufactured in the body through cell division daily. This must be balanced by an output of similar number.

Table 29: Cancers with 5 years' survival Rate

Types of Cancer	**Percentage of 5 years survival**
Childhood acute lymphoblastic Leukaemia	50 -80
Adult acute lymphoblastic Leukaemia	20 -60
childhood Myeloblastic Leukaemia AML	20 -60
Adult acute myeloblastic Leukaemia AAML	10 -20
Breast Cancer	5 -20
Hodgkin's Lymphoma	40 -80

3.7.2 Goals of Cancer Chemotherapy

Goals of Cancer Chemotherapy: Cure induction of Remission: cure or induction of prolonged remission so that macroscopic and microscopic features of cancer disappear, though disease is known to persist e.g. in Acute lymphoblastic leukaemia, Wilm'tumours, Ewing's sarcoma in children, Hodgkin's Lymphoma, testicular teratoma and choriocarcinoma.

Palliation: Shrinkage of evident tumour, alleviation of symptoms & prolongation of life. E.g. in breast cancer, Ovarian canacer, endocarcinoma, CLL, CML Small cell cancer of the lungs & Non-Hdgkins Lymphoma

Insensitive or less sensitive: but may prolong life. Carcinoma oesophagus, cancer of stomach, squalors cell carcinoma of lung, melanoma, Panreatic cancer, melonomasand colorectal cancer

i. **Treatment Options for malignancies:** Chemotherapy is the use of drugs to inhibit or kill proliferating cancer cells, while leaving host cells unharmed, or at least recoverable.4 - basic treatment options of malignancies; Surgery, Radiotherapy, chemotherapy and Immunotherapy and Gene therapy (including biological response modifiers {BRMs}).
   Surgery is the most effective treatment of cancer but it is ineffective for metastasized or disseminated tumours. Radiation is the next most effective treatment after surgery.
   Rapidly dividing cells are the most sensitive. It is useful primarily in cancers that are not widely disseminated. It is often combined with surgery and chemotherapy

i. No Treatment: Before 1940

ii. Surgery: Before 1955
iii. Radiotherapy: 1955 – 1965
iv. Chemotherapy: After 1965
v. Immunotherapy and Gene therapy; Currently

3.7.3 Cell Cycle (cell proliferation)

Tumour cells can be classified as *proliferating cells* and *non-proliferating cells b*ased on the DNA changes in cells, proliferating cycle of tumour cells can be divided into 4 phases

G_1; Pre-synthetic phase (Gap 1 phase or G1 phase). Cell chiefly makes preparations for the synthesis of DNA.

S; Synthetic phase (S phase). Cells are synthesizing their DNA. Here, chromosome material is doubled, with the production of sister chromatids.

G_2; Post-synthetic phase; Preparation for Division. (Gap 2 phases or G2 phase). Where a sequence of biochemical materials occurs. In this phase DNA synthesis has stop while RNA and protein synthesis continue and is the second resting phase in the cell cycle.
Mitosis phase (M Phase). follows the G2 where two genetically identical daughter cells are formed by division of the nucleus through the four stages of prophase, metaphase, anaphase and telephase.

The daughter cell proceeds either to **G1 phase** or enter **G0 phase.**
Cell in G0 phase are not out of the cycle **(but resting),** because they are still capable of proliferating.

G2 phase is also a resting phase where **DNA synthesis** has stop but **RNA and protein synthesis** occur normally (the new cells here undergo growth and differentiation) and finally the remaining cycle is repeated. Cell division requires controlled timing of two events of the cell cycle.
Generally, **in the early stage, the GF of a tumour is bigger and the effect of a drug on the tumour is better.** Cells in G0 phase can be activated by chemical stimuli into **G1 phase. e.g.** skin cells can be stimulated by a wound into dividing and repairing the lesion. Growth factor – many stimuli can initiate Go cells into G1 cells, but the most important is Growth factor acting on growth factor –receptor. GF stimulate the production of signals of two types; **Positive regulators of cells cycle** that control the changes necessary for cell division and **Negative regulators** that control the positive regulators

3.7.4 Classifications and Mechanisms of Action of Antineoplastic Drugs

Classifications of Anticaner Drugs

i. Alkylating agents:nitrogen mustards, busulfan, nitrosoureas, mitomycin
ii. Procarbazine, dacarbazine
iii. **Taxanes:** paclitaxel, docetaxel
iv. **Topoisomerase II inhibitors:** etoposide
v. **Platinum Complexes**: cisplatin, carboplatin
vi. **Anthracyclines:** doxorubicin, daunorubicin, mitoxantrone
vii. **Antimetabolites:** methotrexate, purine antagonists, pyrimidine antagonists
viii. **Tubulin interactive agents**: vincristine, vinblastin
ix. **Miscellaneous agents:** bleomycin, asparaginase, hydroxyurea

3.7.5Mechanisms of Action of Antineoplastic Drugs

Most antineoplastic drugs act on the proliferating cycle of cell

i. Inhibition of nucleic acid (DNA and RNA) synthesise.g. 5-fluorouracil, 6-mercaptopurine, methotrexate, cytarabine, etc.
ii. Destruction of DNA or inhibition of DNA duplicatione.g. alkylating agents, mitomycin C.
iii. Interfering with the transcription to inhibit RNA synthesis e.g. dactinomycin, dauoruicin, and doxorubicin.
iv. Inhibition of protein synthesise.g. vinca alkaloids, epipodophylotoxins, and paclitaxel.
v. Interfering with hormone balance e.g. adrenal corticosteroids, oestrogens, tamoxifen etc.

3.7.6 Principles of cancer chemotherapy

All Cell- normal cell or neoplastic cell must traverse before and during cell division.

vi. Malignant cells spend times in each phase – longest in G1, but may vary.
vii. In adult most of the cells do not constantly divide
viii. Most spent a varying time outside the cell in a quiescent non-proliferating cell called G0 phase cells (resting-phase cells),
ix. Neurons and skeletal muscle cells spent most of their time in G0 phase.
x. Bone marrow & GIT Cells divide daily – Hence are more sensitive

xi. When proliferating cells suffered heavy casualties, G0 phase cells will get into proliferating cycle and become the reasons of tumour recurrence.
xii. G0 phase cells are usually not sensitive to antineoplastic drugs, which is the important obstacle to tumour chemotherapy.
xiii. Many of the effective anticancer drugs exert their action on cells while traversing the cell cycle – cell specific (CCS) drugs
xiv. Cell cycle – Non-specific (CCNSs) drugs- sterilize tumours cells whether they are cycling or resting in the G0 components

3.7.7 Factors That Determine Cancer Drug Response

i. The effect of the GF on the response to chemotherapy: Tumours with a high growth fraction are more susceptible to the Cytotoxic drugs than those with a high percentage of dormant cells (G0 phase). Normal tissues with high GF (*bone marrow, oral/intestinal mucosa, hair follicles*) are also damaged by anticancer drugs, and treatment with many of these drugs may produce bone marrow depression (leukocytopenia and infection, thrombocytopenia and bleeding), stomatitis, GI tract ulceration, and alopecia.

ii. The effect of the speed of cell cycle on response to chemotherapy: The faster the cell cycle proceeds, the more likely that treatment with cytotoxic drugs will 'catch' the cells in a sensitive phase. This forms the basis why cytotoxic drugs are usually given in cycles of treatment at intervals of 3-4 weeks, rather than continuously, since this allows recovery of susceptible tissues, such as the bone marrow.

iii. Synchrony of the cell cycle in the cells of a tumour: if more tumour cells are synchronized in a sensitive phase of the cycle, there will be better chance of respond to a pulse of cytotoxic drug therapy. Attempt is usually made to recruit cells into cycle (for example the recruiting of breast cancer cells with oestrogens). Alternatively, cytotoxic drugs can be used to arrest cells at different point of the cycle, thus modifying the effects of other treatment for instance as it has been demonstrated with a mitotic spindle poison, such as Vinca alkaloids, which might arrest cell in their cycle after which they could be treated with an inhibitor of DNA synthesis like cytarabine as they progress through S-phase.

iv. The effect of tumour size on response to chemotherapy: Large tumours respond poorly to chemotherapy because many of the cells tends to be in G0 phase in which cells are unresponsive to drugs; and penetration of drugs through a poor as vasculature is insufficient to achieve cytotoxic concentrations for a long enough time without producing severe systemic toxicity.

v. Kinetic of cell kill: In general, tumour cell is killing after drug treatment follows first order kinetics, i.e., each treatment results in killing of a constant proportion, rather than a constant number of tumour cells. After initial treatment, the rate of cell kill may change because the growth fraction and mass doubling time change as the tumour mass decreases from a large, bulky tumour to a smaller tumour (this is called "RECRUITMENT"). The slope of the response curve is also different for the residual cells because they are likely to be less sensitive to the drug or present in sites where drug does not penetrate as well. Treatment must continue even in the face of clinical remission until the tumour is totally eradicated. Cure is considered achieved when the DISEASE-FREE SURVIVAL PLATEAU is reached. This time is different for different tumours (e.g., Burkitt's' lymphoma - 8 months; testicular cancer - 1 year). NOTE: There is no clear survival plateau for certain cancers (e.g., breast cancer).

vi. Tumour heterogeneous: in their cell populations, there may be great variability in the responses of individual cell types. Some of these cells are proliferating, some can proliferate but are dormant and others are dying. The fact that tumours are not uniform must be considered. For any tumour therapy to be completely effective the most invasive metastatic cells must be killed. It is therefore difficult to kill every tumour cell during chemotherapy, although, if cure is the aim, this is essential.

vii. Cell cycle phase: The response to certain cell phase-specific drugs depends on the percent of cells in a sensitive phase during the time of exposure. In general, for cycle phase specific agents such exposure should be for at least two cell cycle times. Cells in the G0 phase are, for the most part, refractory to chemotherapy. These cells may re-enter the cell cycle and result in disease recurrence. Most anticancer drugs are effective against cells in one particular phase of the cycle (e.g., vincristine during M; cytarabine during S, etc.). Most drugs have their greatest activity during S phase when cells are undergoing DNA synthesis.

3.7.8 Resistance of cancer cells to chemotherapy.

This is one of the most important problems with cancer chemotherapy. As many as 40-45% of cancers patients may have or may develop resistance to anticancer drugs. The differences in the responsiveness of some cancer cells to drugs as noted, to a specific form of multiple drug resistance (MDR), which seems to be important in many solid tumours is mediated by a P-glycoprotein, which pumps Cytotoxic drugs out of cells before they can act. This pump is inhibited by a Varity of structurally unrelated drugs including nifedipine, verapamil, cyclosporine and tamoxifen, etc. There is

however several different biochemical Mechanisms by Which Tumour cells Develop Resistance to Anticancer Drugs. These include:

i. **Decreased intracellular drug levels**. This could result from increased drug efflux or decreased inward transport. Among the drugs which become resistant by this mechanism are the anthracyclines, dactinomycin, vinca alkaloids, and epidopodophyllotoxins.
ii. **Increased drug inactivation.** Included in this group are the alkylating agents, antimetabolites and bleomycin.
iii. **Decreased conversion of drug to an active form.** This mechanism is most common among the antimetabolites which must be converted to the nucleotide before they are active. G_1
iv. **Altered amount of target enzyme or receptor (gene amplification).** Methotrexate is a classic example here as often in methotrexate resistant tumours there is amplification in the target enzyme dihydrofolate reductase.
v. **Decreased affinity of target enzyme or receptor for drug.** Examples are the antimetabolites and hydroxyurea.
vi. **Enhanced repair of the drug-induced defect.** The alkylating agents typically show resistance by this mechanism although other mechanisms are also important with these drugs.
vii. **Decreased activity of an enzyme required for the killing effect** (topoisomerase II). This is a newly recognised target but decreased activity is important for resistance to doxorubicin, m-AMSA, and the epipodophylotoxins.

Multidrug Resistance (MDR): This is a phenomenon whereby tumours become resistant to several, often unrelated drugs, simultaneously. The multidrug Resistance (MDR1) gene encodes an ATP-dependent efflux pump, called p-glycoprotein that may become amplified in drug-resistant tumours. MDR activity may be reversed by drugs such as calcium channel blockers (e.g., verapamil), cyclosporine, or tamoxifen. Multidrug resistance occurs between several different structurally unrelated antitumor agents that apparently have different mechanisms of action.

3.7.9 Adverse effects of Antineoplastic Drugs

i. **Short-term toxicity:** Common adverse reactions usually appear earlier and many of them occur in rapidly proliferating tissues such as; marrow, gastrointestinal tract, and hair follicle, myelosuppression, gastrointestinal tract symptom and alopecia.

ii. **Long-term toxicity:** The long-term toxicity mainly occurs in the patients who received chemotherapy for many years ago. Examples: carcinogenesis, teratogenesis and sterility.

iii. **Common Toxicities:** Most chemotherapy drugs are active in cells that are rapidly multiplying. Chemotherapy may not be very active in indolent or slow growing tumours, Because of cytotoxic action on rapidly dividing cells they are toxic to normal cells that are actively multiplying. Bone marrow, GI tract, hair follicles are all rapidly multiplying. Thus, common toxicity of chemo agents is - Neutropenia, anaemia, and thrombocytopenia (collectively called myelosuppression or bone marrow (suppression), Mucositis, Nausea, anorexia, vomiting and diarrhoea (GI toxicity). Nausea and vomiting, Alopecia or hair loss, Sterility/Infertility (especially sterility in males), Skin changes, Anxiety, sleep disturbance, altered bowel elimination, Decreased mobility, Hematopoietic system changes and Hypersensitivity (esp. Taxanes, platinum)

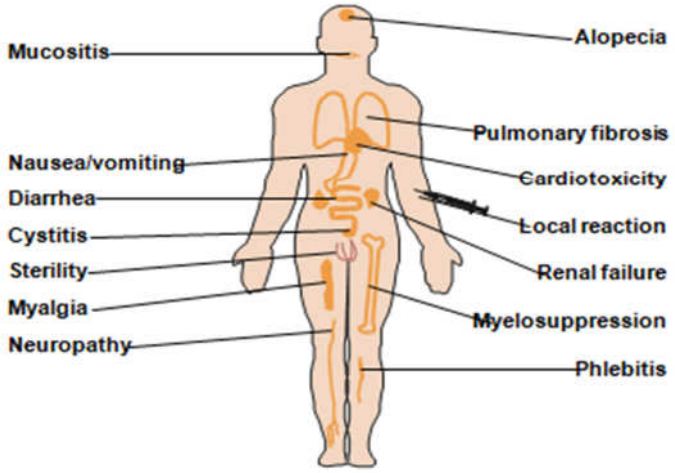

Figure 31: Showing Side Effects of Chemotherapy

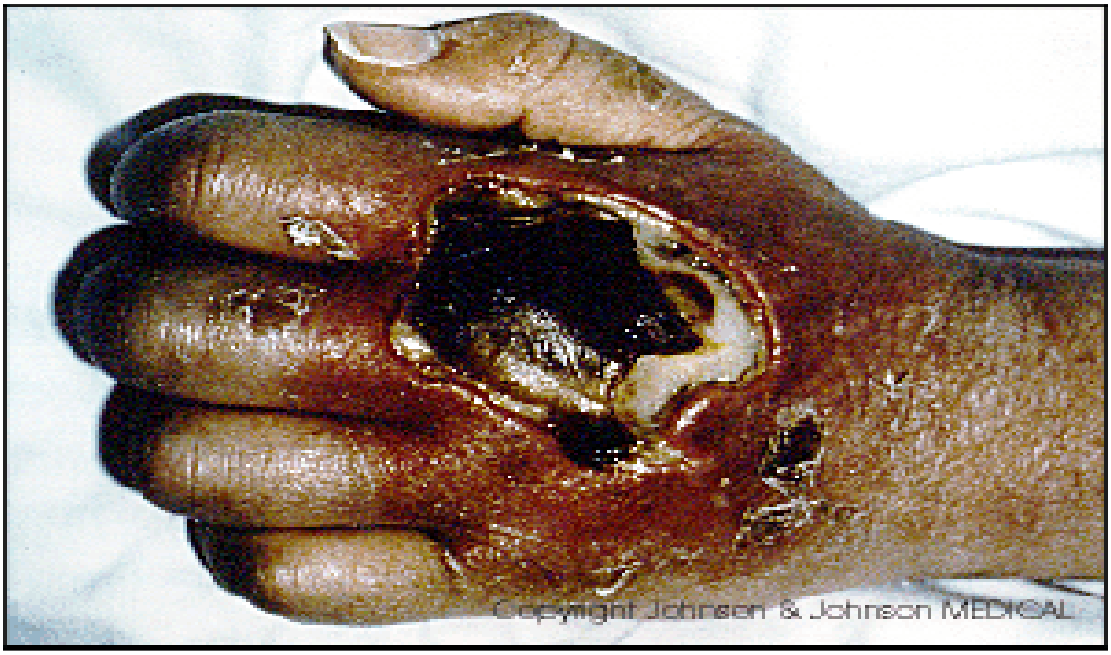

Figure 32: Extravasation of Cytotoxic drug (@ chemotherapy extravasation injuries cancerjournal.net).

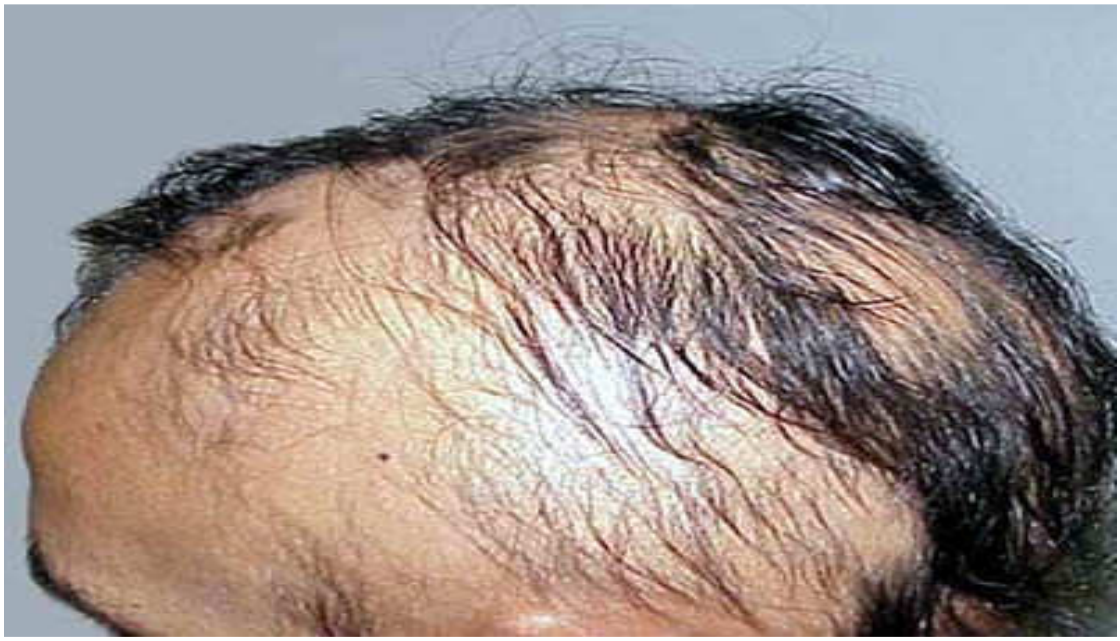

Figure 33: Alopecia (hair loss)(@ medicinenet.com)

Common anticancer drug involved are; Anthracyclins, Etoposide, Irinotecan, Cyclophosphamide, Taxanes, Ifosphamide, Vindesine, Vinorelbine and Topotecan

Alopecia can occur 2-3 days after or within a few weeks of commencement of treatment. Baldness may be temporary, partial or total. Patient can regain hair 3-6 months after stopping treatment

iv. Hand-Foot Syndrome

A local cutaneous reaction can occur and be seen on palms 2-12 days after chemotherapy. It is usually associated with tingling, burning of palms, hand, feet, Pain and peeling. Resolution occurs in 7-14 days after stopping medication

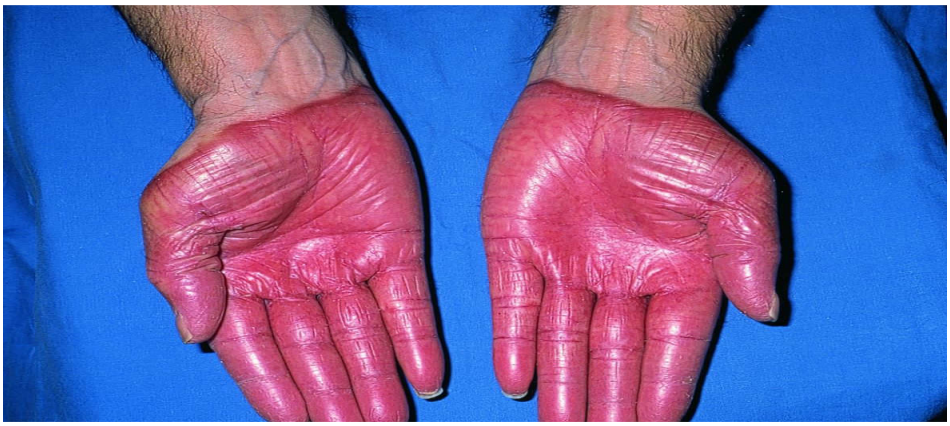

Figure 34: Hand-Foot Syndrome(@cureus.com)

3.8 antiprotozoal Drugs

3.8.1 Antimalarial (Introduction)

Malaria is a major public health problem in warm climates especially in developing countries. It is a leading cause of disease and death among children under five years, pregnant women and non-immune travellers/immigrants.

Malaria parasites are transmitted from one person to another by the bite of a female anopheles' mosquito. The female mosquito bites during dusk and dawn and needs a blood meal to feed her eggs. Like all mosquitoes, anopheles breed in water - hence accumulation of water favours the spread of the disease.

Plasmodium infects the human and insect host alternatively and several phases of the parasite life cycle is described.

3.8.2 Malaria Treatment is classified into two types of drugs

Malaria infection is classified into two broads'classes-based on the main stages of drug targets.**1. Tissue Schizonticides,** drugs that eliminate development or dormant form of the parasites and **2. Blood Schizonticides,** drugs that act on erythrocytic Parasites

Therapeutic classification of antimalarial drugs`

i. **Causal prophylaxis:** (Primary tissue schizonticides): These drugs prevent the maturation or destroy parasite (sporozoites) within infected liver (hepatocytes) cells and thus prevent invasion of erythrocytes. Example; Primaquine**:** Treat all species of malaria; both are commonly used due to high toxicity. Proguanil: Primarily used for *P. falciparum*. It's not effective against *P. Vivax* (weak activity) & rapid development of resistance. ***The only drugs that kills hepatic Parasites***

ii. **Suppressive Prophylaxis:** These are Schizonticides, they inhibit erythrocytic phase & prevent the rapture of the infected erythrocytes, which leads to relief of Rigor & Pyrexia. Examples; Quinine, Chloroquine, Proguanil, Mefloquine, Pyrimethamine, artemisinin & Doxycycline.

iii. **Clinical cure: erythrocytic schizonticides:** These are erythrocytic schizonticides basically used to terminate an episode of malarial fever examples; Artemisinin, Quinine, Mefloquine, Atovaquone, Proguanil, Pyrimethamine, Chloroquine, Sulfonamides and Tetracyclines;

iv. **Fast acting, high efficacy drugs:** Artemisinin, Quinine, Mefloquine, halofantrine and Chloroquine. Used singly to treat malaria and is usually the drug of choice in *P. falciparum,* where delayed treatment could lead to death even if the parasites are cleared from the blood and **slow acting, low efficacy drugs:** Proguanil, Pyrimethamine, and Sulfonamides& Tetracycline. Used in combinations.

v. **Radical curatives:** These drugs attack exoerythrocytic stage (hypnozoites) resulting in clinical curative for total eradication all forms parasites of *P. vivax*&*P. ovale,P. malarae, P. falciparum* etc. from the body.

Suppressive drugs + hypnozoitocidal drugs
Radical cure of the *P. falciparum* malaria can be achieved by suppressive only

Gametocidal: Destroy gametocytes and prevent transmission - Artemisinin; against all plasmodia, Primaquine, Chloroquine and quinine

Radical cures of *P. Vivax* infections – Proguanil, Pyrimethamine; prevent development of sporozoites.

3.7.3 Mode of Action of Specific Agents

i. **The quinolones (**Quinine, Chloroquine, Lumefantrine and Amodiaquine}

Mechanism of action: The asexual malaria Parasites multiply in the erythrocytes by digestion haemoglobin. The digested haemoglobin generates free radicals and **haem** as highly reactive by-products. Haem is sequestered as insoluble material pigment known as ***Haemozoin. Quinolones*** *are thought to* ***interfere*** *with* ***haem handling*** *as by blocking the conversion of* ***haem to haemozoins.*** *Failure to inactivate haem or even enhanced toxicity of drug haem complexes is thought to kill the parasite via oxidative reactions***.**

ii. **Chloroquine:** Well absorbed after oral IM, and SC administration. Selective accumulation in retina: ocular toxicity. T1/2 = 3-10 days, can increase from few days to weeks. tmax 2-3 hrs. 60 % protein bound. Bio transform via Hepatic CYPs in to two active metabolites – dihydrochloroquine & bisedesthychloroquine

Therapeutic uses: Prophylaxis and treatment of acute malaria infections, Hepatic amoebiasis, Giardiasis, Clonorchis sinensis, Rheumatoid arthritis, Discoid Lupus Erythematosus, Control manifestation of lepra reaction, Infectious mononucleosis and Prophylaxis. *Chloroquine is inexpensive and safe but it useful has declined. No longer used in Nigeria.*

Adverse drug reactions: Cinchonism: Flushed and sweaty skin, ringing in the ears (tinnitus), blurred Vision. Impaired hearing and confusion

Others – skin rashes, angioneurotic oedema, photosensitivity, pigmentationand exfoliative dermatitis

Long term therapy may cause bleaching of hair, rarely thrombocytopenia, agranulocytosis, and pancytopenia. Ocular toxicity: High dose, in prolonged therapy

Insomnia, transient depression seizures, rarely neuromyopathy & ototoxicity. Usually following parenteral administration - ST & T wave abnormalities, abrupt fall in BP & cardiac arrest in children reported.

iii. **Amodiaquine:** Pharmacological actions similar, less cutaneous side effects, Bitter Taste and faster acting than chloroquine. Widely used; reduced cost, safety & activity against chloroquine resistant *P. falciparum*. Chloroquine resistant strains may be effective.

Adverse events: headache, photosensitivity. Major reports of toxicities, including agranulocytosis, and hepatotoxicity (on long term administration), have limited the use of the drug for prophylaxis (long-term).

Therapeutic Uses: Can be used for clinical cure of *falciparum* malaria with or without CQ resistance. Not used for prophylaxis. Combined formulation with artesunate has been recently approved for use in *uncomplicated falciparum* malaria irrespective of CQ resistance status; it is p*referred in African countries.*

i. **Quinine &Quinidine:** Quinine remain the mainstay in the treatment chloroquine and multidrug resistant *P. Falciparum* Malaria.

Therapeutic Uses: Malaria (uncomplicated resistant falciparum malaria &severe malaria including cerebral malaria).

Adverse drug reactions: Cinchonism: Tinnitus, headache mental confusion, vertigo, difficulty in hearing & visual disturbances, flushing & marked perspiration. Still higher doses, exaggerated symptoms with delirium, fever, tachypnea, respiratory depression, cyanosis. Myotonia congenita: 300 to 600 mg BD/ TDS. Nocturnal muscle cramps: 200 – 300 mg before sleeping.Varicose veins: along with urethane causing thrombosis & fibrosis of varicose vein mass.

Idiosyncrasy: similar to Cinchonism but occurs in therapeutic doses. Cardiovascular toxicity: cardiac arrest, hypotension and fatal arrhythmias.

Black water fever, Hypoglycaemia.

C/I in Pregnancy: Causes abortion in early Pregnancy by stimulating Myometrium & Premature labour by stimulating Uterus

vi. **PRIMAQUINE:** 8-aminoquinoline: Mechanism of action: Primaquine is converted to electron to generate reactive oxygen radical which interferes with oxygen transport system in the parasites. It is use in preerythrocytic schizonticides, not useful for acute attack. Highly active against gametocytes and hypnozoites.

Therapeutic Uses: Radical cure of relapsing (Vivax) malaria &ovale. Gametocidal for all species of plasmodia. Can be transmission through mosquitoes.

Adverse effects: Nausea, headache, epigastric pain, and abdominal cramps occasionally

Avoid during pregnancy, G6PD deficient: Those with G-6-PD deficiency are highly sensitive and haemolytic anaemia can occur even with 15-30 mg/day.

Atovaquone: Attack mitochondria, hence preventmalaria parasites from making energy. Active against Merozoites (asexual stage of cycle). Other drugs that target food metabolism of the parasites -Prevent formation of Folate e.g. Sulfonamides, Diaminopyrimidines.

vii. **Artemisinin: Artemisinin:** The weed *Artemisia annua* has been used for many centuries in Chinese herbal medicine as a treatment for fever and malaria. In 1971, Chinese chemists isolated from the leafy portions of the plant the substance responsible for its reputed medicinal action. The compound, artemisinin (qinghaosu, arteannuin) derivatives includes: Artemether, Arteether, Artesunate, Arrerolane, Artemether, Arteether, Artesunate, Arrerolane, Artemisinins are prodrugs of the biologically active metabolite dihydroartemisinin, activated by haem and form free radicals which damages lips & vacuole of Parasites membranes. Inactivation of plasmodium proteins, alkylations of haem & interferencewith haems – haemozoins – haematin metabolism.

viii. **Artemisinin & Derivatives:** Artemisinin is not very soluble either in water or oil. Artemisinin derivatives have half-lives of the order of an hour. All artemisinin derivatives are characterised by their extremely rapid elimination from plasma, with elimination half-lives that are mostly less than a few hours. Elimination T1/2 = Artemisinin = 2.9hrs. Dihydroartemisinin = 40 min, Arteether = 3.6hrs, Arteether = 12.4 -30hrs and Artesunate = 2.5mins.

Both Artemether and artesunate are metabolised to dihydroartemisinin by rapid esteratic hydrolysis of artesunate or slower cytochrome P450-mediated demethylation of artemether. Dihydroartemisinin itself and artemisinin are probably metabolised in the liver to inactive metabolites.

Artemisinin, dihydroartemisinin, Artemether and artesunate are available for oral and rectal use in several countries). Artemisinin, Artemether and artesunate can also be given by intramuscular injection. However, artesunate is the only drug that can be administered intravenously. Artesunate is clearly the most rapidly absorbed with time to maximal concentration (T max 15 -30min) considerably shorter than those of the other derivatives.

ix. **Arteether:** A longer t1/2 better and more lipophilic properties than Artemether favouring accumulation in brain tissue and thus the

treatment of cerebral malaria was regarded as advantages over the other compounds.

x. **Artesunate**: Water soluble hemisuccinate derivative. Used for oral, rectal, intravenous and intramuscular administration. Available as tablets and as powder with separate vial containing 5 sodium bicarbonate.

xi. **Antibiotics;** Doxycycline & Tetracyclines Are Protein synthesis inhibitors.

Side effects – esophagitis, photosensitivity.

xii. **Proguanil (Chloroguanide):** Biguanide converted to cycloguanil active compound. Slow-acting erythrocytic schizontocide, also inhibits the pre-erythrocytic stage of *P. falciparum*. Not kill gametocytes but inhibit their development in the mosquitoes. Proguanil, is cyclized in the body to cycloguanil which inhibits plasmodial **DHFRase** in preference to the mammalian enzyme. Acts slowly on erythrocytic stage of Vivax& falciparum. Prevents development of gametes.

Therapeutics Uses: Current use of Proguanil is restricted to prophylaxis of malaria in combination with chloroquine in areas of low-level chloroquine resistance among *P. falciparum*. Causal prophylaxis: 100 – 200 mg daily. Safe during pregnancy.

Adverse effects: Stomatitis, mouth ulcers, depression of myocardium, megaloblastic anaemia, Not a drug for acute attack.

xiii. **Pyrimethamine;** It is a diaminopyrimidines more potent than Proguanil. Inhibitor of *plasmodial DHFRase.*Tasteless so suitable for children.

Its Selective anti-malarial action depends on high affinity for plasmodial enzyme. In contrast to trimethoprim, it has very poor action on bacterial DHFRase. Pyrimethamine is a slowly acting

erythrocytic schizontocide, but **does not** eliminate the **pre-erythrocytic** phase of *P. falciparum.*

Therapeutic Uses: Pyrimethamineused **only** in combination with a **sulfonamide** (S/P) or dapsone. Addition of sulfonamide, retards the development of **resistance**.

If used alone, resistance develops rather rapidly by mutation in the DHFRase enzyme of the parasite.

Adverse events: megaloblastic anaemia, thrombocytopenia and agranulocytosis

3.7.4 Nigeria National Antimalarial Treatment Policy: Regimen Guidelines

Combination Therapy: Antimalarial combination therapy (CT) is the simultaneous use of two or more blood schizonticides drugs with different biochemical targets in the parasites and independent modes of action. Artemisinin-based combination therapy -(ACT) is antimalarial combination therapy with an artemisinin derivative as one component of the combination. Artemisinin combination therapy is what constitute the current national antimalarial treatment guidelines as summary in the tables below.

I. Theoretical basis of ACT

- protect individual drug against occurrence of resistance
- to decrease rate of decline in efficacy
- interrupt spread of resistant strains
- decrease transmission in a region

Combinations Recommended

For uncomplicated malaria

i. Artemether + Lumefantrine
ii. Artesunate + Amodiaquine
iii. Artesunate + SP
iv. Artesunate + Mefloquine
v. Amodiaquine + SP
vi. Artemether + Lumefantrine

ii. Advantages and gains of Artemisinin-based combination therapy

These includes;

i. in uncomplicated malaria Improve clinical cure rates
ii. Delay emergence of resistance
iii. Reduce transmission and widespread use of 1st line Rx with

Artemisinin-based Combination
iv. Therapy Cost effective

Table 30: Current Drugs for Treatment of uncomplicated malaria

Drugs	Dosage form	Strength
Artemether+ Lumefantrine	Tablets	20mg Artemether + 120m Lumefantrine
Use of the different components of these drugs as monotherapy is not recommended		

Table 31: Artemether – Lumefantrine (Coartem)

Weight (Kg)	**Age**	**Dosage**
5 - < 15	6 months - < 3 -4 years	1 tablet b.d x 3/7
15 - < 25	4 years - < 9years	2 tablets b.d x 3/7
25 < 35	9years - < 15years	3 tablets b.d x 3/7
≥ 35	> 15years	4 tablets b.d x 3/7

Drugs	**Dosage form**	**Strength**
Amodiaquine-Artesunate	Tablet	Amodiaquine10mg/kg & Artesunate 4mg/kg
Artesunate + Mefloquine	Tablet	Artesunate 4mg/kg/Mefloquine 15 - 25mg/kg

Table 32: Artesunate + Amodiaquine (Fixed dose combination)

Weight (Kg)	Age	Tablet (strength)	Dosage
≥ 4. 5 - < 9	2 - 116 months	25/67.5	1 tablet b.d x 3/7
≥ 9 - < 18	1 year - < 5years	50/135	1 tablets b.d x 3/7
≥ 18 < 36	6 years - < 13 years	100/270	1 tablets b.d x 3/7
≥ 36	> 14years	100/270	2 tablets b.d x 3/7

Table 33: Artesunate + Amodiaquine (co-blistered)

Weight (Kg)	Age (Years)	Tablet (strength)	Dosage
10 – 20	1 year - < 5years	50/150	1 white tablet + yellow tablet
21 – 40	7 years - < 13 years	50/150	2 white tablets + yellow tablet
≥ 36	Adults	50/150	4 white tablets + yellow tablet

Table 34: Other drugs available for treatment of malaria

Drugs form	Dosage	Strength
Amodiaquine	Tablets	200mg (153.1mg base)
Halofantrine	Tablets	250mg (233 mg base)
Dihydroartemisinin (and other ACT derivatives)	Tablets	20, 60 or 80mg

Table 35: Currently Available Drugs for severe Malaria

Quinine	Injection	300mg/ml in 2 ml ampoule
Artemether	Injection	80mg / ml in 1 ml ampoule
Artesunate	Injection	60 mg /1 ml vial

v. **Artemisinin and Prophylaxis:** Prophylaxis of malaria are not considered to be indications for the artemisinin group of drugs.

3.9 Other Antiprotozoal

3.9.1Trypanosomiasis:

i. **African Trypanosomiasis (sleeping disease:** It is caused by the hemoflagellates *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*.
The organisms are transmitted by *bites of tsetse flies* (genus *Glossina*), which inhabit shaded areas along streams and rivers. The largest number of cases is in the Congo. Annual incidence estimates are about 100 000 cases and 48 000 deaths.

ii. **American Trypanosomiasis (Chagas' disease)** is caused by *Trypanosoma cruzi*

Drug: benznidazole, pentamidine, melarsoprol, *Eflornithine*, benznidazole and nifurtimox

African trypanosomiasis – treatment: Suramin or pentamidine is effective during the early stages but not for the later neurological manifestations for which melarsoprol should be used.
Eflornithine is effective for both early and late stages.
American Trypanosomiasis – treatment: Prolonged (1–3 months) treatment with benznidazole or nifurtimox may be effective.

3.9.2 Leishmaniasis (zoonosis).

i. Visceral leishmaniasis (kala azar) is caused mainly by *Leishmania donovani* in the Indian subcontinent and East Africa.

Treatment: *Sodium stibogluconate or meglumine antimoniate*; resistant cases may benefit from combining *antimonials with allopurinol, pentamidine, paromomycin, or amphotericin B.*

ii. (Muco-) Cutaneous leishmaniasis is caused mainly by *Leishmania tropica*, *L. major, and L. donovani.*

Treatment: Mild lesions heal spontaneously, *antimonials* may be injected intralesionally.

3.9.3 Toxoplasmosis: *T. gondii,* an obligate intracellular protozoan, is found worldwide in humans and in many species of animals and birds. *The definitive hosts are cats*. Humans are infected after ingestion of cysts in raw or under- cooked meat, ingestion of oocysts in food or water contaminated by cats, transplacental transmission of trophozoites or, rarely, direct inoculation of trophozoites via blood transfusion or organ transplantation. Most infections are self-limited in the immunologically normal patient.
Pyrimethamine with sulfadiazine is used for treatment of chorioretinitis, and active toxoplasmosis in immunodeficient patients; folinic acid is used to counteract the fatal megaloblastic anaemia. Alternatives include pyrimethamine with clindamycin or clarithromycin or azithromycin. *Spiramycin is for treatment of primary toxoplasmosis in pregnant women*. Expert advice is essential.

I. Human Trichomoniasis Human trichomoniasis caused by *Tr. vaginalis,* seen in both females and males. It is usually transmitted by coitus and is sometimes asymptomatic. The symptomatic condition *in females* may take the form of a severe vaginitis associated with discharge, burning, and pruritus. *In males* it may produce urethritis, enlargement of the prostate, and epididymitis.

Treatment: Metronidazole or tinidazole is effective.

3.9.4 Giardiasis:

Giardiasis is a common infection of the human small intestine with the protozoan *Giardia lamblia,* spread via contaminated food or water, or by direct person-to-person contact.
Treatment: Metronidazole, mepacrine, or tinidazole

3.9.5Pneumocystis

Pneumocystis carinii, the causative agent of interstitial plasma cell pneumonia, which can also cause extrapulmonary disease in immunocompromised patients (AIDS, etc.)
Treatment: *Co-trioxazole: i.v/p.o. in high daily doses*

3.10. Pharmacology of Antihelmintics Drugs

3.10.1 Helminths infections: Human is the primary host for most helminthes infections. Most worms produce eggs and larva. These pass out of human body and infect secondary host; immature forms invade humans via skin or GIT

3.10.2 Types of worms: Worms live in host's alimentary canal: Roundworms (nematodes) & Tapeworms. Worms or larvae live in muscles, viscera, menninges, lungs. Subcutaneous tissues: Flukes (trematodes) & Intestinal Worms

i. **Round worms (Nematodes)**; Ascaris Lumbricods (most common), Enterobius vermicularis (pin worm), Trichris trichuria (whip worm), Strongyloides stercoralis (thread worm), and Ankylostoma dudenale (hook worm).
ii. **Tape worms (cestodes):** Taenia saginata (Beef) & Taenia solium (pork)

Humans become infected by eating raw or under cooked meat containing larvae of infected cattle or pig.
In some cases, the larva gets encysted in muscles, viscera, brain, and eye resulting in cysticercosis.

iii. **Tissue worms;** Filariae (bancrofti, Loa loa) Adult Filariae live in the lymphatics, causing lymphadenitis, swelling of limb. Microfilaria goes to blood stream to be ingested by mosquitoes.
iv. **Trichnella spiralis:** larva migrates from intestine to tissues of leg or foot producing ulcer

3.10.3 Classifications of antihelmintics

i. Benzimidazole and probenzimidazoles derivatives: Thiabendazole, Mebendazole, Flubendazole, and Albendazole.
ii. Piperazine derivatives: -piperazine citrate, diethylcarbamazine citrate.
iii. Vinylpyrimidine derivatives: -Pyrantel pamoate.
iv. Dyes:(cyanine dyes): -Pyrivinium pamoate
v. Imidazothiazoles: Levimasole.
vi. Macrocyclic lactones: -Ivermectin
vii. Chlorinated compounds: -CCl4, tetrachloroethylene
viii. organophosphates
ix. more recently introduced,
    a. the amino-acetonitrile derivatives,
    b. the cyclic octadepsipeptides, and - the Spiroindoles.

3.10.4 Characteristics of Ideal Antihelmintics:

i. Orally active.
ii. Effective in single dose.
iii. Inexpensive.
iv. Wide safety margin between toxicity to worm and toxicity to host

3.10.5 Mechanism of Actions

The pharmacological basis of the treatment for helminthes generally involves interference with the integrity of parasite cells, neuromuscular coordination, or protective mechanisms against host immunity, which lead to starvation, paralysis, and expulsion or digestion of the parasite.

Cellular Integrity: Many antihelmintics impair cell structure, integrity, or metabolism: e.g. Inhibitors of tubulin polymerization—Benzimidazole and probenzimidazoles (which are metabolized in vivo to active benzimidazoles and thus, act in the same manner); Uncouples of oxidative phosphorylationsalicylanilides and substituted phenols; and
Inhibitors of enzymes in the glycolytic pathway—clorsulon. Specific categories include drugs that act via

i. nicotinic acetylcholine receptors agonists: imidazothiazoles, tetrahydropyrimidines; allosteric modulator: monepantel;
ii. nicotinic acetylcholine receptors antagonist: spiroindoles,
iii. glutamate-gated chloride channels: ivermectin, milbemycins,
iv. GABA-gated chloride channels: piperazine,
v. Inhibition of acetylcholinesterases: coumaphos, naphthalophos.
vi. Organophosphates inhibit many enzymes, especially acetylcholinesterases, by phosphorylating etherification sites. This

phosphorylation blocks cholinergic nerve transmission in the parasite, resulting in spastic paralysis.

i. **Neuromuscular Coordination:** This process may occur by inhibiting the breakdown or by mimicking or enhancing the action of neurotransmitters. The result is paralysis of the parasite, either spastic or flaccid paralysis of an intestinal helminth allows it to be expelled by the normal peristaltic action of the host.

ii. **Benzimidazole:** Benzimidazole and probenzimidazoles derivatives: These are broad spectrum agents' examples include - Thiabendazole, Mebendazole, Flubendazole, and Albendazole.

iii. **Mebendazole *blocks glucose uptake*:** They act by inhibiting the polymerization of helminthes (Nematodes) β – tubulin, thus interfering with microtubules dependent function such as glucose uptake.

They have selective inhibitory action being 250 -400x more effective in producing effects in helminthes than humans.
Cure rate is about 80 -100%

Thiabendazole inhibits cellular enzymes of susceptible helminthes.
Mechanisms of Action
Albendazole is similar to mebendazole
Broad spectrum
Drug of choice for treatment of hydrated disease and cysticercosis.
Used for the treatment of (intestinal nematodes) e.g. ascariasis, tricurasis and strongyloidiasis, pinworm and hookworm

Indication: Hookworm &Roundworms

Side effects: Gastrointestinal, neurological and hypersensitivity reactions, liver damage, and crystal Luria may be induced.

i. **Thiabendazole:** Rapidly metabolized from the liver & excreted in urine in conjugated form

Indication: Treatment of strongyloides & Hookworm.

Side Effects: occasional transient headache, dizziness and drowsiness have been reported & allergic reactions (fever, rashes) can occur.

iv. **Albendazole:** Is also poorly absorbed but, like mebendazole this might be increased by food especially fats. It is extensively metabolized by first pass to sulfoxide & sulfones metabolites. Sulfoxides may be pharmacologically active

Side effects: - Mild GI disturbances may be caused, and it should not be used inpregnancy or in children under the age of 2years.

v. Vinylpyrimidine derivatives: Pyrantel pamoate.

Praziquentel: Very effective broad-spectrum antibiotics, introduced into clinical practice 20years ago. Drug of choice for all forms of schistosomiasis **Mechanism of Action:** Praziquentel: Disrupts Ca^{2+} homeostasis in the parasites by binding to consensus protein kinase C-binding sites in a β – subunit of schisomes voltage gated – calcium channels. This leads to Influx of ion. A rapid prolonged contraction of musculature & paralyses & death of both adult worms and larvae. It also destructs the teguments of the parasite, unmasking novel antigens, & as a result it may become more susceptible to the normal host immune response.

Adverse effects: Praziquntel is considered to be very safe & effective drug, however little adverse effects do occur which has insignificant clinical consequences. This includes GIT disturbance e.g. nausea, Headache, dizziness, and drowsiness; it cures with a single dose (or divided doses in one day). Aching in the muscles & joints, Skin eruptions & low-grade fever.

ADR may be more marked in patients with heavy Work load.
Praziquentel is considered safe in Pregnancy – commonly use in public health programmes.

vi. Piperazine derivatives: piperazine citrate, diethylcarbamazine citrate

Piperazine: It irreversibly inhibits neuromuscular transmission in the worm Piperazine citrate, probably by acting on GABA, the inhibitory neurotransmitter, or GABA gated- gated chloride channels in nematodes muscles. The response of Nematodes muscle to acetylcholine at neuromuscular junction causing flaccid paralysis in worms which becomes easily dislodged by gut movement, & expelled in faeces.
Adverse effect: Piperazine may cause hypersensitivity reactions (Urtecaria & Bronchospasm), GIT disturbances, *Neurological symptoms* (including "worm wobble"), Parasthesiaes Occasional dizziness, vertigo & incoordination and may precipitate epilepsy.

C/I: In pregnancy and Patients with Liver & Renal compromise
DiethylCarbamazine Citrate (DEC): DEC is a Piperazine derivatives (same to that of piperazine citrate due to piperazine moiety). DEC causes alterations in the microfilarial surface membranes, thereby rendering them recognized as foreign bodies by the host and destroyed by its defence mechanism. It may also interfere with parasite Arachidonate metabolism.

(Note that piperazine citrate and diethyl carbamazine citrate are vermifuges and note the mechanism, while diethylcarbamazine citrate is vermicide for filarial).

Indication: Drug of choice in treatment of filariasis and its active against ascariasis.

Side effects: ADR though common, it's usually transient GIT disturbances e.g. Nausea, anorexia & vomiting, Arthralgia's. General feeling of weakness malaise, fever, headache. Allergic reaction (urticarial), and asthmatic attacks following the first dose are due to products of destruction of (dying microfilariae) the parasite, and reactions are minimised by slow increase in dosage over the first 3 days.
After symptom of reaction subsides, larger doses can be given without problem.

viii. Macrocyclic lactones: -Ivermectin

Ivermectin acts by opening helminthes glutamate - gated chloride channels (found only in invertebrates) & increasing chloride conductance; by binding to novel allosteric sites on Ach – Nicotinic receptors to cause an increase in transmission leading to motor paralysis; or by binding to aminobutyric acid receptors. May cause immediate reactions due to the death of the parasites.

Indication: Drug of choice for treatment of filaria & strongyloidiasis
Side effects: It may cause immediate Mazotti reactions (fever, headache, dizziness, somnolence, hypotension, tachycardia, peripheral oedema, urticaria, swollen and tender lymph nodes and abdominal pain) due to the death of the *microfilaria (early stage in the lifecycle of certain parasitic nematodes)*.

It can be effective in a single dose, but it works best if repeated at 6–12-month intervals. Fatigue, dizziness, GI disturbance, corneal opacities & other eye lesions.

Ix .Niclosamide: Used to treat tapeworm with Praziquentel. Synthesis of niclosamide.

Niclosamide: *blocks glucose uptake* by intestinal tapeworms. Irreversibly damage the worm scolex (i.e. the head that is usually attached to the host intestine, making the worm to separate & expelled from the intestine. It interferes with helminthes metabolism where it inhibits mitochondrial oxidative phosphorylation, inhibits respiration, block glucose uptake by the cestodes. After initial attack of the drug, helminthes (*Taenia solium*)

become highly sensitive to the proteolytic enzymes of the host intestine and undergo partial digestion.

Indication: The drug of choice in treatment of most tapeworm infestations. (Cestodes) such as *Taenia saginata, Taenia*

*solium*and*Hymenolepis nana.*
No systemic absorption of the drug occurs. The digestive juice of the host facilitates the drug penetration into various cestodes.

Very important note: In case of *Taenia solium*, (pork tapeworm): - laxative should be given within 1-2 hours after drug use to expel the dead worms and to avoid cysticercosis [as the drug is not active against the larval form (cystcerci)]. This cysticerci results from release of live ova from worm segments damaged by the drug and migrate to the stomach. Now Praziquantel is the drug of choice in case of *Taenia solium* to avoid such limitation.

Side effects: It may cause some mild GI symptoms: Infrequent and transient nausea & vomiting may occur.

i. **Levimasole:** Levimasole has Nicotine – like actions, stimulating & subsequently blocking the neuromuscular junctions as in Pyrantel pamoate resulting in the paralysis and expelled worm in faeces. Ova are not killed

Potent stereo specific inhibitor of fumarate reductase in various nematodes, such inhibition causes contraction in helminthes, followed by tonic paralysis and subsequent elimination of the worm.

Indications: used for treatment of round worm as Ascariasis, and hook worm as ancylostomiasis.

Side effects: Following single dose, adverse effects are few & transient GIT disturbances it may cause abdominal pain, nausea &vomiting. Headache, and dizziness and skin eruptions. Higher concentration has nicotinic actions on autonomic ganglion

4.0 CONCLUSION

You have learnt in this section definition terms use in antimicrobial chemotherapy, Types and sources of antimicrobial chemotherapy, the basic Mechanisms of action of antimicrobials and the mechanisms of antimicrobial resistance. We also discuss various drugs used in protozoal, helminthes and viral infection and details discussion on antimalarials, antituberculosis and anticancer drugs.

5.0 SUMMARY

Infectious diseases are still a serious problem, compounded by the development of antibiotic resistance in many bacteria and the relative lack of newer antimicrobial agents to combat these multi-resistant organisms. Appropriate aggressive short-course treatment is recommended for ensuring clinical and microbiologic cure, optimal patient adherence, and minimal generation of antibiotic resistance.
The word “antimicrobials” include all agents/drugs that act against all types of microorganisms (Bacteria (Antibacterial) drugs, Fungi (Antifungal) drugs, Protozoa (Antiprotozoan) drugs, Antihelminthic drugs and Viruses (antiviral) drugs. Most modern antibiotics come from species of microorganisms that live in the soil to commercially produce synthetic antibiotic.

Features of ideal antimicrobial drugs are, antimicrobial agents should possess 1. Selective toxicity; it causes greater harm to microorganisms than to host, 2. spectrum of activity that should be effective and kill wide range of microorganisms, 3. effective of combining drugs with good synergistic effects in fight infections, 4, minimal or no adverse Effects, Allergic Reactions to the host 5. It should not suppress normal GIT flora and should be effective against microbial resistant.

General Mechanisms of action of Antibacterial Drugs includes, Inhibition of cell wall synthesis e.g. penicllins, cephalosporins. Injury to plasma/Cell membrane: e.g. polymixin B and colistin, inhibition of protein synthesis e.g. Aminoglycosides, macrolides, inhibition of nucleic acid synthesis: e.g. quinolones, metronidazole, and rifampin and Inhibition of essential metabolites synthesis e.g. Sulfonamides and trimethoprim.

Antiviral Drugs selectivity has been a problem because viruses use the metabolic machinery of the host. Antiviral drugs target specific steps of life cycle, especially enzymes that function in the life cycle (e.g., amantadine, vidarabine, acyclovir, and azidothymidine). Human interferon is used to treat some viral infections.

Antiprotozoal drugs

Major antiprotozoal are malaria; Malaria infection is classified into two broad classes based of the main stages of drug targets.1. Tissue Schizonticides, drugs that eliminates development or dormant form of the parasites and 2. Blood Schizonticides, drugs that act on erythrocytic Parasites. Antimalarial drugs can be classified based on therapeutic antimalarial activity which are 1. Causal prophylaxis: (Primary tissue schizonticides): Primaquine, Proguanil, 2. Suppressive Prophylaxis:

These are Schizonticides. Examples; Quinine, Chloroquine, Proguanil, Mefloquine, Pyrimethamine, artemisinin and Doxycycline, 3. Clinical cure: erythrocytic schizonticides examples; Artemisinin, Quinine, Mefloquine, Atovaquone, Proguanil, Pyrimethamine, Chloroquine, Sulfonamides, Tetracyclines, 4. Fast acting, high efficacy drugs: Artemisinin, Quinine, Mefloquine, halofantrine and Chloroquine. Slow acting, low efficacy drugs: Proguanil, Pyrimethamine, and Sulfonamidesand Tetracycline. Used in combinations and 5. Radical curatives: These drugs attack exoerythrocytic stage (hypnozoites) resulting in clinical curative for total eradication all forms parasites of *P. vivax*&*P. ovale*,*P. malarae*, *P. falciparum* etc. from the body. Gametocidal: Destroy gametocytes and prevent transmission - Artemisinin; against all plasmodia, Primaquine, Chloroquine, quinine. Radical cures of *P. Vivax* infections – Proguanil, Pyrimethamine; prevent development of sporozoites.

Nigeria National Antimalarial Treatment Policy is Artemisinin Combination Therapy: Antimalarial combination therapy (CT) is the simultaneous use of two or more blood schizonticides drugs with different biochemical targets in the parasites and independent modes of action. Artemisinin-based combination therapy (ACT) is antimalarial combination therapy with an artemisinin derivative as one component of the combination. Artemisinin combination therapy is what constitutes the current national antimalarial treatment guidelines as summary in the tables below.

Advantages and goals of Artemisinin-based combination therapy include improve clinical cure in uncomplicated malaria, delay emergence of resistance, reduce transmission and widespread use of 1st line Rx with Artemisinin-based Combination and Cost-effective therapy.

Currently recommended combination antimalarial on the national malaria treatment guidelines for uncomplicated malaria in are Artemether + Lumefantrine, Artesunate + Amodiaquine, Artesunate + SP, Artesunate + Mefloquine, Amodiaquine + SP, and Artemether + Lumefantrine.

Artemisinin and Prophylaxis: Prophylaxis of malaria is not considered to be indications for the artemisinin group of drugs.

Antiprotozoal

i. Trypanosomiasis: benznidazole, pentamidine, melarsoprol, *Eflornithine,* benznidazole and nifurtimox, Leishmaniasis (zoonosis). *Sodium stibogluconate or meglumine antimoniate*
ii. Toxoplasmosis: Pyrimethamine with sulfadiazine Alternatives includes pyrimethamine with clindamycin or clarithromycin or azithromycin. *Spiramycin is for treatment of primary toxoplasmosis in pregnant women*. Expert advice is essential.
iii. Human Trichomoniasis Treatment: Metronidazole or tinidazole is effective
iv. Giardiasis: Treatment: Metronidazole, mepacrine, or tinidazole
v. Pneumocystis: *Cotrimoxazole: i.v/p.o. in high daily doses*
vi. Helminthes infections: Human is the primary host for most helminthes infections. Most worms produce eggs and larva. These pass out of human body and infect secondary host; immature forms invade humans via skin or GIT.

Types of worms**:** Worms live in host's alimentary canal: Roundworms (nematodes) & Tapeworms. Worms or larvae live in muscles, viscera, menninges, and lungs. Subcutaneous tissues: Flukes (trematodes) & Intestinal Worms.

An ideal Antihelmintics should be orally active, effective in single dose, inexpensive and wide safety margin between toxicity to worm and toxicity to host.

Final Thought: "The desire to take medicines is one feature which distinguishes man, the animal from his fellow creatures. It is one of the most serious difficulties with which we have to contend" - Sir William Osler (1894)

SELF ASSESSED EXERCISES

i. Explain the various adverse effects of antineoplastic drugs.
ii. Outline the features of antimicrobial drugs.

6.0 TUTOR- MARKED ASSIGNMENT

1. define antibiotic and antimicrobial? What are the characteristics of an Ideal antimicrobial?
3. what are the rational for ideal antimicrobial. Outline national malaria treatment plan for uncomplicated malaria.
4. Classify antiretroviral according to their mechanisms of actions and outline the adverse effects of one NNRTI, NRTI drugs PI drug.

5. Discuss the mechanisms of actions of anticancer chemotherapy and principles of cancer chemotherapy

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UNIT 3 MODE OF ACTION OF DRUG ACTING ON SPECIFIC DISEASES

CONTENTS

1.0 INTRODUCTION

The course provides knowledge of the basic principles of pharmacotherapy, with special attention to mode of action topical diseases of public health importance. Here you will be expose to the drugs used in obstetrics and Gynaecology and principles of drug prescription in pregnancy and its dangers.
Diabetes Mellitus (DM) is a chronic disease resulting from deficiency in glucose metabolism, caused by relative or complete deficiency in insulin secretion from the beta cells of the pancreas resulting in chronic increase blood sugar (hyperglycaemia).

DEFINITION OF TERMS

- **Abortion:** The termination of pregnancy before the foetus reaches the stage of viability which is usually less than 21 to 22 weeks gestation (or less than 600 gm in weight).
- **Amniotic fluid:** Approximately one litre of fluid in a sac which surrounds the foetus. This fluid protects and cushions the foetus during its development.
- **Apgar scoring:** Rating system for new-born babies, measuring the baby’s general condition on a scale from 1 to 10.
- **Obstetrics:** Obstetrics deals with the care of women's reproductive tracts and their children during pregnancy, childbirth and the postnatal period. A doctor performing such practice is called Obstetrician.
- **LMP:** Last Menstrual Period. It is the time elapsed for 14 days prior to fertilization
- **EDC or EDD:** The Due Date. EDC stands for the old-fashioned "estimated date of confinement." EDD is the more modern "Estimated Day of Delivery." The average pregnancy “gestation” is 40 weeks or 280 days from the first day of the last menstrual period (LMP). For a 28-day cycle, EDD is calculated by taking the

LMP and adding 9 months and 7 days to it. If the cycle is longer than 28 days, add the difference between cycle length and 28 days. Nagele's Rule: Subtract 3 months from the 1st day of the LMP and add 7 days.

i. **Gravida**: It is the number of times the mother has been pregnant, regardless of whether these pregnancies were carried to term. A current pregnancy, if any, is included in this count. A nulligravida or gravida 0 is a woman who has never been pregnant. A primigravida or gravida 1 is a woman who is pregnant for the first time or has been pregnant one time. A multigravida or more specifically a gravida 2 (also secundigravida), gravida 3, and so on, is a woman who has been pregnant more than one time. An elderly primigravida is a woman in her first pregnancy, who is at least 35 years old.

ii. **Parity:** It is the number of times the woman has delivered after the age of viability. It includes the births after 24 weeks or those having weight of 500 grams. TPAL method Para is often recorded in 4 numbers: T= the number of term deliveries (after 37 weeks) P= the number of premature deliveries (> 20 and < 37 wk.) A= the number of abortions either spontaneous of therapeutic) L= the number of living children There can be 4 numbers after the "P" for "Para." The first number is how many term pregnancies. The second number is how many premature babies. The third number is how many abortions or miscarriages the fourth number is how many living children survive.

iii. **Gestation:** Gestation is the carrying of an embryo or foetus inside a female viviparous animal. Mammals during pregnancy can have one or more gestations at the same time (multiple gestations). The time interval of a gestation is called the gestation period.

iv. **Trimester:** The pregnancy is divided into 3 trimesters. The first one is from LMP up until 12 or 13 weeks. The second trimester is from 12-13 weeks until 28 weeks. The third trimester is from 28 weeks until delivery.

v. **Miscarriage:** Miscarriage is the spontaneous end of a pregnancy before 24 weeks of gestation.

vi. **Stillbirth:** It is the birth of a baby after the age of viability when it has no vital functions at birth, i.e. no heart rate, no umbilical cord pulsation, etc.

vii. **Ectopic Pregnancy:** An ectopic pregnancy, or eccysis, is a complication of pregnancy in which the embryo implants outside the uterine cavity.

viii. **Hyperemesis:** Hyperemesis gravidarum (HG) is a severe form of morning sickness, with "unrelenting, excessive pregnancy-related nausea and/or vomiting that prevents adequate intake of food and fluids

ix. **Ante partum Haemorrhage:** Also called prepartum haemorrhage, it is the bleeding from the vagina during pregnancy from the 24th week gestational age to term.

x. **Postpartum Haemorrhage:** It is the loss of greater than 500 ml of blood following vaginal delivery, or 1000 ml of blood following caesarean section.

Pregnancy Induced Hypertension It is the condition of high blood pressure during pregnancy. It is also called Gestational hypertension.

xi. **Pre-eclampsia:** It is when a pregnant woman develops high blood pressure and protein in the urine after the 20th week of pregnancy.

xii. **Eclampsia:** It is an acute and life-threatening complication of pregnancy, is characterised by the appearance of tonic-clonic seizures, which are not due to preexisting or organic brain disorders, usually in a patient who has developed pre-eclampsia.

Pre-eclampsia and eclampsia are collectively called **Hypertensive disorder of pregnancy and toxemia of pregnancy. Symptoms:** Typically, patients show signs of pregnancy-induced hypertension and proteinuria prior to the onset of the hallmark of eclampsia, the eclamptic convulsion. Other cerebral signs may precede the convulsion such as nausea, vomiting, headaches, and cortical blindness.

xiii. **Polyuria:** increase in the frequency of urine output

xiv. **Polydipsia:** excessive thirst

xv. **Polyphagia:** increase in hunger.

xvi. **Heart failure:** As a state in which the heart cannot provide sufficient cardiac output to satisfy the metabolic needs of the body. Heart failure occurs when cardiac output is inadequate to provide the oxygen needed by the body

xvii. **Definition of pain:** Unpleasant sensory and emotional experience associated with actual or potential damage Pain is redefined as a perception instead of a sensation because it is always a psychological state.

It was coined from the Latin word "peona " meaning punishment. Pain is always subjective• It is differently experienced by each individual.

xviii. **Nociception:** Coined by Sherrington – Latin: noxa means injury – it means the ´perception of noxious stimuli´

Mechanism by which noxious peripheral stimuli are transmitted to the central nervous system to elicit a mechanical response. Potentially damaging stimuli (mechanical, thermal, or chemical)

xix. **Pain – Receptors**: Specialised naked nerve endings found in almost every tissue of the body, usually activated by stimuli (mechanical, thermal, chemical).

Distinguished from other receptors by their higher threshold, and they are normally activated only by stimuli of noxious intensity-sufficient to cause some degree of tissue damage.

xx. **Location of nociceptors**: Superficial skin layers, Deeper tissues, Periosteum, joints, arterial wall, liver capsule, pleura. Other deeper tissues are sparse pain nerve endings. But wide spread tissue damage results in pain.
Large internal organs do not contain nerve endings. Polymodal nociceptors respond to all three types of stimulus

xxi. **Chemical Neurotransmitters of Pain:** Histamine, bradykinin, acetylcholine, serotonin, and substance P are chemicals that increase transmission of pain

xxii. **Prostaglandins**: are chemical substances that are believed to increase the sensitivity of pain receptors by enhancing the pain provoking effect of bradykinin
There are 2 main types of fibres involved in the transmission of nociception: Myelinated, A delta fibre – "fast pain", Type C fibres – "second pain"
Chemicals that reduce or inhibit the transmission or perception of pain include endorphins and enkephalins.

2.0 OBJECTIVES

By the end of this unit, you will be able to:

- define terms use in specific diseases
- classify drugs use in obstetrics and gynaecology
- identify the basic mechanism of actions of drugs use in obstetrics and gynaecology
- state the adverse effects and contraindications of drugs use in obstetrics and gynaecology
- describe the causes of specific diseases
- explain the types of drugs use in specific diseases
- describe the adverse effects and contraindications of drugs use in obstetrics and gynaecology
- classify analgesics and Describe the adverse effects, drug interactions and contraindications of analgesics use in the management of pain
- give prescription of drugs in pregnancy and lactation
- list vaccines use in pregnancy.

3.0 MODE OF ACTIONOF DRUG USE IN OBSTETRICS AND GYNAECOLOGY

3.1 Drug use on the Uterus (UTEROTONICS)

Medications that relax the muscle in the pregnant uterus – Tocolytics – or increase uterine contraction – uterotonics – play a vital role in modern obstetric care.

Uterine stimulants: oxytocic or abortifacients
Posterior Pituitary hormones: Oxytocin, Desamino oxytocin
Ergot alkaloids: Ergometrine, Methylergometrine
Prostaglandins: PGE2, PGF2α, Misoprostol
Miscellaneous: ethacridine and quinine
The other hormone is vasopressin

iii. Oxytocin

It is synthesised in the supra-optic and para ventricular nuclei of the hypothalamus. Sensory stimuli from cervix, vagina and breast suckling stimulate the Secretion of oxytocin. The expulsive phase is triggered by sustained distension of uterine cervix and vagina, increased by Oestrogen secretion, while ovarian polypeptide *Relaxin* inhibits its release. Antidiuretic hormone (ADH), pain, haemorrhage and dehydration increase secretion.
Mode of action: Receptor and voltage mediated calcium channels & amniotic and prostaglandin decidual production
Oxytocin: Preparations used includes; Synthetic oxytocin, Syntometrine, Desamino oxytocin and Oxytocin nasal solution. Etc.

Physiological Role of oxytocin

On Uterus: Uterine contraction**.** Oxytocin is very important for cervical dilation before birth and causes contractions during the second and third stages of labour. It assists the uterus in clotting the placental attachment point postpartum- during the first few weeks of lactation. However, in knockout mice lacking the oxytocin receptor, reproductive behaviour and parturition are normal. Sensitivity increases to 8-fold in last 9 weeks and 30 times in early labour. Clinically oxytocin is given only when uterine cervix is soft and dilated.

Breast; Stimulates my epithelial cells leading to milk ejection, milk-*let-down / milk ejection reflex'*. This reflex (naturally) is initiated by the stimulus of suckling, which leads to the release of oxytocin. Sensitivity increases to 8-fold in last 9 weeks and 30 times in early labour.

Oxytocin Effects on other systems: CVS: Small doses cause vasodilatation, producing diastolic hypotension, reflex tachycardia and flushing. **Kidneys:** Higher doses (100 m.I.U.) produce Anti-Diuretic Action leading to decreased urine output, due to constriction of renal cortical vessels (in the presence of oestrogens). Pulmonary oedema can get precipitated if large amounts of i.v fluids and oxytocin are infused together **CNS:** Appears to function as a peptide neurotransmitter in hypothalamus and brainstem to regulate autonomic neurons, can produce emotional behaviours, maternal bonding, adult bonding, enhance social behaviours in autism.

Pharmacokinetics of oxytocin: Not effective when administered orally, intravenously and also as nasal spray (impaired milk ejection Metabolised by liver & kidneys. Half-life = has a half-life of 3-5 minutes and duration of action of approximately 20 minutes.

Therapeutic Indications of Oxytocin: Therapeutic indication in Pregnancy:

Early: to accelerate abortion, to stop bleeding following evacuation of the uterus and used as an adjunct of abortion along with other abortifacient agents.

Late: To induce labour, to facilitate cervical ripening for effective induction, Augmentation of labour, and Uterine inertia.
Labour: In active management of third stage of labour, following expulsion of placenta.

Puerperium: To minimise the blood loss and to control the PPH.
Diagnostic: Contraction stress test to the determination of respiratory function of the feta placental unit during induced contractions.
Induction & augmentation of labour (Mild preeclampsia, Uterine inertia, Incomplete abortion (Post maturity and maternal diabetes etc.).

Post-partum uterine haemorrhage.

Impaired milk ejection.

Adverse effects: At recommended doses relatively safe when used, and side effects are uncommon, excessive dosage or long-term administration over a period of 24 hours or longer, can cause tetanic uterine contractions, uterine rupture, postpartum haemorrhage, and water intoxication, sometimes fatal. Decreased heart rate, arrhythmia, brain damage, seizures, death in the foetus/neonate, due to increased uterine motility.

Maternal death due to: a) Hypertension, b) Uterine rupture

Water intoxication

Contraindications: Hypersensitivity, Prematurity, Abnormal fetal position, evidence of fetal distress and Cephalopelvic disproportion.
Precautions: Multiple pregnancy, Previous suction and Hypertension

ii. **Carbetocin:** A newer analogue of Oxytocin. has advantages quoted are, much rapid onset and longer duration of action. The half-life is much longer (45 minutes) as **compared** to that of oxytocin (4- 10 minutes). Reported to be successful in controlling uterine atony in nearly 84 – 94 % patients.

Side effects include: nausea, vomiting, diarrhoea, headache, hypertension and bronchospasm.
C/I: Should not be used in patients with CVS, pulmonary, hepatic and renal diseases.

iii. **Vasopressin:** Not commonly used as an oxytocic. It has more prominent oxytocic effect on non-pregnant uterus than oxytocin. Foetal hypoxia is a powerful stimulus for its release and foetal distress can lead to high umbilical cord blood levels of vasopressin. If this vasopressin passes from foetal to maternal circulation, significant oxytocic potency can be added to the maternal oxytocin.

iv. **Amide Alkaloids (**Ergometrine &) Methylergometrine - Selectively contracting uterus smooth muscle

Ergotamine: Contracting arteries and veins

Pharmacological effects

Uterine smooth muscle stimulation: Selectively and determined by the functional state of the uterus.

Vessel-contracting effect: Directly contract artery and venous vessels, which can damage vascular endothelial cells at high dose, lead to dry gangrene of the extremities after long term use

α-receptor blocking effect: Reverse the BP-elevating effect of NA
Ergot poisoning was once common associated with abortion, until 1935, when ergometrine was isolated and recognised as the oxytocic principle in ergot. Active substances: Alkaloids, LSD, histamine, Ach and other amines. Onset of ergometrine is quicker (45-60 secs) than methergine (90 secs). Duration is similar (3hrs)

Ergot derivatives: includes **Ergometrine & Methyl ergometrine** are ergot alkaloids, closely related to lysergic acid (LSD) derived from a fungus, ***claviceps purpurea*** a Fungus that grows on rye, wheat etc. **Methergine** is semi synthetic, derived from lysergic acid.

Mechanism of Action/Effects on the Uterus: Ergometrine is known to act at dopamine, serotonin and α-adrenergic receptors, but its powerful effect in causing uterine muscle contraction is not associated with any one particular receptor type ***- partial agonistic.***

Indications

- Post-partum haemorrhage (3rd stage of labour)
- Used for prevention/control of PPH (delivery/LSCS) bleeding after abortion and to ensure normal involution of uterus

Side effects

- Nausea, vomiting, diarrhoea, abdominal pain, chest pain
- Hypertension (palpitation, severe HTN, Stroke & MI)
- Vasoconstriction of peripheral blood vessels (toes & fingers)
- Gangrene

Contraindication- Hypertension, Cardiac disease

v. Prostaglandins (PGs) (Dinoprostone（PGE_2, Dinoprostone（ PGF_{2a}, sulprostone and carboprost) are Prostaglandins (PGs) are C 20 fatty acid compounds containing cyclopentane ring, derivatives of Prostanoic acid were first isolated from human seminal fluid with probable origin from prostate gland, hence named Prostaglandins act as local hormones. PGE2, PGF2α and recently PGE1, found useful for the induction of abortion, induction/augmentation of labor and control of PPH.

The pharmacological effects are: Contraction of smooth muscles of uterus, blood vessels, GIT and bronchioles, Prostaglandins (PGs)
Clinical effects: Myometrial contraction• Softening and dilatation of cervix, inhibition of secretion of progesterone by corpus luteum. Response of the uterus to PGs is maximum in the middle trimester (13th to 20th weeks). Prior administration of mifepristone (anti-progestin drug) sensitizes the uterus to the action of PGs.
Therapeutic uses: Induction of abortion (pathological), Induction of labour (fetal death in utero) and Postpartum haemorrhage.

Side effects: Nausea, vomiting, diarrhoea, fever, flushing and bronchospasm.

CVS side effects: tachycardia, increased mean arterial pressure and pulmonary artery pressure.

Use caution in hypertension, diabetes, angina epilepsy and raised intra-ocular pressure.

Contraindicated in bronchial asthma, uterine scar, cardiac renal or hepatic diseases.

Anaesthetic implications: Because of their action on the bronchiolar tone and pulmonary vasculature, they can lead to V/ Q mismatch and arterial desaturation.

vi. **Dinoprostone i**s a PGE2 - Use as Vaginal **pessary**/gel
Clinical use: In late (2nd Trimester) *therapeutic abortion, Also for cervical ripening and induction of labour*

Advantages: Mobile patient, Reduce need for syntocinon
Side effect: Nausea, vomiting, diarrhoea, fever, uterine hyper stimulation, HTN and bronchospasm

vii. Carboprost

Clinical use: Postpartum haemorrhage (Usually in patients that did not respond to ergometrine).

Side effects: Nausea, vomiting, diarrhoea, fever, bronchospasm, dyspnoea, pulmonary oedema, HTN and cardiovascular collapse

vii. **Mifepristone:** Antiprogestogenic steroid, sensitizes myometrium to prostaglandin-induced contractions & ripens the cervix

Clinical use: Medical termination of pregnancy up to 63days of Gestation& Medical management of miscarriage/IUD
Side effects: Gastro intestinal cramps, rash, urticarial, headache and dizziness,

Contraindication: severe asthma

Misoprostol: Misoprostol is a synthetic analogue of PGE1, and was originally developed to prevent gastric ulceration in patients using long-term non-steroidal anti-inflammatory drugs (NSAID) therapy.

It acts through PG receptors to initiate uterine contractions. Because it is inexpensive and does not need refrigeration, it is a useful adjunct to other uterotonics in the management of postpartum haemorrhage, as well as early pregnancy loss.

3.1.2 Tocolytic: Uterine Relaxants

Decrease uterine contractility/motility in patients who are experiencing true Preterm Labour (with cervical changes). Used to delay/postpone labour, arrest threatened abortion & treatment of dysmenorrhea. Suppression of labour to create additional time for in utero fetal maturation, delay delivery so antenatal corticosteroids can be delivered to facilitate fetal lung maturation and to allow safe transport of mother to an appropriate facility.

They are likely to succeed only if cervical dilatation is < 4 cms, taking up of the lower segment is minimal, effective in reducing the risk of delivery within 24 to 48 hours only.

Classification of Tocolytics

i. β2 adrenergic receptor agonists: Terbutaline, salbutamol, Retodrine and Isoxsuprine
ii. Oxytocin receptor antagonist: Atosiban
iii. Magnesium Sulphate
iv. Others. Calcium channel blockers: Nifedipine & Nicardipine, Prostaglandin synthetase inhibitors: Indomethacin, aspirin, ibuprofen, sulindac, Nitric oxide donors: Nitro-glycerine and Anaesthesia Halothane

Contraindications: Rupture of membranes, Placenta previa, abruption placenta, severe toxemia of pregnancy, Intra uterine infection and Intra uterine death of the foetus.

i. Tocolytic: Terbutaline

Prototype: – Terbutaline -most commonly used, β 2 adrenergic receptor agonists

Mechanism of action is through beta 2 receptor stimulation, causing smooth muscle relaxation. Used in uncomplicated premature labour between 24th to 33rd weeks of gestation. Should not be administered for more than 48 hours, as it can lead to increased risk to the mother.

Adverse Effects: maternal side effects include tremors, malaise, weakness, dyspnea, tachycardia, chest pain, vomiting, diarrhoea,

constipation, pulmonary oedema, dysrrhythmias, and anaphylactic shock. Fetal side effects include tachycardia and potential, hypoglycaemia

Drug interactions: General anaesthetics--- can produce additive hypotension, Corticosteroids--- pulmonary oedema

iv. Tocolytic therapy – Magnesium Sulfate

Calcium antagonist and CNS depressant----relax smooth muscles of the uterus through calcium displacement, increases uterine perfusion---beneficial for the foetus, less expensive with lesser adverse effects than beta-sympathomimetics, excreted by the kidneys and crosses the placenta, Maintenance dose be titrated to keep uterine contractions under control. Contraindicated for clients with migraine, impaired kidney function and recentmyocardial infarction.

Adverse Reactions: – Mother: flush, feelings of increased warmth, perspiration, dizziness, nausea, headache, lethargy, slurred speech, sluggishness, nasal congestion, decreased GI action, increased pulse rate, and hypotension.

- foetus: decreased heart rate and slight hypotonia with diminished reflexes and lethargy for 24 to 48 hours
- Toxicity: respiratory depression and arrest, circulatory collapse, cardiac arrest – Antidote for toxicity: calcium gluconate (10mg IV push over 3 minutes.

v. **Atosiban (Tractocile):** A β –adrenoceptor agonists (Oxytocin receptor antagonist)

Used inhibition of uncomplicated preterm labour between 24-33 weeks (Tocolytic). Given as IVI then continue infusion until no contraction for 6 hrs.

Contraindication: severe PET, eclampsia, IUGR, IUD, placenta previa, placental abruption, abnormal CTG, SROM after 30/40
Side effects: Nausea, vomiting, headache, hot flushes, tachycardia, hypotension and hyperglycemia

3.2. Hypertensive Disorders in Pregnancy

It is associated with severe maternal obstetric complications. Incidence is 5-10%., The most frequent cause of iatrogenic prematurity, Preterm delivery, Intrauterine growth restriction (IUGR), Perinatal death, Maternal cerebrovascular accidents, Placental abruption

Hypertension in Pregnancy: Systolic B.P. ≥ 140 mmHg and/or Diastolic B.P. ≥ 90 mmHg. Documented on two occasions At least 6 hours apart not more than 7 days apart. Readings should be confirmed using appropriate measurement technique, and should be remeasured after 10-15 minutes of rest.

Other Criteria (Not part of definition currently):

i. SBP increased by 30mmHg DBP increased by 15mmHg Mean Arterial Pressure increased by 20mmHg
ii. Non-severe hypertension: SBP 140-159 mmHg or DBP 90-109 mmHg.
iii. Mild: SBP 140-149 mmHg or DBP 90-99mmHg.
iv. Moderate: SBP 150-160 mmHg or DBP 100-110 mmHg.
v. Severe hypertension: SBP > 160 mm Hg or DBP > 110 mmHg or both.

Anti-Hypertensive Therapy in Pregnancy: the following class of drugs are drug of choice during Pregnancy; Sympathomimetics, adrenergic Receptor blocking agent, Alpha and Beta Blockers: Labetalol, Alpha Blockers: Methyldopa, Vasodilators (Hydralazine, Prazosin and Sodium nitroprusside), calcium channel blockers (Nifedipine, Nocardia), and ACEI Inhibitors (Captopril, lisinopril)

Anti-hypertensive drugs contraindicated in pregnancy: These drugs should be avoided because they may cause poor fetal renal function, malformation or can cause IUGR; ACE inhibitors, 2. Minoxidil, Sodium Nitroprusside, diltiazem, Atenolol and Propranolol

Antihypertensives of Choice (DOC) in Pregnancy
JNC 8: labetolol (first line), nifedipine, methyldopa

The choice of drugs given during pregnancy are: - Alpha and Beta blockers (Labetalol hydrochloride), calcium channel blockers (Nifedipine), alpha blockers (Methyldopa), and Vasodilators (Hydralazine hydrochloride).

Mild /Moderate Hypertension/PET:
Alpha Methyldopa

Mechanism of action: Drugs of first choice. Central and peripheral anti-adrenergic action. It is effective and safe for both mother and foetus.

Side effects maternal: postural hypotension, haemolytic anaemia, sodium retention excessive sedation and coomb's test may be positive.
fetal: intestinal ileus

Other Side effects: Headache, dizziness, dry mouth, postural hypotension, nightmares, mild psychosis, depression, hepatitis & jaundice. Important to stop drug in postnatal period

Contraindications: hepatic disorders, psychic patients and -CCF
Dose: orally 250mg bid may be increased to 1 gm tid depending upon the response. IV infusion 250-500mg

Labetolol 100-200mg BD/TDS PO max 2.4g/24hr
ACE inhibitors are contraindicated in pregnancy
Severe Pre-eclampsia / HTN

IV Labetolol (ß blocker): - Side effects: headache, nausea, vomiting, postural hypotension & liver damage. Contraindication: Asthma, marked bradycardia

IV hydralazine (vasodilator): Acts mainly on arteries and arterioles, causing a fall in Blood Pressure accompanied by reflex tachycardia and an increase cardiac output.
Side effects headache, nausea, vomiting, dizziness, flushing, tachycardia, palpitation & hypotension. Because of hypotension preload with gelofusin adv.

- Contraindication- SLE, severe tachycardia and myocardial infarction.

Magnesium Sulphate: Clinical use: Prevention & treatment of seizure in eclampsia / severe pre-eclampsia
Dose: 4g IV stat then 1g/hr to be continued 24hr after last seizure
Side effects: nausea, vomiting, flushing, drowsiness, confusion, loss of tendon reflexes, hypotension, decrease U/O, respiratory depression, arrhythmias and cardiac arrest. Because of toxicity, Mg levels monitored. It is associated with severe maternal obstetric complications.
Incidence is 5-10%., The most frequent cause of iatrogenic prematurity, Preterm delivery, Intrauterine growth restriction (IUGR), Perinatal death, Maternal cerebrovascular accidents and Placental abruption.

3.2.1anticonvulsants Used in Pregnancy

Magnesium Sulphate

Mechanism of Action: Decreased acetylcholine in motor nerve terminals, which is responsible for anticonvulsant properties, thereby reduces neuromuscular irritability. It also decreases intracranial oedema & helps in diuresis. Its peripheral vasodilatation effect improves the uterine blood supply. Has depressant action on the uterine muscles & CNS.
Dose: 4g IV stat then 1g/hr to be continued 24hr after last seizure

Indications: It is a valuable drug lowering seizure threshold in women with pregnancy induced hypertension (eclampsia / severe pre-eclampsia), Used in preterm labour to decrease uterine activity.

Contraindications: Heart block, impaired renal function and Pregnant women actively progressing labour.

Adverse effects

Magnesium Sulphate (MgSO4) is relatively safe and is the drug of choice. Muscular paresis [diminished knee jerks]and respiratory failure. Also, nausea, vomiting, flushing, drowsiness, confusion, loss of tendon reflexes, hypotension, decrease U/O, respiratory depression, arrhythmias, cardiac arrest can occur. Renal function to be monitored. Because of toxicity, Mg levels monitored; Maternal (Severe CNS depression and Evidence of muscular paresis), Fetal (Tachycardia, Hypoglycaemia)
Antidote: Injection of calcium gluconate 10% 10 ml IV.

3.2.2 Contraception and Pregnancy

i. **Progesterone: Diazole** - Synthetic progestin (but not low doses used in oral contraceptives), when given during first 14 weeks, it causes masculinization of female foetus's genitals. FDA pregnancy (cat X). **Progestin** exposure is associated with increase prevalence of cardiovascular abnormalities
ii. **Combined Oral contraceptive pills**, when taken during early stages of unrecognised pregnancy, are believed to be teratogenic agents.
iii. **Diethylstilboestrol [DES] (Human teratogen Cat X):** Commonly used in 1940's & 1950's to prevent abortion; in 1971 determined that DES caused increase incidence of vaginal & cervical cancer in women who had been exposed to DES in utero. In addition, high percentage suffers from reproductive dysfunction (Vaginal adenosis, cervical erosions, Transverse vaginal ridges and vaginal adenocarcinoma).

3.3 Mode of Action of Drug Used in Diabetes Mellitus (Dm)

Diabetes Mellitus (DM) is a chronic disease resulting from deficiency in glucose metabolism, caused by relative or complete deficiency in insulin secretion from the beta cells of the pancreas resulting in chronic increase blood sugar(hyperglycaemia).

Symptoms of DM includes Polyuria, Polydipsia, and Polyphagia. For public health purposes, patient will notice presence of ants where they pass

urine and often in severe cases crystal where deposit where the sites. Urine also tastes sweet. Patient with NIDDM tends to lose weight despite excessive eating.

3.3.1 Two types of DM

i. Insulin dependent diabetes mellitus (IDDM) or type -1, often referred as referred to as juvenile-onset with no insulin secretion.
ii. Non-insulin-dependent diabetes mellitus (NIDDM) or type. Referred to as maturity onset or adult onset diabetes with relative (deficiency) secretion of insulin.

Insulin is released from the beta cells of the islet of Langerhans in the pancreas in response to an increase in blood glucose. Insulin promotes the uptake of glucose, protein (amino acids), and fatty acids transport and storage in the liver and body tissues.

Glucose is converted to glycogen for future needs in the liver and muscle after meals. Usual blood glucose level in the blood is 70 – 110mg/dL). Blood glucose greater than 180mg/dL result in secretion of sugar in urine with diuretic effects – Polyuria.

Drugs used to control diabetes mellitus – a chronic disease that affects carbohydrate metabolism.

There are two groups of antidiabetic agents: insulin and oral hypoglycaemic agents

i. Oral hypoglycaemic agents are synthetic preparations that stimulate insulin release or alter metabolic response to hyperglycaemia
ii. ii. Insulin is a protein secreted from the beta cells of the pancreas, it is necessary for carbohydrate metabolism and plays an important role in protein and fat metabolism.

3.3.2 Mode of action of specific antidiabetic agents

i. Insulin: Mode of Action

Insulin can be produced from animals (Pork or Beef), or from humans using DNA technology. Insulin promotes the uptake of glucose, protein (amino acids), and fatty acids transport and storage in the liver and body tissues.

Types of insulin: there are 3types of insulin

Rapid -acting – regular insulin: onset of action = 30 -60 minutes; with duration 6 to 8 hours.

Intermediate -acting – NPH, Lente- contain protamine (a protein that prolongs the action of insulin): onset of action = 1 – 2hours; peak = 6 to 12 hours with duration 18 to 24hours

Long -Acting – Ultra Lente – contain 1g crystal which dissolves slowly to prolong duration. Duration: onset of action is 4 to 8hour and peak 14 to 20hour; duration of action is 24 to 36hours.
Available also are

Insulin lispro (Humalog) – a new rapid onset insulin approved in 1996 ha on of onset in 5 minutes; but duration of actions is 2 -4hours. It can be administered 5 minutes before meal time.

Insulin Combinations: There are combinations of insulin commercially premixed; Humulin 70/30, Novolin 70/30 and Humulin 50/50 (70/30 = 70% NPH and 30% regular).
Usually concentrations of insulin are 100U/mL, and insulin is packaged in a 10mL vial.

Insulin is given parenterally only.
Insulin Cannot be administered orally. It is destroyed by first pass metabolism in the GIT

Adverse effects of Insulin: Hypoglycaemia, Hypersensitivity reactions and Lipodystrophy (tissue atrophy or hypertrophy at injection site)

Oral Hypoglycaemic Agents

ii. **Sulphonylureas: (**Tolbutamide – short acting, Chlorpropamide – long acting)

Mechanism of action: Stimulates beta cells to secrete insulin

Uses: Non-insulin dependent Diabetes Meletus (NIDDM)

Adverse effects: Similar to Insulin-Hypoglycaemia and Hypersensitivity reactions.

Drug-drug interactions: Aspirin, anticoagulant, anticonvulsants, Sulfonamides and some NSAIDs.

iii. **Non-sulfonylureas: (Newer agents)**
Biguanides: (Metformin (Glucophage)

Mechanism of action

It decreases hepatic production of glucose from stored glycogen which result in decrease blood glucose level after meals. Decrease absorption of glucose from the small intestine. Also increase in insulin receptor sensitivity. And advantage of no hypoglycaemia effects.

Adverse effects: Nausea, anorexia and vomiting. Abdominal crampingand flatulence.

iv. **Alpha - Glucosidase inhibitor (Acarbose)**

Mechanism of Action: Inhibits the digestive enzyme in small intestine responsible for the release of glucose from the complex carbohydrates (CHO) in diets. This prevent CHO absorption and therefore excretion without absorption.

Uses: For patients who do not achieve result with diet alone.

Adverse effects: Weight loss

v. **Thiazolidinediones: Troglitazones:** (Troglitazones Unrelated to other antidiabetic drugs)

Mechanism of action: Decreases insulin resistance, and helps muscle cells respond to insulin and effect to utilisation of glucose.
Uses: May be used with sulfonylureas, metformin, or insulin
Adverse effects: Similar to sulfonylureas but do not cause hypoglycaemia

vi. Hyperglycaemic Drugs (Glucagon):

Mechanism of Action: A Hyperglycaemic hormone secreted by alpha cells of the islets of Langerhans. Glucagon causes increase blood sugar by stimulating glycogenolysis (breakdown to glucose) in the liver (protects body cells).

Uses: Insulin induced hypoglycaemia when other methods are not available or not working

Adverse effects: Commonly causes hypoglycaemia

vii. Diazoxides (Proglycem)

This is chemically related to thiazides diuretics

Mechanism of action: Increase blood sugar by inhibiting insulin release from the beta cells and stimulating release of epi (adrenaline from the adrenal medulla).

Uses: Chronic hypoglycaemia caused by hyperinsulinism due to islet cell carcinoma or hyperplasia. Parenteral form is used for malignant hypertension.

Adverse effects: Usually do not cause hypoglycaemia.

3.4 Mode of Action of Drug Used in Cardiac Failure

Heart failure occurs when cardiac output is inadequate to provide the oxygen needed by the body. As a state in which the heart cannot provide sufficient cardiac output to satisfy the metabolic needs of the body
It is commonly termed congestive heart failure (CHF) since symptoms of increase venous pressure are often prominent. Heart Failure is the final common pathway for many cardiovascular diseases whose natural history results in symptomatic or asymptomatic left ventricular dysfunction. Cardinal manifestations of heart failure include dyspnea, fatigue and fluid retention. Risk of death is 5-10% annually in patients with mild symptoms and increases to as high as 30-40% annually in patients with advanced disease.

3.4.1 Main causes of heart failure

Coronary artery disease, Hypertension, Valvular heart disease, Cardiomyopathy and Cor pulmonale.

Causes of left ventricular failure: This includes; Volume over load: Regurgitate valve High output status, Pressure overload: Systemic hypertension, outflow obstruction; Loss of muscles: as in Post MI, Chronic ischemia Connective, tissue diseases Infection, Poisons (alcohol, cobalt, Doxorubicin) and Restricted Filling: Pericardial diseases, Restrictive, cardiomyopathy and tachyarrhythmia.

3.4.2 Cardiac Function

Dependent upon: Adequate amounts of ATP, Adequate amounts of Ca++, Coordinated electrical stimulus and Adequate Amounts of ATP, which is needed to maintain electrochemical gradients; Propagate action potentials, Power muscle contraction, Adequate Amounts of Calcium
Calcium is ‘glue’ that links electrical and mechanical events.
Coordinated Electrical Stimulation
Heart capable of automaticity

3.4.3 Pathophysiology of Cardiac Performance

From haemodynamic stand point HF can be secondary to systolic dysfunction or diastolic dysfunction

i. **Preload:** is the volume of the blood that fills the ventricles in diastole, when it is increase, it causes the overfilling of the heart which increases the work load. Starling Law: within limits, the Ventricular performance is related to the degree of myocardial stretching. When Lt Ventricular performance (e.g. stroke volume or CO) is plotted as a function of LV function curve, therefore when preload is increase, it leads to increase in ventricular stretching and will enhance the ventricular function. The limit is End Diastolic Pressure (EDP) of 15mmHg when plateau of performance.

On the other hand, marked stretching causes deterioration of ventricular function and EDP of 20mmHg or more result in pulmonary congestion. In HF, preload usually increases because of increase in blood volume and venous return. Reduction of preload is the goal of salt restriction and diuretic therapy. Vasodilators also reduce preload by redistributing the blood into peripheral veins away from the heart.

ii. **Afterload** – is the systemic vascular resistance against the heart must pump the blood, this frequentlyincreases CHF which leads to decrease CO.
This set the stage for the use of drugs that decrease arterial tone in CHF.

iii. **Contractility:** in patient with low output failure, there is reduction in the intrinsic contractility of myocardium resulting in reduction of pump performance; here comes the role of +ve inotropic drugs

iv. **Heart Rate:** which is the major determinant of CO (i.e. CO = S.V. x Heart rate). The heart rate increases as the SV decreases, this is the 1st compensatory mechanism
Neurohormonal changes

Neuro - hormonal reflex involves; The sympathetic nervous and the renin–angiotensin–aldosterone system. These compensatory mechanisms increase the work of the heart and can further contribute to the decline in the cardiac function.

v. **Myocardial Hypertrophy:** Is the most important intrinsic compensatory mechanism, the increase in myocardial mass helps

to maintain cardiac performance in the phase of pressure or volume overload. However, after initial beneficial effect, hypertrophy can lead to ischaemic changes, impairment of diastolic filling and alteration in ventricular geometry (remodelling) due to proliferations of abnormal myocardial cells and CT which die at the accelerated rate leaving the remaining myocardial cells subject to even greater overload.

Symptoms HF: Orthopnoea, paroxysmal nocturnal dyspnea, Low cardiac output symptomsand Abdominal symptoms: Anorexia, nausea, abdominal fullness, Rt hypochondrial pain.

3.4.4 Drug Used to treat CHF

i. Cardiac inotropic agents: Cardiac Glycosides (Digoxin, Digitoxin, Ouabain)
ii. Sympathomimetics (B1 -adrenergic agonist): (dopamine, dopamine)
iii. Phosphodiesterase inhibitors (amrinone, milrinone)
iv. Diuretics (Loop diuretics e.g. Frusemide, K+ sparing diuretics e.g. Spironolactone)
v. ACI –Captopril, Enalapril, Lisinopril
vi. ARB – Candesartan, Losartan, Valsartan
vii. Beta Blockers - Bisoprolol, Carvedilol
viii. Other possible medications that might be prescribed are anticoagulants (blood thinners). These drugs may be prescribed if you are a heart failure patient with atrial fibrillation, or have another problem with your heart where adding this drug is indicated. Anticoagulants are not used to treat heart failure without the presence of atrial fibrillation. Cholesterol lowering drugs (statins)
Your doctor may prescribe this class of medication if you have high cholesterol or have had a heart attack in the past.

CARDIAC GLYCOSIDES

i.Digoxin

Cardiac glycosides come from the plants of foxglove family (Digitalis spp) & related plant. Digitalisis one of the oldest drugs in clinical use (1200AD). There are two types in clinical use –**Digoxin and Digitoxin**
Digoxin -Chemistry: The basic structure of glycosides consists of three components; A sugar moiety, A steroid moiety & A lactone.
The sugar moiety consists of unusual 1 -4 chains linked monosaccharides A steroid nucleus containing an unsaturated lactone at C- 17 position and Glycosides residue at C-3. The lactone ring is essential for activity and can retain biological activity even when the steroids is removed.

Digoxin –Mode of Action

It is thought that digitalis increases vagal activity and inhibits Na+/K+ ATPase in myocytes this leads to a transient increase's intracellular concentration of Na+ leading to increases influx of Ca++ via Na/Ca2+ exchanger. This result in increased contractility (Positive inotropic effect). Increased parasympathetic (Vagal) tone and decreased sympathetic effect on the heart this suppressed AV node conduction increasing refractory period, thereby decrease conduction velocity and result in decreased heart rate.

This result in increased CO through their +ve inotropic effect. They slow heart rate by relieving the sympathetic tone & through their vagotonic effects. They reduce the heart size by reliving Frank –Starling relationship.

They increase cardiac efficiency by increasing CO, force of cardiac contractility, decrease O2 consumption (decrease heart size & rate).
Blood Pressure – Remain unchanged following the administration of cardiac glycosides.

In CCF, the CO is reduced but the total peripheral resistance is increased, & these effects are reversed by cardiac glycosides.

Cardiac glycosides bring about diuresis by increasing both CO & renal blood flow; the latter in turn reverses the renal compensatory mechanism activated in CCF. Consequently, the production of aldosterone is reduced, sodium retention is reversed, & the excretion of oedematous fluid. Cardiac glycosides have vagotonic effect & may decrease impulse formation in the SA nodes. Although automaticity is not directly influenced by digitalis conductance velocity is decreased. The electrophysiologic properties of digitalis make it a useful compound in the treatment of atrial arrhythmias (for its vagotonic effect).Atrial flutter (for its depressant effect on atrioventricular conductance). Atrial fibrillation (also for its vagotonic effects)

Digoxin: Clinical Benefit: Decreases morbidity in patients with heart failure, does not decrease mortality, improves symptoms of CCHF, CHF refractory to other drugs, can be combined with other drugs and Withdrawal of digoxin in stable patients carries considerable risk.

Indications: Moderate/severe systolic CHF and bradycardia

Digoxin: Adverse Effects: This is frequent and may be fatal. Toxicity may result from overdose or decrease in metabolism and excretion. Hypokalaemia (stemming from the use of thiazides diuretics, diarrhoea & vomiting), Arrhythmias occurring de novo –Atrial/Ventricular ectopic, bradycardia (pulse < 60b/min). CHF exacerbation, Visual disturbances (blurred or yellow vision, halos), Gastrointestinal (Anorexia, nausea, vomiting and diarrhoea), Psychiatric (Delirium, fatigue, malaise, confusion, dizziness and abnormal dreams and Headache), Pulmonary disease, Renal insufficiency and Hypoestrogenism.

Contraindications: The following agent are C/I

Quinidine – Should not be used with digoxin because it displaces digoxin from binding sites**.**

Bretylium should not be used with digoxin because it releases Norepinephrine.
Carotid sinus stimulation should be discouraged as it may precipitate ventricular fibrillation.

Drug treatment of Digoxin toxicity

Antidigoxin Antibodies: The antidigoxin or the antidigoxin antibodies (Digibind) have been used to control digoxin intoxication.
β Stimulants: Dopamine; Peripheral dopaminergic receptor agents are useful in the useful in the treatment of CCF

Diuretics: These include; Thiazides: (chlorothiazide & hydrochlorothiazide

(HCTZ), Loop Diuretics (furosemide, bumetanide) and Potassium Sparing Diuretics (spironolactone).

Mechanism of Actions: Diuretics derived its mode of action from the principle that water follows Sodium(Na+). 20-25% of all Na+ is reabsorbed into the blood stream in the loop of Henle. 5-10% in distal tubule & 3% in collecting ducts. If it cannot be absorbed it is excreted with the urine.

Diuretics reduces venous pressure and ventricular preload. This results in reduction of oedema and cardiac size, which improves pump efficiency.
Aldosterone: Aldosterone may cause myocardial and vascular fibrosis and baroreceptor dysfunction in addition to its renal effects. For this reason, the aldosterone antagonists, spironolactone and eplerenone,

decrease morbidity and mortality in severe heart failure. (M.H., Farjoo Jan. 2007)

Adverse effects of Diuretics: Side effects of diuretics include; electrolyte losses [Na+ & K+], Dehydration fluid losses [dehydration], Myalgia, Nausea, Vomiting and diarrhoea, Dizziness and Hyperglycemia.

Contraindications: Renal Failure.

iii. Other drugs use in heart failure

Angiotensin Converting Enzyme Inhibitors (ACEI).
ACE Inhibitors & ARBs
These drugs reduce peripheral resistance and afterload.
They also reduce salt and water retention and, in that way, reduce preload.
The reduction in tissue angiotensin also reduces sympathetic activity.
These drugs reduce the long-term remodelling of the heart and vessels.

Calcium Channel Blockers (CCB) (diltiazem, verapamil, nifedipine)
Mechanisms of Action CCB:

i. Decrease automaticity & conduction in SA & AV nodes
ii. Decrease myocardial contractility
iii. Decreased smooth muscle tone
iv. Decreased Peripheral vascular resistance (PVR)

Adverse effects of CCBs: Cardiovascular: hypotension, palpitations and tachycardia, Gastrointestinal: constipation & nausea and Others: rash, flushing & peripheral oedema

3.5ANTIHYPERTENSIVE DRUGS

3.5.1 Normal Blood Pressure Regulation

Blood Pressure = Cardiac output (CO) X Resistance to passage of blood through precapillary arterioles (PVR)
Physiologically CO and PVR are maintained minute to minute by arterioles

v. Post capillary venules and Heart
vi. Kidney is the fourth site
vii. Volume of intravascular fluid
viii. Baroreflex, humoral mechanism and renin-angiotensin-aldosterone system regulates the above 4 sites
ix. Local agents like Nitric oxide

In hypertensives – Baroreflex and renal blood-volume control system – set at higher level. All antihypertensives act via interfering with normal mechanisms

Table 36: Classification of Blood Pressure levels

Category	**Systolic blood Pressure (mmHg)**	**Diastolic blood Pressure (mmHg)**
Optimal blood pressure	< 120	< 80
Normal blood pressure	< 130	< 85
High -normal blood pressure	130 -139	85 -89
Grade 1 Hypertension (Mild)	140 -150	90 -99
Grade 2 Hypertension (Moderate)	160 -179	90 -100
Grade 3 (Hypertension)	≥ 180	≥ 110
Isolated systemic hypertension (Garde 1)	140 -150	< 90
Isolated systemic hypertension (Garde)	≥ 160	≥ 90

3.5.2 Causes of Hypertension

i. Genetics-some people are prone to hypertension simply because of their genetic makeup
ii. Family History- your risk for high blood pressure/hypertension increases if it is in your family history
iii. Environment, Inactivity, Stress, Obesity, Alcohol, High Sodium Diet, Tobacco Use, Age and Menopausal Medications
iv. intrauterine factors (the 'Barker hypothesis') is supported by the finding that hypertension in adult life is strongly associated with **low birth weight.**

3.5.3 Antihypertensive Agents: Classifications

i. Angiotensin-converting enzyme inhibitors (ACEI) & Angiotensin II receptor blockers (ARBs)
ii. Diuretics
iii. Calcium channel blockers
iv. Adrenergic agents

Alpha1 blockers & Beta blockers (cardio selective and nonselective)
Centrally acting alpha blockers
Combined alpha-beta blockers
Peripheral-acting adrenergic agents

v. Vasodilators

3.5.4 Mechanisms of Action of Specific Antihypertensive Agents

i. **ACE inhibitors:** Captopril, Lisinopril, Enalapril, ramipril and fosinopril etc.

Mode of Action for ACEIs: ACE Inhibitors work in the lungs to inhibit Angiotensin Converting Enzyme from turning Angiotensin I into Angiotensin II. This result in decreased BP due to a decrease in blood volume, PR, & cardiac load. ACEI causes an increase of bradykinin which causes protracted dry cough.

ACEI, inhibits vasoconstriction and release of aldosterone which inhibits the retention of sodium and water

Indications for Use

Hypertension: Hypertension especially for malignant hypertension and, Hypertension secondary to renal arterial stenosis. ACE inhibitors reduce the risk of cardiovascular mortality caused by hypertension."

Heart Failure: By decreasing arteriolar tone & improves blood flow to the heart, by decreasing afterload, cardiac output increases and venous dilation increase causing a decrease in pulmonary congestion and peripheral oedema.
Dilates the vessels of the kidneys increasing renal flow and helps to excrete sodium and water. This helps to decrease oedema and blood volume. Prevents pathologic changes in the heart that result from reducing the angiotensin II levels in the heart.

Myocardial Infarction (MI): Decreases the chance of heart failure after an MI. Should be given for 6 weeks post MI. If heart failure occurs, it should be considered for permanent use.

Nephropathy: Slows renal disease of diabetic or nondiabetic origins. Decreases glomerular filtration pressure.

Indications for Use: Type 2 Diabetes -It decreases morbidity in high risk patients. Increased levels of angiotensin II have a correlation to type 2 diabetes.

ACE inhibitors increase kinin levels, which increase production of prostaglandins and nitric oxide. Prostaglandins and nitric oxide improve muscular sensitivity to insulin. May preserve pancreatic function and prevent onset of diabetes especially with people who have hypertension.

Adverse Effects

First-Dose Hypotension: Usually occurs with initial dose. Worse in patients with severe hypertension, or are on diuretics, or are sodium or volume depleted.

Cough: Persistent, dry, irritating, non-productive cough can develop with all ACE inhibitors." (Lehne, 2007, pg. 466) Due to rise in bradykinin which occurs due to inhibition of kinase II. Occurs in 5-10% of patients and is more common in women and the elderly.

Hyperkalaemia: Potassium levels rise due to the inhibition of aldosterone, which causes potassium to be retained by the kidneys.

Renal Failure: Can cause renal insufficiency in people who have bilateral renal artery stenosis, because dropping the pressure in the renal arteries in these patients can cause glomerular filtration to fail.

Fetal Injury: In the second and third trimesters a foetus can experience hypotension, hyperkalaemia, skull hypoplasia, renal failure, and death.

Angioedema: swelling of lips, mouth, nose etc. Kinin accumulation may also underly *angioedema* (painful swelling in tissues which can be life-threatening if it involves the airway).

Others (Rare): Rashes, urticaria, Dysgeusia: loss or alteration of taste, and Neutropenia etc.

Drug Interactions: Antihypertensive agents can cause an increased effect of medications especially with diuretics.
ACEI causes **Potassium** increasing effects of result in an increased risk of hyperkalaemia due to the suppression of aldosterone.

Lithium: ACEI causes an increase to risk of lithium toxicity.

Allopurinol: Increases hypersensitivity to medication

NSAIDS: Reduce antihypertensive effects of medication

Contraindications: Pregnancy: ACEI causes fetal death due bilateral renal artery stenosis, hypersensitivity and hyperkalaemia

ii. Angiotensin Receptor Blockers (ARBs)

Examples of ARBs: Candesartan, Losartan, Valsartan, Irbesartan, Telmisartan, eposartan and Olmesartan

Mode of Action of ARBs: Inhibit synthesis of Angiotensin II, by competitive inhibition of angiotensin -11 at tissue binding sites. Resulting in decrease in peripheral resistance and blood volume. Block the receptors in brain, kidneys, heart, vessels and adrenal tissue

Clinical indications of ARBs; Their uses include the following:
Hypertension, especially in:

a. young patients (who have higher renin than older ones)
b. diabetic patients
c. hypertension complicated by left ventricular hypertrophy.

Heart failure.

Diabetic nephropathy.

Advantage

Less likely to cause hyperkalaemia
Persistence of cough is rare
Adverse effects of ARBs
Upper respiratory infections
May cause occasional dizziness, inability to sleep, diarrhoea, dyspnea, heartburn, back pain and fatigue

The AT_1 antagonists are extremely well tolerated but are TERATOGENIC.

iii. **Direct Renin Inhibitors (Aliskiren)**

Orally active renin inhibitors reduce plasma renin activity. Licensed for treatment for essential hypertension.

iv. Calcium Channel Blockers (CCBs) (

Phenylalkylamines: Verapamil
Benzothiazepines: Diltiazem
Dihydropyridines (DHPs); 1st Generations: Nifedipine, 2nd Generations: Isradipine, Nicardipine, Felodipine and 3rd Generations: Amlodipine

Mechanism of action (CCBs): CCBs blocks influx of Ca++ in smooth muscle cells – relaxation of SMCs – decrease BP. Three types Ca+ channels in smooth muscles. Normally, L-Type of channels admit Ca+ and causes depolarization (excitation), contraction coupling through phosphorylation of myosin light chain, contraction of vascular smooth muscle – elevation of BP.

CCBs block L-Type channel: *Resulting in* smooth Muscle relaxation and causes negative chronotropic, ionotropic and chronotropic effects in heart

Dihydropyridines (DHPs) drugs have highest smooth muscle relaxation and vasodilator action followed by verapamil and diltiazem
Other actions: DHPs have diuretic action

CCBs: Indications: Hypertension: Useful in hypertension as peripheral arteries dilators leading to decrease peripheral vascular resistance by relaxing vascular smooth muscle. Dysrrhymias, Angina, Migraine and Headaches.

CCBs are used as monotherapy or in combination and is tolerated well in renal failure. *Calcium Channel Blockers has advantages of,* unlike diuretics no adverse metabolic effects, except mild adverse effects like – dizziness, fatigue etc.

Do not compromise haemodynamic – no impairment of work capacity
No sedation or CNS effect
Can be given to asthma, angina and PVD patients
No renal and male sexual function impairment
No adverse fetal effects and can be given in pregnancy
Minimal effect on quality of life

Adverse effects: Cardiovascular: hypotension, palpitations, tachycardia. Gastrointestinal: constipation, nausea. Other: rash, flushing, peripheral oedema and dermatitis.
Contraindications: CCBs is contraindications unstable angina, Heart failure, Hypotension, Post infarct cases and Severe aortic stenosis.

v. **Potassium (K+) Channel activators:** Diazoxide, minoxidil, pinacidil and nicorandil.

Mode of Action: Leaking of K+ due to opening and result in hyper polarization of SMCs and relaxation of SMCs

vi. **ADRENERGIC BLOCKERS**

Centrally acting Adrenergic Blockers: ***Alpha Methyldopa, Clonidine***

alpha-adrenergic blockers: α – adrenergic blockers: Prazosin, Terazosin, Doxazosin, Phenoxybenzamine and Phentolamine

Non selective alpha blockers: Phenoxybenzamine, Phentolamine

Specific alpha-1 blockers: Prazosin, Terazosin and Doxazosin
Beta-adrenergic blockers

I. Non selective: Propranolol
ii. others: (nadolol, timolol, pindolol and labetolol) and Cardioselective:

Metoprolol (others: atenolol, acebutolol, esmolol, betaxolol)

Centrally acting Adrenergic Blockers (Alpha *Methyldopa, Clonidine)*
Mechanism of Action: They act on alpha-2 receptors in the brain and causes inhibition of adrenergic discharge in medulla **(inhibit sympathetic outflow)**– fall in PVR and fall in BP.
Uses: Central acting Adrenergic blockers are use in hypertension, either alone or with other agents. Usually used after other agents have failed due to side effects.

Alpha-Methyldopa (Aldomet): Is a prodrug, a precursor of Dopamine and Noradrenaline'. It is converted to **alpha methyl noradrenaline** which acts on alpha-2 receptors in the brain and causes inhibition of adrenergic discharge in medulla.

Uses: Drug of Choice in Hypertension during pregnancy. Also, may be used for treatment of severe dysmenorrhea, menopausal flushing, and glaucoma.

Adverse effects: Various adverse effects –Sedation, Dry mouth, blurred vision, cognitive impairment, postural hypotension and positive coomb`s test etc.

Contraindications – Depression, Caution in renal impairment.

vii. **Beta-adrenergic blockers**

Non selective: Propranolol (others: nadolol, timolol, pindolol and labetolol) and Cardioselective: Metoprolol (others: atenolol, acebutolol, esmolol, betaxolol)

Mechanism of Actions: Bind to beta adrenergic receptors and blocks the activity. All beta-blockers have similar antihypertensive effects – irrespective of additional properties. They cause reduction in CO but no change in BP initially but slowly. Adaptation by resistance vessels to chronically reduced CO – antihypertensive action.

Other mechanisms included decreased renin release from kidney (beta-1 mediated), reduction decreased central NA outflow, reduction in glomerular filtration rate (non-selective ones) and reduction in heart rate and CO (ISAs).

Contraindications: Partial and complete heart block, COAD and asthma, Peripheral vascular disease.

Adverse effects: Major drawbacks are Rebound hypertension, Raised LDL and lowered HDL and impaired carbohydrate tolerance in diabetics, Fatigue, lethargy (low CO?) – decreased work capacity, Loss of libido – impotence, Cognitive defects – forgetfulness and nightmares etc.
Difficult to stop suddenly, therefore cardio-selective drugs are preferred now

Cardio- selective Beta-adrenergic blockers**:** Metoprolol (others: atenolol, acebutolol, esmolol, cetamolol).

Mechanism of Action: Vasodilators: Directly relaxes arteriolar smooth muscle Result: decreased systemic vascular response, decreased afterload, and peripheral vasodilation.

Advantages of cardio-selective over non-selective and can be use in patients with asthma, diabetes mellitus, peripheral vascular disease and also lower incidence of changes in lipid profile

Advantages: Overall: beta-blockers as first line of drug

i. No postural hypotension
ii. No salt and water retention
iii. Low incidence of side effects
iv. Low cost
v. Once a day regime
vi. Cardio protective potential

Preferred: In young non-obese patients, Prevention of sudden cardiac death in post infarction patients and progression of CHF, Angina pectoris and post angina patients, Post MI patients – useful in preventing mortality and in old persons, carvedilol – vasodilatory action can be given

Uses: Treatment of hypertension, may be used in combination with other agents, Sodium nitroprusside and diazoxide IV are reserved for the management of hypertensive emergencies.

Adverse Effects: Hydralazine: dizziness, headache, anxiety, tachycardia, nausea and vomiting, diarrhoea, anaemia, dyspnea, oedema and nasal congestion.
Sodium nitroprusside: bradycardia, hypotension, possible cyanide toxicity.

Vasodilators: Hydralazine: Directly acting vasodilator
Mechanism of Action: Hydralazine molecules combine with receptors in the endothelium of arterioles causing NO release consequent relaxation of

vascular smooth muscle – fall in BP. Causes fall in BP due to stimulation of adrenergic system leading to

Uses: Moderate hypertension when 1st line fails – with beta-blockers and diuretics, Hypertension in Pregnancy,

Adverse Effects: Cardiac stimulation producing palpitation and rise in CO even in IHD and patients – anginal attack resulting in tachycardia, increased Renin secretion – Na+ retention. These effects are countered by administration of beta blockers and diuretics (controversial).

Sodium Nitroprusside: Rapidly and consistently acting vasodilator

Mechanisms of Actions: RBCs convert nitroprusside to NO – relaxation also by non-enzymatically to NO by glutathione and relaxes both resistance and capacitance vessels and reduces total peripheral resistance and CO (decrease in venous return). Unlike hydralazine it produces decrease in cardiac work and no reflex tachycardia.

Uses: Hypertensive Emergencies: in saline/glucose and infused slowly with 0.02 mg/min initially and later on titrated with response (wrap with black paper).

Improves ventricular function in heart failure by reducing preload

Adverse effects: palpitation, pain abdomen, disorientation, psychosis, weakness and lactic acidosis.

3.6 Mode Action of Drug Use in Pain Management

3.6.1 Introduction

Pain is the most COMMON reason clients seek medical advice. Pain is a protective mechanism or a warning to prevent further injury
"But pain is a perfect misery the worst of evils Excessive Overturns All patience" John Milton in Paradise Lost.

3.6.2 Clinical types of pain

Pain stimuli (Mechanical / thermal stimuli) Fast pain: Sharp well localized, pricking type.
Chemical stimuli; Slow pain: poorly localised, dull, throbbing (K+, ADP, ATP – Bradykinin, histamine – Serotonin, Prostaglandins, Substance P, CGRP)
Somatic, Visceral, Referred pain: Convergence & facilitation theory
Projected pain: Radiating Pain, Hyperalgesia

3.6.3 Analgesic classifications:

Analgesics: Drugs which relieve pain due to multiple causes without causing loss of consciousness.

Drugs which relieve pain due to single cause or specific pain syndromes (ergotamine, carbamazepine, nitrates) are not classified as analgesics. Corticosteroids also not classified as analgesics
Analgesics are classified as: Opioid analgesics e.g. Morphine and morphine like drugs, Non-steroidal anti-inflammatory drugs (NSAIDs) e.g. Paracetamol, diclofenac, ibuprofen etc.

Mechanisms of actions specific analgesics

i. **Opioid Analgesics:** All opioid analgesics mimic endogenous endorphins by stimulating opioid receptors in the central and peripheral nervous systems which results in relief of pain. Opioids are particularly useful in pain management as they: Hyperpolarize second-order pain transmission neurons by increasing K+ conductance, evoking an inhibitory postsynaptic potential reduce transmitter release from presynaptic terminals of nociceptive primary afferents the descending control system, showing the main sites of action of opioids on pain transmission.

Adverse Effects: The toxic effects of morphine are an extension of their pharmacological effects. Idiosyncrasy and allergy – Urticaria, itch, swelling of lips and bronchospasm (these are rare). A local reaction at injection site may occur due to histamine release. Allergy is uncommon and anaphylactoid reaction is rare. Apnoea This may occur in new born when morphine is given to mother during labour. Others are death due to respiratory failure, Respiratory depression, Nausea and vomiting, Constipation and Drowsiness and sedation.

Contraindications: Some reasons that people should not use opioids include:

Significant respiratory disease; Comatose patients, unless near death; and Pheochromocytoma (in some cases).

Precautions: Care should be exercise in the following conditions; Infants and the elderly, patients with Bronchial asthma, Head injury, Hypotensive states and hypovolemia, Undiagnosed acute abdominal pain, Hypothyroidism, liver and kidney disease and patients with Unstable personalities.

Drug interactions: Drugs which potentiate morphine are Phenothiazines, TCA, MAO inhibitors, Amphetamine and Neostigmine. Morphine retards

absorption of many orally administered drugs by delaying gastric emptying.

Uses: Morphine / parenteral congeners indicated as analgesic in traumatic, visceral, ischaemic (myocardial infarction), Postoperative, burns, and cancer pain. Relieves anxiety and apprehension in serious and frightening disease accompanied by pain: myocardial infarction, Surgeries: Epidural and intrathecal injection of Morphine is being used for analgesia in abdominal, lower limb and pelvic surgeries, labour, postoperative, cancer and other intractable pain.

Preanesthetic medication. produces segmental analgesia for 12 hours without affecting sensory, motor or autonomic modalities.

ii. **Codeine (Methyl Morphine)**

Codeine is low-efficacy opioid a prodrug (t1/2 3 h). It lacks efficacy for severe pain, most of its actions 1/10th those of morphine. Large doses cause excitement. Dependence much less than with morphine.

Uses: principal use: mild to moderate pain & cough. It is said that 60 mg codeine = 600 mg aspirin.

iii. **Pethidine**

Pethidine differs from morphine in that it does not usefully suppress cough, less likely to constipate, less likely to cause urinary retention & prolong childbirth little hypnotic effect. shorter duration of analgesia (2-3 h).

iv. **Methadone**

Principal feature of methadone is long duration, analgesia may last for 24 h. If used for chronic pain in palliative care (12- hourly) an opioid of short t ½ should be provided for breakthrough pain rather than an extra dose of methadone. Also used in opioid withdrawal• Dose: 2.5 mg to 10 mg oral or IM

v. **Fentanyl:** Pethidine congener 80-100 times potent than morphine in analgesia and resp. depression

Uses: Injectable form exclusively used in anaesthesia. Transdermal patch available used in cancer or other types of chronic pain.

vi. **Dextropropoxyphene:** Less analgesic, antitussive, and less dependence. Its analgesic usefulness equal to codeine. Commonly combined with paracetamol. Dextropropoxyphene interacts with warfarin, enhancing its anticoagulant effects.

vii. **Tramadol:** Relieves pain by opioid as well as other mechanisms, 100 mg IV Tramadol = 100 mg IM morphine.

Adverse effects: Less respiratory depression, sedation, constipation, urinary retention, increase intraciliary pressure & dependence than morphine. As effective as pethidine for postoperative pain and as morphine for moderate chronic pain.

viii. **Pentazocine**: Weak μ antagonist action and marked κ agonist action. Analgesia is primarily spinal (K1). can cause a withdrawal syndrome in addicts. shorter duration of pain relief 4-6 hrs, less dependence, sedation & resp. depression• **Use:** post-operative, moderately severe burns.

ix. **Non-opioid analgesics**

Non-opioid analgesics include nonsteroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, and acetaminophen.

Mechanisms of Actions: NSAIDs inhibit cyclooxygenases (COX-1 and COX-2), thereby disrupting the production of prostaglandin, an important mediator of pain and inflammation. Consequently, NSAIDs possess antipyretic, analgesic, and anti-inflammatory effects, and are particularly effective in the management of musculoskeletal pain (e.g., rheumatic disorders, inflammatory joint pain).

Acetaminophenpossesses antipyretic and analgesic effects and is the most commonly used over-the-counter (OTC) oral analgesic drug. It is generally well tolerated, but overdose can result in significant hepatotoxicity with the risk of acute liver failure.

Table 37: Classification of NSAIDs

Drug Class	**Common agents**	**Activity profile**	**Side effects**
Nonsteroidal anti-inflammatory drugs	•Ibuprofen •Diclofenac •Indomethacin •Naproxen •Ketorolac •Aspirin •Meloxicam	•Analgesic •Antipyretic •Anti-inflammatory •Antiplatelet effect	•Gastric and intestinal ulcers, bleeding, and perforation •Renal function impairment •Acute renal failure •Deterioration of chronic renal failure •Chronic analgesic nephropathy •Increased risk of heart attack and stroke (with the exception of aspirin and naproxen).
COX-2 inhibitors (selective NSAID)	•Celebrex (celecoxib)	Celebrex (celecoxib)	•Increased cardiovascular risk •Renal side effects •Deterioration of chronic renal failure •Increase in blood pressure
Other non-opioid analgesics	•Acetaminophen	•Analgesic •Antipyretic	•Hepatotoxicity •Acute liver failure in cases of intoxication •Limited nephrotoxicity

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NSAIDs Agents: (Ibuprofen, diclofenac, indomethacin, naproxen, aspirin)

Mechanism of action

Reversible inhibition of the enzyme's cyclooxygenase 1 and 2 (COX-1 and COX-2) → decreased prostaglandin synthesis.

Effects includes Analgesic, Antipyretic and Anti-inflammatory (antirheumatic).

With the exception of aspirin, only minor antiplatelet function

Adverse effects: Gastric and duodenal ulcers with the risk of

gastrointestinal bleeding and perforation, Risk increases with duration and dose of treatment, Prophylaxis: simultaneous administration of proton pump inhibitors, Increased risk of heart attack and stroke (with the exception of aspirin and naproxen), Renal function impairment: prostaglandins normally maintain renal blood flow by inducing vasodilation of the afferent arterioles. NSAIDS inhibits prostaglandin production, which leads to harmful hypoperfusion of the kidneys and reduced GFR. Electrolyte and fluid abnormalities (oedema, hyperkalaemia, hyponatremia). Worsening of hypertension. In rare cases, acute renal failure

Analgesic nephropathy: prolonged NSAID use results in tubulointerstitial nephritis and papillary necrosis (increase creatinine/BUN ratio, slight increase K+). Pseudo allergic reactions, Urticaria and angioedema and Asthma - Aspirin-exacerbated respiratory disease (AERD)

Indications

i. Acute pain, rheumatoid arthritis, non-rheumatoid joint pain
ii. Especially as an alternative to nonselective NSAIDs for patients with a history of peptic ulcer disease and platelet disorders (e.g., Glanzmann thrombasthenia)
iii. Contraindications
iv. Severe heart failure, recent myocardial infarction, gastrointestinal bleeding

Other non-opioid analgesics Agent
Acetaminophen

Mechanism of Action: Reversibly inhibits cyclooxygenase in the CNS. Is peripherally inactivated no anti-inflammatory effect, minimal gastric side effects

Effects: antipyretic and analgesic effects
Adverse effects

i. Hepatotoxicity due to acetaminophen overdose
ii. Minimum toxic dose: 7.5 g/day in adults
iii. Leading cause of acute hepatic failure in the US. Exhaustion of hepatic metabolic pathways causes increased formation of a toxic metabolite of acetaminophen, N-acetyl-p-benzoquinoneimine (NAPQI). Glutathione initially inactivates NAPQI, but its reserves are eventually depleted, leading to NAPQI build-up. NAPQI causes irreversible oxidative hepatocyte injury → liver cell necrosis.
iv. Acute kidney failure occurs in approx. 50% of patients with acute hepatic failure.

Uses: Fever and pain (Good tolerability)
Preferred analgesic/antipyretic drug during pregnancy
Contraindications: Severe liver impairment - Maximum daily dose of acetaminophen: 4 g (adults).

3.7 Prescription in Pregnancy And Lactation

3.7.1 Introduction

The prevalence of medication use during pregnancy is widespread and on the rise. More than 80% of pregnant women take over the counter (OTC) or prescription drugs during pregnancy, with only 60% of these patients consulting a health care professional when selecting a product. There is a delicate risk-benefit estimation concerning the health of both the mother and the foetus that must be considered in the use of drugs during pregnancy. There is limited research data on drugs during pregnancy and breast-feeding. Women of reproductive age, infants and children were historically excluded from drug research trials. Hence data from adult men had to be "translated" or "extrapolated" to pregnant/ nursing women as well as children until in the 1990's, research standards shifted.

In general, drugs should NOT be used during pregnancy unless absolutely necessary as many can harm foetus. About 2-3% of all birth defects result from drugs that are taken to treat disorder or symptom**.**
Physicians, Pharmacists and Public health practioners play a vital role in educating and counselling pregnant women on the risks associated with a drug. Informing a pregnant woman of the risks and possible fetal defects can reduce the number of complications. Certain health conditions and/or risk factors that may pose significant risks to woman and/or foetus. These are; Asthma, Anaemia/ blood disorder, Diabetes, Epilepsy, Hypertension, infection, pre-existing obesity and underlying mental health conditions etc. Others are maternal advanced age, maternal personal and family medical history and lifestyle choices etc.

3.7.2 How a drug affects the foetus:

How a drug affects the foetus depends on the foetus's stage of development and the strength and dose of the drug. Generally, women who are at the risk of conceiving or who wish to become pregnant should withdraw all unnecessary medications 3-6 months before conception. Certain drugs taken early in pregnancy (15-21 days after fertilization) during the period of blast genesis may act in an all or nothing fashion; Killing the foetus or not affecting it at all. During this early stage the foetus is highly resistant to birth defects.

The foetus is highly vulnerable to birth defects between 3rd week and 8th week after fertilization; which is the period of organogenesis. At this stage drugs may cause a miscarriage, an obvious birth defect, or a permanent but subtle defect, that is noticed later in life. At 9th week the embryo is referred to as a foetus. Development during this time is primarily maturation and growth. Exposure to drugs during this period is not associated with major congenital malformations but they may alter the growth and function of normally formed organs and tissues.

3.7.3 Potential impact of drugs on fetal growth and development

i. **Teratogen:** a medicine or other chemical capable of producing a permanent structural or functional birth defect, growth impairment, or fetal death.

Teratogen acts with specificity to produces a specific abnormality or constellation of abnormalities. Example, thalidomide produces phocomelia, and valproic acid produces neural tube defects. Teratogens demonstrate a dose-effect relationship.
Teratogen must reach the developing conceptus in sufficient amounts to cause their effects. The effect that a teratogenic agent has on a developing foetus depends upon the stage during development when the foetus is exposed.

ii. **Teratogenic agents**

Infections: collectively grouped under the acronym TORCH for Toxoplasmosis, Other organisms (parvovirus, HIV, Epstein-Barr, herpes 6 and 8, varicella, syphilis, enterovirus), Rubella, Cytomegalovirus and Hepatitis etc.

Maternal diet: the best characterised is the role of low folic acid and Neural Tube Defects (NTDs). More recently the focus has been on dietary iodine levels and the role they also play on neural development.

Maternal drugs: affects either prescription drugs (therapeutic chemicals/agents, thalidomide limb development), non-prescription drugs (smoking), and illegal drugs (Cannabis/Marijuana, Methamphetamine/Amphetamine, Cocaine, Heroin and Lysergic Acid Diethylamide).

Environment Factors: (smoking, chemicals, heavy metals, radiation) and maternal endocrine function (maternal diabetes, thyroid development) and maternal stress.
Teratogen synergism, different environmental effects can act individually or in combination on the same developing system. For example, neural

development can be impacted upon by alcohol (fetal alcohol syndrome), viral infection (rubella) and/or inadequate dietary folate intake (neural tube defects). These effects may also not be seen as a direct effect on a system or systems but result in a reduced birth weight and the potential postnatal developmental effects. Consider also this in relation to the increasing support to the fetal origins hypothesis

Table 38: Effects of teratogens at various stages of fetal development

Stages of Fetal development	**Effects of teratogen exposure**
Pre-implantation Conception - week 2	"All or Nothing"
Embryonic Period Week 3 -8	Gross Malformations, Anatomic abnormalities
Fetal Period Week 9 – term	Effects are usually functional (Rather than anatomic structure)

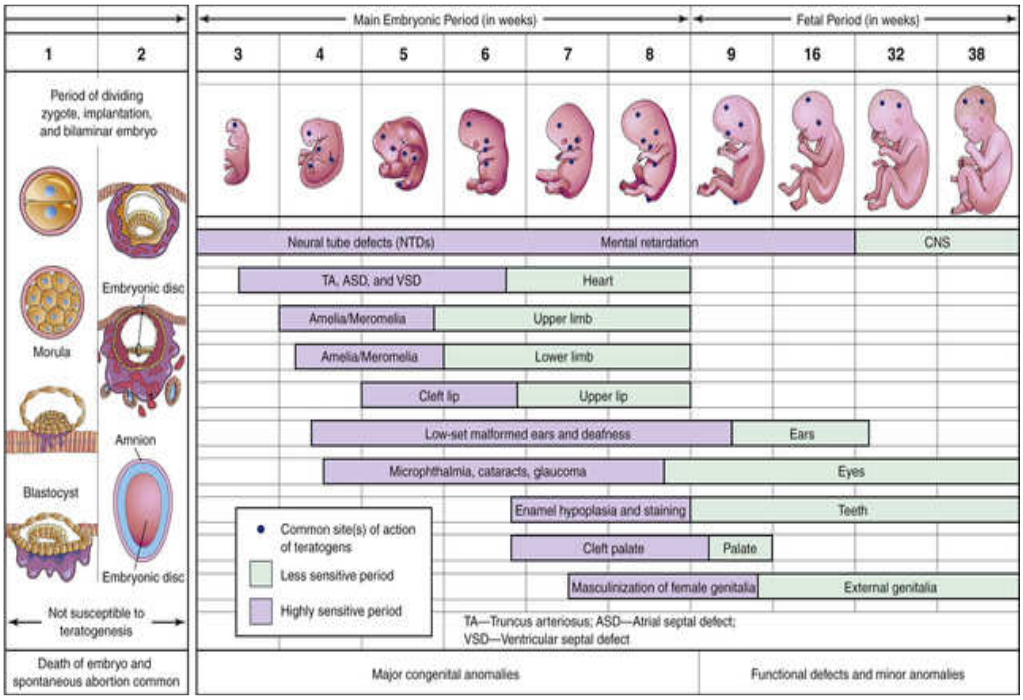

Figure35: Effects of teratogens at various stages of development of the foetus. (@ Moore KL1993.)

iii. **Teratogenesis:** A teratogen is a chemical substance that can induce a malformation during development.
It is the greatest concern for many, the incidence of major structural abnormalities (i.e. life-threatening or require surgical correction) is between 1-3% of births. Half are identified at/near birth; half are identified later or on autopsy. The incidence of minor structural abnormalities is unknown as well as the incidence of functional abnormalities.

Mechanisms of Teratogenesis: Genetic interference (25%), gene mutation, chromosomal breakage, interference with cellular function, enzyme inhibition, and altered membrane characteristics. The response of the developing embryo to these result in failure of cell–cell interaction crucial for development, interference with cell migration, or mechanical cellular disruption.

iv. **Pregnancy Risk categories:** FDA Risk Categories (Do the Benefits Outweigh the Risks?)

Drug use during pregnancy continues to remain a major concern due to the unknown effects on mother and foetus. To help guide physicians in their selection and interpretation of the risks associated with the drug, the FDA introduced a drug classification system in 1979 (Table.). 1983 FDA classified drugs into 5 categories according to probable risks to foetus see table below. Most information provided in this classification is derived from animal studies and uncontrolled studies in humans such as post marketing surveillance reports. To date, very few well-controlled studies have been conducted in pregnant women, most likely due to ethical considerations. Two important limitations of the classification include:

All new FDA-approved medications are classified as Category C
There are no FDA regulations requiring further studies or seeking more data; therefore, changes in the classification are rare.
In addition, the classification is often not changed when new data become available.

Drugs in categories A and B most likely carry little or no risk to the foetus.
Drugs in categories C and D most likely carry some risk to the foetus.
Drugs in category X are contraindicated during pregnancy.

Table 39: Risk Category of drugs during Pregnancy

Category	Study outcome/Abnormality	Examples
A	Adequate studies in pregnant women have failed to demonstrate a risk to the Foetus	inj. Mag sulfate, thyroxine
B	Adequate human studies are lacking, but animal studies have failed to demonstrate a risk to foetus Or Adequate studies in pregnant women have failed to demonstrate a risk to the foetus, but animal studies have shown adverse effects on the foetus	Penicillin V, Amoxicillin, cofactor, erythromycin, paracetamol, lignocaine

C	No adequate studies in pregnant women and animal are lacking or have shown an adverse effect on foetus, but potential benefit may warrant use of the drug in pregnant women despite potential risk	Morphine, codeine, corticosteroids, adrenaline, thiopentane, bupivacaine
D	There is evidence of human foetal risk, but the potential benefit from use of the drug may be acceptable despite the potential risk	Aspirin, phenytoin, carbamazepine, valproate, lorazepam
E	Studies in animals or humans have demonstrated foetal abnormalities, and potential risk clearly outweighs the possible benefit	Oestrogen, isotretiroin, ergometrine

If possible, drug therapy should be delayed until after the first trimester, especially when there is danger of drug-induced developmental defects. Potential fetal risks must be compared to maternal benefits when drug therapy is required. Minimum therapeutic dose should be used for as short a time period as possible.

3.7.4 Clinical example of approach to drug therapy in pregnant woman

Case 1: Thlama is a 30 years old farmer with a seizure disorder who is now pregnant. She presented you in antenatal that she in on Carbamazepine for epilepsy. She seeks your advice on how to prevent seizures during the pregnancy.

What would be your decision? To treat or not to treat?

i. Can the expectant woman safely go without medications to control the condition? – **No, unsafe**.
ii. Can the condition be safely managed without meds? **-No**
iii. What med does she currently use to prevent seizures?

Carbamazepine (anticonvulsant, mood stabilizer) is in Pregnancy Category D, and is one of the "Drugs that Should Be Avoided during pregnancy because of proven or strongly suspected teratogenicity."
Which antiepileptic drug (AED) is best for Thlama?

The drug should be with least teratogenic and effective for her disorder.
AEDs such as valproate and phenobarbital were associated with a higher risk of major malformations than newer AEDs such as lamotrigine and levetiracetam. Topiramate was associated with an increased risk of cleft lip compared with that of a reference population.

Lamotrigine = C, levetiracetam = C. Pregnancy Category C meds pose LESS risk to foetus than Pregnancy Category D.
Decision: Discuss with Physician/neurologist and arrange provider-patient counselling discussion. Obtain new medication order as appropriate. Provide patient education.

3.7.5 Principles of Prescribing in Pregnancy

Prescribing in pregnancy is a balance between the risk of adverse drug effects on the foetus and the risk of leaving maternal disease untreated.

Principles of minimise prescribing;

i. Where possible use non-drug therapy. Prescribe drugs only when definitely needed.
ii. As far as possible, avoid medication in initial 10 weeks of gestation d Use 'tried and tested' drugs whenever possible in preference to new agents; use the smallest effective dose;
iii. remember that the foetus is most sensitive in the first trimester;
iv. consider pregnancy in all women of childbearing potential;
v. discuss the potential risks of taking or withholding therapy with the patient;
vi. seek guidance on the use of drugs in pregnancy in the British National Formulary, Drug Information Services, National Teratology Information Service (NTIS);
vii. As far as possible, avoid medication in initial 10 weeks of gestation
viii. Warn the patient about the risks of smoking, alcohol, over-the-counter drugs and drugs of abuse.
ix. Use drugs for the shortest period necessary If possible, give drug intermittent
x. Over-the-counter drugs cannot be assumed to be safe

3.7.6 Medications You Should Avoid During Pregnancy

Rules about pregnancy medications are constantly changing, such that it can be over whelming for the physician to know what to prescribe to sick pregnant woman. It usually comes down to weighing the benefits for a mother with a health condition even one as simple as a headache, against potential risks to her developing baby. The major challenges to prescription in pregnancy are that Scientists can't ethically perform drug studies on a pregnant woman. Therefore, it's not accurate to say a medication is 100 percent safe for a pregnant woman (simply because it's never been studied or tested).

In the past, medications were assigned to five letter categories based on their level of risk. Category A was the safest category of drugs to take.

Drugs in Category X were never to be used during pregnancy. In 2015, the Food and Drug Administration (FDA) started to implement a new labelling system for drugs. Below is a sampling of a few of the drugs that we know pregnant women should avoid.
The following drugs are common example of drugs that should generally be avoided in pregnant women.

i. **Antibiotics:** Some examples of antibiotics often linked to adverse drug reactions in pregnant includes Tetracycline, Chloramphenicol, Ciprofloxacin and levofloxacin, Primaquine, Sulfonamides, Trimethoprim, etc.

Tetracyclines: Discoularation and deformation of teeth, retarded bone growth.

Chloramphenicol: Chloramphenicol is an antibiotic that's usually given as an injection. This drug can cause serious blood disorders and Gray baby syndrome.

Ciprofloxacin and levofloxacin: Ciprofloxacin and levofloxacin are also the types of antibiotics drugs that ca cause problems with the baby's muscle and skeletal growth as well as joint pain and potential nerve damage in the mother.

Fluoroquinolones can increase the risk of aortic tears or ruptures trusted Source. This can result in life-threatening bleeding. People with a history of aneurysms or certain heart diseases may be at an increased risk of side effects. Fluoroquinolones may also increase the chances of having a miscarriage**.**

ii. **Antimalarial - Primaquine:** Primaquine is a drug that's used to treat malaria. There isn't a lot of data on humans who've taken this drug during pregnancy, but animal studies suggest it's harmful to developing foetuses. It can damage blood cells in a foetus.

Sulfonamides: Sulfonamides are a group of antibiotic medications.

They're also known as sulfa drugs. The majority of these types of drugs are used to kill germs and treat bacterial infections. They can cause jaundice in new-borns. Sulfonamides may also increase the chances of having a miscarriage.

Trimethoprim: Trimethoprim is a type of antibiotic. When taken during pregnancy, this drug can cause neural tube defects. These defects affect brain development in a developing baby.

iii.Analgesics

Codeine: Codeine is a prescription drug used to relieve pain. The drug has the potential to become habit-forming. It can lead to withdrawal symptoms in new-borns.

Ibuprofen: Most experts agree that ibuprofen is probably safe to use in small to moderate doses in early pregnancy. It's especially important to avoid ibuprofen during the third trimester of pregnancy, however. During this stage of pregnancy, ibuprofen is more likely to cause heart defects in a developing baby.

Indomethacin: Premature closure of ductus arteriosus

Thalidomide: Phaecomelias, multiple defects

iv. **Anticancer drugs:** (Methotrexate) Cleft palate, hydrocephalus, multiple defects, foetal death.

v. **Antithyroid**: Foetal goitre, other abnormalities
Iotretitoin- Craniofacial, heart and CNS defects

vi. Contraceptives:

Androgens	Virilization, limb, oesophageal, cardiac defects,
Progestin	Virilization of female foetus
Stiboestrol	Vaginal carcinoma in teenage female offspring

vii. **Anticoagulants:** W**arfarin**It can cause birth defects

viii. **Antihypertensives: ACI inhibitors**: Hypoplasia of organs, growth retardation, foetal loss

ix.CNS Agents

Alcohol: Low IQ baby, growth retardation, foetal alcohol syndrome

Lorazepam: birth defects or life-threatening withdrawal symptoms in a baby after birth

Clonazepam:	withdrawal symptoms in new-borns
Phenytoin:	Hypoplastic phalanges, cleft lip/palate, microcephaly
Phenobarbitone	Various malformations
Carbamazepine	Neural tube defects, other abnormalities
Valproate acid	Spina bifida and other neural tube defects

Lithium Foetal goitre, cardiac abnormalities, other abnormalities

3.7.7 Drug Use during Lactation

Most drugs administered to lactating women are detectable in breast milk. Fortunately, the concentration of drugs achieved in breast milk is usually low. Infant would receive in a day is substantially less than what would be considered **a "therapeutic dose."**

However, if the nursing mother must take medications and the drug is a relatively safe one, she should optimally take it 30–60 minutes after nursing and 3–4 hours before the next feeding. Particular caution should be applied to sedative-hypnotics, Lithium Tetracyclines, antihistamines, morphine and tetracycline are excreted in milk so should be avoided to mothers who are breast feeding

i. Maternal Drug Actions
Effect on reproductive tissue may be altered by endocrinal environment due to pregnancy. Effect on other tissues not changed much, but altered physiologic context may require treatment e.g. cardiac glycosides & diuretics for heart failure and insulin for pregnancy induced diabetes

ii. **Therapeutic Drug Actions:** The Foetus emerging area of 'Fetal Therapeutics'

Corticosteroids: e.g. dexamethasone for lung maturation in premature labour

Phenobarbitone: for neonatal jaundice or decrease intra cranial bleeding

Zidovudine or nevirapine: alone or in combination to prevent vertical transmission Pharmacodynamics.

iii. **Predictable Toxic Effects**

Opioids: dependance, neonatal withdrawal syndrome, respiration depression

ACE inhibitors: renal damage

Diethylstilboestrol: adenocarcinoma of vagina after puberty

iv. **Teratogenic Drug Actions: Birth Defects**

Incidence of major structural defects (abnormalities) is about 6% of all pregnancies. 3% are caused by drugs or environmental factors/exposure. 3% have a genetic or unknown cause 1/2 of the birth defects are obvious at birth.

Toxic Effects of Drugs on the Embryo, Foetus, or Neonate may vary from no effect, Little, Serious- fetal toxicity, Spontaneous abortion, Death, Fetal malfunction to Fetal malformations.

Some abnormalities have multiple causes- genetic factors, environmental factors, chemicals or drugs.

3.7 Special Issues Needing Prescription in Pregnancy

3.8.1 Drug Management of Cough, Cold, and Allergy in Pregnancy

It is very common for women to experience cough, cold, or allergy symptoms during pregnancy. The use of multiple OTC medications to treat these symptoms increases from the first to the third trimester. It had revealed that, 92.6% of the obstetric population interviewed self-medicated with OTC medications.

i. **The common cold** is typically caused by numerous viruses and, therefore, is usually self-limiting. Pregnant women should be advised to first try non-pharmacologic treatments such as a saline nasal spray, the use of a humidifier, and increased hydration. The most commonly used cough, cold, and allergy products include antihistamines, decongestants, antitussives, and expectorants.

ii. It appears that the older sedating antihistamines, also known as first-generation agents, are safe in pregnancy. The recommended first-line agent is chlorpheniramine (Piritin), which is Category B. According to the Collaborative Perinatal Project, chlorpheniramine use during pregnancy was not associated with an increased risk of malformations.

iii. **Diphenhydramine (Benadryl)** is also an option in patients who need symptomatic relief from allergy or cold symptoms. It is also Category B and was not associated with an increased risk of malformations; however, it can cross the placenta and has been reported to have possible oxytocin-like effects at high doses when used during labour. The newer non-sedating or second-generation antihistamines, such as loratadine, fexofenadine, and cetirizine, have not been extensively studied.

iv. **Cetirizine** may be alternative to chlorpheniramine in the second or third trimester if a first-generation antihistamine is not tolerated.

v. **Oral decongestants:** Administration of both inhaled and oral decongestants occurs during pregnancy. Pseudoephedrine and phenylephrine are the most common oral OTC decongestants used, with 25% of pregnant women using pseudoephedrine as their oral decongestant of choice. However, its use should be avoided during the first trimester due to associated risk of defects from vascular disruption known as gastroschisis. Inhaled decongestants such as oxymetazoline and phenylephrine are both Category C and appear to be safe for use.

vi. **Dextromethorphan:** The primary cough remedy used during pregnancy is dextromethorphan. Many studies however, suggest that there is no association between dextromethorphan use and an increased risk of birth defects. However, many of the OTC products containing dextromethorphan also contain alcohol and should be avoided during pregnancy.

vii. **Guaifenesin:** Guaifenesin is the expectorant typically found in most OTC cold medications. Its use appears to be safe during pregnancy, with the exception of the first trimester.

3.8.2 Drug management of Pain in Pregnancy

i. **Acetaminophen:** is the most commonly used OTC analgesic in pregnancy, with at least 65.5% of women taking it at some point during pregnancy and 54.2% taking it during the first trimester. The use of single-ingredient acetaminophen products during pregnancy has not been associated with increased risk of a broad range of birth defects. Due to its antipyretic effects, single-ingredient acetaminophen products have been associated with a decreased risk of some birth defects arising from febrile infection during pregnancy.

ii. **Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs):** should be avoided if possible, during pregnancy. Although recent study found that the use of NSAIDs in early pregnancy does not appear to be a major risk factor for birth defects, there were a few moderate associations between NSAIDs and specific birth defects. Another major concern is the increased risk of miscarriage that has been associated with the use of non-aspirin NSAIDs during pregnancy. The use of NSAIDs during pregnancy is also associated with premature closure of the ductus arteriosus, foetal renal toxicity, and inhibition of labour. Although there are limited reproductive studies involving the use of narcotic analgesics in human pregnancies, these drugs have been used in therapeutic doses for many years by pregnant women without a link to an elevated risk of birth defects.

iii. **Opioids:** The use of opioids should be reserved for pain that is not managed with acetaminophen and, when possible, the lowest effective dose should be used.

3.11.3 Management of GIT Disorders in Pregnancy:

The most common GI problems that occur during pregnancy include nausea, vomiting, acid reflux, diarrhoea, and constipation. Drug therapy may be required when lifestyle modifications cannot provide adequate relief of symptoms.

i. **Nausea & Anorexia:** While nausea and vomiting are common indicators of early pregnancy, an extreme manifestation of the condition is termed hyperemesis gravidarum. Severe hyperemesis gravidarum complications—including weight loss >5% of initial body weight, electrolyte imbalance, and dehydration— are the second most common reason for prenatal hospitalisation. A variety of medications with different mechanisms of action that have been used to treat nausea and vomiting of pregnancy.

ii. **Dyspepsia:** Acid reflux is another common problem estimated to occur in 30% to 50% of all pregnancies. Due to the pressure on the uterus, acid reflux during pregnancy is less likely to respond to lifestyle modifications such as elevation of the head when sleeping, eating small frequent meals, or avoiding eating within 3 hours of bedtime.

iii. **OTC antacids:** OTC antacids are considered the agents of first choice with the exception of magnesium trisilicate and sodium bicarbonate, which should be avoided during pregnancy. Long-term use of high-dose magnesium trisilicate has been associated with increased risk of foetal nephrolithiasis, hypotonia, and respiratory distress; sodium bicarbonate has been associated with metabolic acidosis and fluid overload. A variety of agents that have been used to treat acid reflex during pregnancy Non-absorbable antacids like aluminium hydroxide [Cat B] If taken in early pregnancy, increase of congenital malformations. Sucralfate [Cat B], H2 blockers [Cat B] are safe. All PPIs (Cat B), except Omeprazole [Cat C], Lansoprazole Safest PPI in pregnancy.

iv. **Diarrhoea and constipation** are also frequent problems associated with pregnancy. Lists agents used to treat these conditions includes Loperamide (Cat3)

v. **Castor oil and mineral oil** should be avoided for the treatment of constipation. Alosetron is only indicated for irritable bowel syndrome (IBS)–associated diarrhoea. Bismuth subsalicylate (Pepto-Bismol, Kaopectate) should be avoided in pregnancy

because the salicylate moiety can lead to increased perinatal mortality.

vi. **Bulk laxatives [Cat B**] containing bran, isapghula or methylcellulose are best for simple constipations.

3.8.4 Immunisations:

Women who are considering pregnancy or those already pregnant should be advised on the importance of receiving vaccines. Informing these patients of the benefits of receiving certain vaccinations can significantly reduce the occurrence of preventable diseases. With the many vaccines available, and pharmacists at the front lines as immunisers, it is important to discuss the agents utilised for specific groups of patients. The following are a few of the current recommendations for vaccine use during pregnancy.

The most current update to the immunisation schedule was the recommendation to administer tetanus, diphtheria, and acellular pertussis (Tdap) vaccine with each pregnancy during the 27th to 36th week of gestation. This is different from prior recommendations that were dependent upon previous vaccination history. Waiting until the second trimester is reasonable to minimise concerns about possible adverse reactions. Healy et al concluded that the infants of mothers immunised either before their pregnancy, or in early gestation, displayed insufficient antibodies to aid in infant protection from disease. Furthermore, the antibodies that were transferred were lost within a 6-week period, which could possibly place the infant at risk of infection.

Influenza vaccination should be recommended for all pregnant women for prevention of seasonal influenza and can be administered in any trimester. It is most beneficial when given as early as available in the flu season. The immunisations contraindicated during pregnancy are live vaccinations, which include Live attenuated vaccines (influenza (LAIV); measles, mumps, zoster varicella, MMR & polio) should be given 3 months before pregnancy or post-partum. Live virus vaccines are contra-indicated in pregnancy secondary to potential risk of fetal infection. Killed virus, toxoid, or recombinant vaccines may be given during pregnancy

3.8.5 Learning deficits and /or behavioural abnormalities

There are certain situations that require judicious use of drugs during pregnancy such as Hypertension, Epilepsy, Diabetes and infections that could seriously endanger the mother and foetus. Drugs which may stimulate uterine smooth
muscles are contraindicated during pregnancy e.g. purgatives, anti-malarial drugs and ergot alkaloids.

Drugs capable of crossing placenta and affecting the foetus are barbiturates, alcohol, narcotic and nonnarcotic analgesic.

3.9 Principles of Drug Therapy During Breastfeeding

i. Is the drug therapy necessary?
ii. What is the safest option for the infant?
iii. If there is the possibility of harm, monitor infant blood levels of the drug
iv. Minimise infant exposure

a. Strategies to minimise infant exposure to drug

v. Postpone pharmacotherapy until the baby is weaned if possible; use nonpharmacological strategies when possible.
vi. Although most maternal medications probably pose no harm to the breastfeeding infant, their effects have not been fully studied.
vii. If drug needs to be used, then, when possible:

viii. Mother should take the medication immediately AFTER feeding the baby… to reduce (if possible) the amount of drug in the breast milk
ix. Avoid breast-feeding during peak effect
x. Avoid drugs with long half-life or active metabolites
xi. Drugs that are highly protein-bound are preferred
xii. Use caution if baby is severely ill; a neonate; or preterm. They may not have adequate drug metabolizing enzymes
xiii. **Herbs:** Herbs to Be Avoided During Lactation. *Herbal remedies for nursing mothers pose a health risk to their infants*.

4.0 CONCLUSION

In this unit, you have learnt examples of mode of actions of drugs used in different diseases and outlined in pharmacodynamic principles.

5.0 SUMMARY

Digoxin, a Cardiac glycoside come from the plants of foxglove family (Digitalis spp) & related plant. Digitalis-is one of the oldest drugs in clinical use (1200AD). There are two types in clinical use –Digoxin and Digitoxin

Digoxin is thought to increase vagal activity and inhibits Na+/K+ ATPase in myocytes this leads to a transient increase's intracellular concentration of Na+ leading to increases influx of Ca++ via Na/Ca2+ exchanger. This

result in increased contractility (Positive inotropic effect), Increased parasympathetic (Vagal) tone and decreased sympathetic effect on the heart this suppressed AV node conduction increasing refractory period, thereby decrease conduction velocity and result in decreased heart rate.

This result in Increase CO through their +ve inotropic effect, they slow heart rate by relieving the sympathetic tone & through their vagotonic effects and reduce the heart size by reliving Frank –Starling relationship.
Digoxin: Clinical Benefit includes; decreases morbidity in patients with heart failure, improves symptoms of CCHF

Toxicity may result from overdose or decrease in metabolism and excretion, hypokalaemia (stemming from the use of thiazides diuretics, diarrhoea & vomiting). Arrhythmias occurring de novo – Atrial/Ventricular ectopic, visual – blurred or yellow vision, halos and Psychiatric manifestations (– Delirium, fatigue, malaise, confusion, dizziness and abnormal dreams and Headache) etc.

Blood Pressure = Cardiac output (CO) X Resistance to passage of blood through precapillary arterioles (PVR). All antihypertensives act via interfering with normal mechanisms
Mode of Action of Specific Antihypertensive Agents

ACE inhibitors: Captopril, Lisinopril, Enalapril, ramipril and fosinopril etc. CE Inhibitors work in the lungs to inhibit Angiotensin Converting Enzyme from turning Angiotensin I into Angiotensin II. This result in decreased BP due to a decrease in blood volume, PR, & cardiac load. ACEI causes an increase of bradykinin which causes protracted dry cough.

ACEI, inhibits vasoconstriction and release of aldosterone which inhibits the retention of sodium and water

Indications for Use in Hypertension, Heart Failure, Myocardial Infarction (MI) and type 2 Diabetes.

Adverse Effects are First-Dose Hypotension: Usually occurs with initial dose. Worse in patients with severe hypertension, or are on diuretics, or are sodium or volume depleted. Cough: Persistent, dry, irritating, non-productive cough can develop with all ACE inhibitors." Other adverse effects include Hyperkalaemia, Renal Failure, Fetal Injury, Angioedema and Rarely Rashes, urticaria, Dysgeusia: loss or alteration of taste, and Neutropenia etc.

Pain is the most COMMON reason clients seek medical advice. It is a protective mechanism or a warning to prevent further injury

Analgesics are among drugs which relieve pain due to multiple causes without causing loss of consciousness. Drugs which relieve pain due to single causes or specific pain syndromes (ergotamine, carbamazepine, nitrates) are not classified as analgesics. Corticosteroids also not classified as analgesics

Analgesics are classified as Opioid analgesics e.g. Morphine and morphine like drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) e.g. Paracetamol, diclofenac, ibuprofen etc. adverse effects can usually an extension of their pharmacological effects, idiosyncrasy and allergy – Urticaria, itch, swelling of lips and bronchospasm (these are rare), allergy is uncommon and anaphylactoid reaction is rare, apnoea This may occur in new born when morphine is given to mother during labour.

Others are death due to respiratory failure, Respiratory depression, Nausea and vomiting, Constipation and Drowsiness and sedation.;
NSAIDs Agents such as Ibuprofen, diclofenac, indomethacin, naproxen, aspirin reversibly inhibition of the enzyme's cyclooxygenase 1 and 2 (COX-1 and COX-2) → decreased prostaglandin synthesis resulting in analgesic, Antipyretic and Anti-inflammatory (antirheumatic). with the exception of aspirin, only minor antiplatelet function

Adverse effects include gastric and duodenal ulcers with the risk of gastrointestinal bleeding and perforation, risk of increases with duration and dose of treatment. Renal function impairment: prostaglandins normally maintain renal blood flow by inducing vasodilation of the afferent arterioles. NSAIDS inhibits prostaglandin production, which leads to harmful hypoperfusion of the kidneys and reduced GFR.

Pregnant and lactating women are commonly orphaned from benefits of drug therapy, even when solid data on safety/effectiveness exist. If "Safe use of a drug in pregnancy has not been established. It should not be administered to women of childbearing age unless, in opinion of treating physician, expected benefits to patient markedly outweigh possible hazards to child or foetus". Allow evidence-based counselling and always consider risk of untreated maternal condition

Drugs and Age of Patients - The adjustment of dose and dosing regimen for children and the elderly needs a special consideration because of several differences as compared to an adult individual. The differences may be due to many factors which include changes in Pharmacokinetic parameter, Body weight, Surface area and Genetic predisposition. An important determinant of drug distribution is the volume of distribution, and the determinant for drug metabolism and excretion is elimination half-

life. It is an established fact that the volume of distribution and elimination half-lives of drugs in new born, adults and elderly have considerable differences.

SELF ASSESSED EXERCISES

i. Discuss the medications to avoid in pregnancy.
ii. Give the classes of NSAIDs and the corresponding side effects.

6.0 TUTOR- MARKED ASSIGNMENT

1. What is Teratogenesis? Briefly outline FDA 2015 categories teratogenic drugs
2. What are the Principles of drug prescription in Pregnancy?
3. Classify antihypertensives, discuss the pharmacology of cardiac Glycosides
4. Lists tocolytics and the mechanisms of actions and adverse effects.
5. Tabulate drugs use in the management of pain. Mention mechanisms of action, indications and adverse effects of a named analgesic.

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MODULE 3 PHARMACOTHERAPEUTICS IN PUBLIC HEALTH

Unit 1 Taking Drug History & Evidence Based Medicine
Unit.2 Pharmacovigilance/Pharmacovigilance in Public Health Programmes
Unit 3 Rational Use of Medicines/Drug Dependence and Substance Abuse

UNIT 1 TAKING DRUG HISTORY AND EVIDENCE BASED MEDICINE

CONTENTS

1.0 INTRODUCTION

A medication history taking is a detailed, accurate and complete account of all prescribed and non-prescribed medications that a patient had taken or is currently taking prior to current admission or medical care. It provides valuable insights in to patient's allergic tendencies, adherence to pharmacological and non-pharmacological treatments and self-medication with complementary and alternative medicines etc. Interviewing a patient in collecting the data medical history is called medication history interview.

Without an accurate medication history, prescribers may inadvertently make incorrect decisions about a patient's treatment, causing harm if previously discontinued medicines are restarted, or if current medicines are omitted or prescribed at the wrong dose for the patient. In 2010, the National Patient Safety Agency issued a rapid response report about the importance of avoiding missed doses of medicines [1], highlighting the need to identify a list of critical medicines (including some long-term medicines such as anticonvulsants and anti-Parkinsonian treatments), although this list does not exclusively apply to medication histories.

A study had reported that up to 67% of patients admitted to a general medical ward had at least one error associated with their medication history; the most common being an omission, medicines added that the patient did not take, and incorrect frequency and dosage. In a systematic review by Tam et al. (Tam et al 2005) demonstrated that 41% of medication history errors were clinically important, with 22% having the potential to cause harm, and the EQUIP study demonstrated that 30% of prescribing errors were due to medicines missing on admission. Some of these errors may be attributed to the limitations of the sources used to obtain the history.

Health care professionals are increasingly required to base clinical decisions on the best available evidence. Evidence based medicine (EBM) is a systematic approach to clinical problem solving which allows the

integration of the best available research evidence with clinical expertise and patient values.
An early critique of statistical methods in medicine was published in 1835. However, until recently, the process by which research results were incorporated in medical decisions was highly subjective. Called "clinical judgment" and "the art of medicine", the traditional approach to making decisions about individual patients depended on having each individual physician determine what research evidence, if any, to consider, and how to merge that evidence with personal beliefs and other factors.

In the case of decisions that applied to groups of patients or populations, the guidelines and policies would usually be developed by committees of experts, but there was no formal process for determining the extent to which research evidence should be considered or how it should be merged with the beliefs of the committee members. There was an implicit assumption that decision makers and policy makers would incorporate evidence in their thinking appropriately, based on their education, experience, and ongoing study of the applicable literature.

2.0 OBJECTIVES

By the end of this unit, you will be able to:

- identify the significance of history taking
- describe how to take medication history
- explain the approach to patient while taking medication history
- define evidence-based practice as it is used in physical therapy
- recognise the 5-step processes in Evidence-Based Practice
- compare and contrast arguments for and against evidence-based practice
- state the key research methods needed to locate medical evidence
- identify and describe the steps included in supporting evidence-based practice
- define and describe types of studies in evidence-based practice
- describe strategies to apply evidence-based practice to clinical cases

3.0 MAIN CONTENT

3.1 Definition of Terms

Medication; a chemical substance or other form of medicine that is used to treat or prevent disease.

Hospital admission; admission of a Covered Person to a Hospital as an Inpatient for Medically Necessary and Appropriate care and treatment of an Illness or Injury.

Medical Care; the provision of what is necessary for a person's health and wellbeing by a doctor, nurse, or other healthcare professional.

Medical treatment; the management and care of a patient to fight disease or disorder**.**

Short-term treatment; involves a treatment duration of approximately one month.

Long-term treatment; a treatment which helps meet both the medical and non-medical needs of people with a chronic illness or disability who cannot care for themselves for long periods.

3.2 Taking Drug History

In patient's drug history, care should be taken to write clearly and explicitly, all entries should be signed and dated. Technician complying the drug history should be able to identify any drug omissions, errors on the drug chart or potential problems for discharge. These should be highlighted to the relevant clinical pharmacist who will be able to detect the clinical significance and take the necessary action.

3.2.1 Importance of accurate drug history

The goal of medication history interview is to obtain information on aspects of drug use that may assist in overall care of patient. The information obtain can be utilised to: Compare medication profile with the medication administration record and investigate the discrepancies or verify medication history taken by other staffs and provide additional information where appropriate.

Although doctors usually obtain medication histories during their initial patient interview, there is evidence that those obtained cannot be accurate. When doctors review a patient on admission, the patient may not be able to provide an accurate list of medicines, especially if they are confused or particularly distressed by the cause of their admission.

i Preventing prescription errors and consequent risk to patients.
ii Useful in detecting drug –related pathology or changes in clinical signs that may be the result of drug therapy.

iii It should encompass all currently and recently prescribed drugs, previous adverse drug reactions including herbal or alternative medicines and adherence to therapy for better care plan.

3.2.2 Informant (Information Sources)

i Patient
ii Family or Caregiver
iii Medication Vials / Bubble packs
iv Medication List
v Community Pharmacy
vi Medication Profile from other facility

Patients should always be consulted unless if it is not physically possible (e.g. they are unconscious or confused). If appropriate, the patient's parent, partner or career may be consulted instead of, or in addition to, the patient. Direct discussion with the patient may also highlight issues with medicines adherence and identify other medicines that the patient uses (e.g. over the counter medicines, herbal medicines or medicines from specialist clinics). Patients should also be consulted to confirm any previous allergies or intolerances to medicines.

3.2.3 Challenges with Difficult Clients

i Belief – physician has information
ii Unfamiliar with medications and names
iii Difficulty recalling
iv Medicated clients (sedated, confused)
v Disease affects mental status
vi Language barrier
vii Hearing impairment
viii Elderly clients
ix Caregiver administers or sets up medications
x Medication vials or list unavailable

3.2.3 Interviewing the client

i. Introduce yourself
ii. Inform client of reason for you being there
iii. Inform client of importance of maintaining a current medication list in chart

It is vital that the interviewer clearly introduce himself (in line with the 'Hello my name is' campaign Dr/Pharm. Bassi, and explain the purpose of their consultation with the patient. Careful questioning techniques must

be used as some patients may not consider non-oral medications (e.g. inhalers, eye drops, creams or patches) as medicines or they may fail to mention medicines that they do not consider important, such as oral contraceptives or hormone replacement therapy, or other products they may be regularly taking, such as herbal medicines or dietary supplements.

Patients are encouraged to bring their medicines into hospital to aid medicines reconciliation, prevent missed doses and reduce undue costs. The patient should always be consulted when assessing their own medicines and pharmacy practitioners should always consider:

i that some medicines may have been left at home if the patient stores some separately (e.g. eye drops stored in the refrigerator, patients with most of their medicines dispensed in a multi-compartmental compliance aid [MCCA]);
ii the doses that the patient takes may not be those stated on the dispensed label because of deliberate action by the patient, advice from the prescriber (e.g. phosphate binder dose adjusted according to their serum phosphate), or a dispensing error;
iii medicines brought in may not belong to the patient — he or she may have brought in the wrong medicines or "borrowed" medicines from a relative;
iv the patient may not be taking the medicine at all. The date of dispensing may indicate an adherence issue.

3.2.5 Issues Regarding manner

i Use language that the patient understands
ii Present facts and concepts in simple words logical order
iii Use open ended questions

3.2.6 Questions to Ask

Which community pharmacy do you use?
Any allergies to medications and what was the reaction?

Which medications are you currently taking:

i The name of the medication
ii The dosage forms
iii The amount (specifically the dose)
iv How are they taking it (by which route)?
v How many times a day
vi Any specific times
vii For what reason (if not known or obvious)

What prescription medications are you taking on a regular or as needed basis? How many do you take at a time? Do you have to cut the tablet? What over-the-counter (non-prescription) medications are you taking on a regular or as needed basis?

What herbal or natural medicines are you taking on a regular or as needed basis?

What vitamins or other supplements are you taking?
Have you recently started any new medicines?
Did a doctor change the dose or stop any of your medications recently?
Are any of the medications causing side effects?
Have you change the dose or stopped any medications because of unwanted effects? Do you sometimes stop taking your medicine whenever you feel better?
Do you stop taking your medicine if it makes you feel worse?
Have you recently started any new medications?
Did a doctor change the dose or stop any of your medications recently?
Did you change the dose or stopped any of your medications recently?

3.2.7 Medication History Taking TIPS

Balance open-ended questions (what, how, why, when) with yes/no questions

i Ask non-biased questions
ii Avoid leading questions
iii Explore vague responses (non-compliance)
iv Avoid medical jargon – Keep it simple
v Avoid judgmental comments
vi Various approaches can be used:
- 24 hours' survey (morning, lunch, supper, bedtime)
- Review of Systems (head to toe review)
- Link to prescribers (family physician, specialists)

Prompt for questions for: Pain medications, Stomach medications, Medications for bowels, sleeping aids and ask for Samples. E.g. Eye or ear drops, nose sprays, Patches, creams & ointments, Inhalers (puffers) or Injections (needles).

Use non-biased questions that do not lead the patient into answering something that may not be true. E.g. Fosamax must be taken on an empty stomach first thing in the morning and you must remain upright for 30 minutes. That is how you are taking it, right? Avoid judgmental comments such as: I see that you have been on lorazepam for quite some time, you're likely addicted to them.

If medication vials available: Review each medication vials with patient, confirm content of bottle and Confirm instructions on prescription vials are current.
If bubble packs available: Review each medication with patient, confirm patient is taking entire contents.

3.2.8Additional Questions to Explore (Effectiveness/Compliance)

Are any of the medications causing side effects?
Have you changed the dose or stopped any medications because of unwanted effects? Do you sometimes stop taking your medicine whenever you feel better?
Do you sometimes stop taking your medicine if it makes you feel worse?

Table 40: Cards for Medication History Script

Medication History script	**Additional questions**
Allergies • Do you have any allergy to or avoid any medications due to side effects? • what type of reactions do you have? • When do you take them	Do you have any: • Eye or ear drops, nose sprays • Patches, creams & ointments • Inhalers (puffers) • Injections (needles)
Prescription Medication: • What prescription medications are you taking on a regular or as needed basis? • When do you take them	Do you receive any: • Needle (Injections) • Sample from the doctors consulting room • Study medication?
non-prescription Medication • What over-the-counter medications are you taking on a regular or as needed basis • When do you take them	Do you frequently take • Pain medications • Stomach medications • Medications for bowels • Sleeping aids
Herbal, supplements, Vitamins: • What herbal or natural medicines are you taking on a regular or as needed basis? • What vitamins or other supplements are you taking? • When do you take them	Did you or your doctors change any of your medications

3.3 Client Education

Encourage ownership
Educate client to bring medications from home at each appointment

Educate client to carry a list of current medications (prescription and OTC)
Encourage family members/ caregivers to become involved
Encourage one pharmacy

3.4 Reconciliation and Documentation

Upon discovering a discrepancy

i Update the list if minor (e.g. OTC taken as needed)
ii Include medications prescribed by other physicians (e.g. specialist)
iii Inform physician if client is not taking as prescribed

Medication histories have traditionally been documented in the 'Drug history' section of a doctor's clerking; if the interviewer identified any errors with this list, they would usually document these in the subsequent progress notes. To avoid having information scattered across multiple sections, and to facilitate improved documentation of changes made to a patient's pre-existing medicines, some hospitals or National health insurance scheme (NHS) trusts have implemented specific proformas for recording medication histories. To view a sample medicines reconciliation form. These proformas can be designed to prompt the recording of details concerning the sources used to confirm the medication history and any additional relevant information about the patient's medicines, including:

3.5 Adherence Problems

details, for patients taking warfarin, of the indication, target INR, most recent INR and dose; details of a patient's MCCA (e.g. the name of the community pharmacy that dispensed them, how many weeks at a time they're supplied with them, and how many they have left at home); restrictions on supplies issued in primary care (e.g. patients issued a maximum of seven days because of risk of overdose).

Maintaining and using an accurate medication history

Once an accurate medication history has been obtained, this information should be documented in the patient's medical notes. The medical team should be informed if any changes to the inpatient prescription are required, ensuring a patient's medicines prescribed on admission correspond to what the patient was taking before admission, unless there are any deliberate changes. Any changes, deletions or additions to the patient's regular medicine should be clearly documented to facilitate the provision of accurate information about changes made to a patient's medicines during their admission for GPs.

3.6 Documenting Medication Histories

Medication histories have traditionally been documented in the 'Drug history' section of a doctor's clerking; if pharmacists identified any errors with this list, they would usually document these in the subsequent progress notes. To avoid having information scattered across multiple sections, and to facilitate improved documentation of changes made to a patient's pre-existing medicines, some NHS trusts have implemented specific proformas for recording medication histories. To view a sample medicine reconciliation form, click here. These proformas can be designed to prompt the recording of details concerning the sources used to confirm the medication history and any additional relevant information about the patient's medicines.

3.7 Wrapping Up

i. Thank the patient for their time and information.
ii. Ask them if they have any other questions.
iii. Remind them that if questions do come up, they tell their nurse that they would like to talk to the pharmacist and we will stop back in.
iv. Remind patient that we will be in to discuss any changes to medications and provided updated list prior to discharge.

3.8 Evidence Based Medicine

3.8.1 Introduction Evidence-based medicine is the application of the scientific method into healthcare decision-making. It is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. Medicine has a long tradition of both basic and clinical research that dates back at least to Avicenna.

The term "evidence-based medicine", as it is currently used, has two main tributaries. Chronologically, the first is the insistence on explicit evaluation of evidence of effectiveness when issuing clinical practice guidelines and other population-level policies. The second is the introduction of epidemiological methods into medical education and individual patient-level decision-making.

"Evidence-based medicine" was first introduced in the mainstream medical literature in a 1992 article, "Evidence-based medicine: A new approach to teaching the practice of medicine," which presented EBM as "a fundamentally new approach" emphasising "question formulation, search and retrieval of the best available evidence, and critical appraisal of the study methods to ascertain the validity of results".

3.8 Sources of Information

As EBM gained prominence in the late 1990s and beyond, three streams of evidence dissemination developed:

i Systematic reviews gained increasing prominence in the medical literature,
ii Knowledge search engines (including internet engines such as Google, and Medline interfaces such as Ovid) became standard tools for medical literature searching, and
iii Knowledge distillation and "push" services developed as a way to compile and disseminate concise reviews of evidence on specific topics or questions (e.g., ACP Journal Club, Info Poems, etc.).

In order to decide what to do in practice, we also need to know how we'll know when we are there – that is, what kind of outcomes do we seek?

Medical outcomes can be broadly grouped into 3 categories.

i **Surrogate markers of disease** - Some outcomes (e.g. Hb A1c blood pressure or cholesterol levels) are merely surrogate markers of disease. We measure these surrogate markers because we think they tell us something prognostic about the expected course of a person's disease process, but they do not directly impact on how a patient feels from day to day.
ii **Stage or extent of disease** - Others measure actual stage or extent of disease (e.g. the stage of a diabetic ulcer, or the angiographic extent of disease). These may have a more direct bearing on a patient's quality of life or extent of suffering, but still do not provide direct measures of long-term quality of life.
iii **Patient-oriented outcomes** - The most important outcomes for guiding medical decisions are those that affect how patients feel and the quality of their lives – that is, patient-oriented outcomes such as mobility, suffering, longevity, and other considerations that bear directly on how a patient experiences his or her quality of life. In short, patient-oriented outcomes have primarily to do with long-term morbidity or mortality

An even simpler way to break down the types of outcomes that may be considered is into "disease oriented" outcomes such as blood sugar, blood pressure, flow rate, coronary plaque thickness, or "patient oriented outcomes" such as reduced morbidity, reduced mortality, symptom improvement, improved quality of life, or lower cost.

3.10 Concepts of Evidence-Based Medicine

"Evidenced-based medicine is the concept of formalising the scientific approach to the practice of medicine for identification of "evidence" to support our clinical decisions. It requires an understanding of critical appraisal and the basic epidemiologic principles of study design, point estimates, relative risk, odds ratios, confidence intervals, bias, and confounding. By using this information, clinicians can categorise evidence, assess causality, and make evidence-based recommendations. Evidence-based medicine allows analysis of complicated material so that we can make the best possible clinical decisions for the populations we serve."

The concept of evidence-based medicine (EBM), defined as the ''integration of best research evidence with clinical expertise and patient values'' is based on,

i A process of Life-long self-directed learning in which caring for patients creates the need for important information about clinical and other health care issues.

ii EBM recognises that the research literature is constantly changing. What the evidence point to as the best method of practice today may change next month or next year. The task of staying current, although never easy, is made much simpler by incorporating the tools of EBM such as the ability to track down and critically appraise evidence, and incorporate it into everyday clinical practice. The work of people in the field of Paediatric and child health centres on the problems of children and their families and care givers. Questions about diagnosis, prognosis, and treatment often arise and sometimes the answers to these questions need to be sought. EBM allows the integration of good quality published evidence with clinical expertise and the opinions and values of the patients and their families or care givers.

Deciding on how to treat patients should not be based solely on the available evidence. Other factors such as personal experience, judgement, skills, and more importantly patient values and preferences must be considered. The practice of EBM should therefore aim to deliver optimal patient care through the integration of current best evidence and patient preferences, and should also incorporate expertise in performing clinical history and physical examination.

Figure 36: Theories and Methods

3.11 The Five Steps Ebm Model

The practice of EBM involves five essential Steps. First, converting information needs into answerable questions; second, finding the best evidence with which to answer the questions; third, critically appraising the evidence for its validity and usefulness; fourth, applying the results of the appraisal into clinical practice; and fifth, evaluating performance.

3.11.1 Step 1: Formulating answerable clinical questions

One of the difficult steps in practicing EBM may be the translation of a clinical problem into an answerable question. When we come across a patient with a particular problem, various questions may arise for which we would like answers.

These questions are frequently unstructured and complex, and may not be clear in our minds. The practice of EBM should begin with a well formulated clinical question.

This means that we should develop the skill to convert our information needs into answerable questions. Good clinical questions should be clear, directly focused on the problem at hand, and answerable by searching the medical literature. A useful framework for making clinical questions more focused and relevant has been suggested by Sackett et al. They proposed that a good clinical question should have four (or sometimes three) essential components: the patient or problem in question; the intervention, test, or exposure of interest; comparison interventions (if relevant); and the outcome, or outcomes of interest. Thus, an answerable clinical question should be structured in the PICO (Patient or Problem,

Intervention, Comparison, Outcome/s) or PIO (Patient or Problem, Intervention, Outcome/s) format.

To illustrate the concept of PICO/PIO,

Imagine that you have a 45-year-old male with hypertension presents to your clinic for follow up. At a prior visit he was screened for diabetes. His haemoglobin A1C has been 7.0% on two occasions, which is a new diagnosis of diabetes.

His blood pressure is well controlled at 125/80. He has no evidence of microalbuminuria or kidney disease.
You recall from medical school that ACEI are good for preventing diabetic kidney disease, but you're not sure if this fact applies to this patient.

You want to find this answer.

We will walk you through the process of developing a clinical question!
You decide to use ''clinical score'' as a measure of improvement. The PICO format consists of 4 basic components to keep in mind. The key components of your clinical question would be:

i **Problem and Population:** What is the disease or condition? What are the important characteristics of my patient?
ii **Intervention**: What is the intervention I am looking for? Is it realistic (availability, cost, convenience, etc.)? Is this different from how I currently practice?
iii **Comparison:** What is the alternative to the intervention?
iv **Outcome:** Is it something patients care about? Or is it something only physiologists/pharmacists care about?
So, how do I develop a clinical question? Focusing the PICO question
v **Population:** Starting with your patient, ask "How would I describe a group of patients similar to mine?" Be precise but brief. —target the appropriate specificity (DM/HTN patients who are normotensive on medication without microalbumuria is too specific, etc.). **"In adult patients with diabetes mellitus II and hypertension"**
vi **Intervention/Comparison:** Ask "What is the main intervention I am considering?"and "What is the main comparison/control?" Be specific, but consider feasible alternatives.

Ask "What is the main intervention I am considering?"and "What is the main comparison/control?"
In this Patient: **"An ACEI"**

Outcomes: Ask "What can I hope to accomplish?" or "What could this exposure really affect? “Select patient-oriented outcomes instead of “the numbers.”

Ask "What can I hope to accomplish?" or "What could this exposure really affect? “
Are these outcomes our patient cares about?

“Prevent development of microalbumuria?” OR “Prevent worsening of eGFR?”

Ask yourself patient oriented question: Are these outcomes our patient cares about?

The Patient Is What Matters

There two outcomes our patient cares about?

i **Disease-Oriented Evidence (DOE):** Measures outcomes that are markers for disease, the “Silent numbers”
ii **Patient-Oriented Evidence That Matters (POEMs):** Measure outcomes that our patients care about. They have the potential to change the way we practice!

Physicians may be focused on a number (e.g., GFR, A1C, LDL, BP, etc.) of disease-oriented evidence and overlook the broad goal in mind. What matters is if it changes the patient’s overall morbidity, morality, or quality of life (patient-oriented evidence). For example, no one ever dies of high blood cholesterol. They die from the *effects* of high cholesterol, like a fatal heart attack or a stroke. We often get side-tracked into tracking the numbers when the patient is what truly matters. We need to look at the evidence in the context of the patient and make sure we are doing things that make them live longer or live better!

Characteristics of DOEs and POEMs

i Disease-Oriented Evidence (DOE): Pathophysiological parameters such as Laboratory values or Biochemical markers, Pharmacology e.g. size of tumour, Blood pressure and Aetiology
ii Patient-Oriented Evidence That Matters (POEMs): this includes; Morbidity e.g. Symptoms or Daily function, Mortality and Quality of Life (as perceived by the patient)

Another way of looking at this is that the disease-oriented evidence focuses on the mechanism of action (the internal gears, dials, or “settings” that a patient has).

Instead of looking at the patient-oriented outcomes that the patient is able to see, feel and detect (the external effects of it on their life, like symptoms, their daily functioning or their quality of life.)

3.11.2 Step 2: Finding the evidence

Once you have formulated your clinical question, the next step is to seek relevant evidence that will help you answer the question. There are several sources of information that may be of help.

i Traditional sources of information such as textbooks and journals are often too disorganized or out of date.

ii You may resort to asking colleagues or ‘‘experts’’ but the quality of information obtained from this source is variable.
Secondary sources of reliable summarised evidence which may help provide quick evidence-based answers to specific clinical questions include Archimedes. Other important sources of evidence include the online electronic bibliographic databases, which allow thousands of articles to be searched in a relatively short period of time in an increasing number of journals. The ability to search these databases effectively is an important aspect of EBM. Effective searches aim to maximise the potential of retrieving relevant articles within the shortest possible time. Studies have shown that, even in countries where hospitals have facilities for internet access allowing health care personnel access to a number of electronic databases, many people are not familiar with the process of carrying out efficient searches and often conduct searches which result in too few or too many articles. It is therefore important for health care professionals to undergo basic training in search skills, either through their local library services or through the attendance at formal courses.

iii **basic search principles**

Convert the clinical problem into an answerable question.
The key to successful searching is to convert your clinical problem into a clear answerable question, which should ideally be framed in the PICO/PIO format as discussed above.
Generate appropriate keywords

A word list can be generated, based on keywords from the clinical question. For example, from the clinical question above, the following keywords could be used for the search:

"In adult patients with diabetes mellitus II and hypertension" such would include words like; ACEI, Blood Glucose (A1c), Blood Pressure, Microalbumuria and Morbidity, mortality

Choose a bibliographic database: Numerous online databases are available. These include the Cochrane Library databases, *MEDLINE, EMBASE, and CINAHL*.

i.Conduct the search

Once the key words and databases have been identified, the next thing is to run the search. You can limit your search by publication type (for example, randomized controlled trials or review articles); by date of publication; by language, by study population, and so on. Example of a basic search strategy to try to find evidence to answer the clinical question I formulated earlier, we can use the keywords generated to search the Cochrane database of systematic reviews and PUBMED, using the following search strategy:
When this search strategy was used to search the Cochrane database of systematic reviews in 2014, four articles were retrieved, but only one of these was relevant. Other strategies that may be used to improve the sensitivity and specificity of literature searches have been described by Sackett et al.

Table 41: Some compare and contrast examples of DOEs and POEMs.

Disease oriented evidence (DOE)	**Patients oriented evidence that matters**
Intensive treatment can **lower blood glucose levels** in patients with type 2 diabetes	Intensive treatment in patients with type 2 diabetes does not decrease **Mortality**
Beta – carotene and Vitamin E are **good-antioxidants**	Neither beta – carotene or Vitamin E prevent **Cardiovascular disease or cancer**

Your literature revealed, there is no evidence that driving an A1c below 9% decreases mortality and the outcomes that the UKPDS study shows only microvascular outcomes like less diabetic retinopathy and the ACCORD study shows that driving the A1c<6% is associated with increased mortality.
Similarly, antioxidants have not panned out to demonstrate effects to prevent heart disease or cancer. (for more information, see the accompanying reference).

The question is, do patients care enough about their eyes that they are willing to risk dying earlier than they would otherwise?

Table 42: Here are some more examples.

Disease oriented evidence (DOE)	**Patients oriented evidence that matters**
The drug **varenicline** can help smokers **stop smoking** (which should lead to a decrease in cardiovascular events).	Varenicline increases the **risk of cardiovascular events.**
Older antiarrhythmic medications can **decrease irregular heartbeats** in patients with asymptomatic arrhythmias.	Medical treatment of asymptomatic arrhythmias **increases mortality by 10%.**

The drug Varenicline (Chantix) can help smokers quit, but has been shown to itself, increase the risk of CV events.
Older antiarrhythmics that were commonly used to prevent arrhythmias (according to the methods you may recall learning about in medical school with class IA-c) turned out to actually increase mortality.

3.11.3 Step 3: Appraising the evidence

After you have obtained relevant articles on a subject, the next step is to appraise the evidence for its validity and clinical usefulness. Although there is a wealth of research articles available, the quality of these is variable. Putting unreliable evidence into practice could lead to harm being caused or limited resources being wasted. Research evidence may be appraised with regard to three main areas: validity, importance, and applicability to the patient or patients of interest. Critical appraisal provides a structured but simple method for assessing research evidence in all three areas. A detailed discussion of the critical appraisal of randomised controlled trials and systematic reviews will be provided in the two articles of the series.

3.11.4 Step 4: Applying the evidence

When we decide after critical appraisal that a piece of evidence is valid and important, we then have to decide whether that evidence can be applied to our individual patient or population. In deciding this we have to take into account the patient's own personal values and circumstances. The evidence regarding both efficacy and risks should be fully discussed with the patient or parents, or both, in order to allow them to make an informed decision. This approach allows a ''therapeutic alliance'' to be formed with the patient and the parents and is consistent with the fundamental principle of EBM: the integration of good evidence with clinical expertise and patient values. The decision to apply evidence should also take account of costs and the availability of that particular treatment in your hospital or practice. A practical illustration of issues to

consider before applying research evidence will be provided in the fourth article of the series.

Reviewing the Patient with the evidence, "In adult patients with diabetes mellitus II and hypertension"

Intervention: "ACEi"
Comparison: "Placebo"
Outcome: "Prevent worsening of eGFR?"
Is eGFR an outcome
our patient cares about?

So, let's go back to one of our PICO questions. "in adult patient with DM/HTN, does an ACEi when compared to placebo prevent worsening of eGFR?" Is eGFR an outcome our patient cares about?
The outcome measured "eGFR" is a disease-oriented outcome (DOE). eGFR is an intermediary marker. It is not something patients care about if it does not help them live longer or better
Can you think of a way to rephrase the question to make the outcome patient-oriented evidence that matters (POEM)?

i. **Possible POEM Alternatives:**"In patients with diabetes, are ACEi associated with lower mortality rates?" Or "In patients with diabetes, do ACEi delay progression toward end-stage kidney disease requiring dialysis?" Or "In patients with diabetes, do ACEi delay progression toward end-stage kidney disease requiring a kidney transplant?"

ii. **You now search If** the audience wants to know the answer,
Cochrane 2012: Antihypertensive agents for preventing diabetic kidney disease.

Related to our clinical questions,

ACEi reduced the risk of death (all-cause mortality) when compared to placebo (POEM)
ACEi reduced the risk of new onset of microalbuminuria, macroalbuminuria or both when compared to placebo, with similar benefits in people with and without hypertension, and when compared to calcium channel blockers (DOE)
ACEi were found to prevent new onset DKD and death even in normoalbuminuric people with diabetes, and therefore can be used for our patient.

iii. Alternate Clinical Queries

After developing a "best" case-based PICO question, the next step is exploring other searchable clinical queries. These are a list of flexible alternative questions since the answer to your precise question may not match the current scientific literature. Typically, the alternatives involve reasonable variations of your interventions/comparison or alternative outcomes.

For example, for the DMII/HTN introductory case, a 2012 Cochrane study shows the following variants of what was ACTUALLY STUDIED:

i I & C: ACEi versus placebo, ACEi versus ARB, ACEi versus "other active agents" (BB, CCB), combination ACEi+ARB vs ACEi alone

ii O: POEM: all-cause mortality

iii O: DOEs: microalbuminuria, macroalbuminuria, blood pressure, doubling of Cr/progression to ESKD

iv O: time to dialysis/kidney transplant (while a great patient-oriented measure, was not a measure because follow-up only ranged from 6–72 months.)

3.11.4 Step 5. Evaluating performance

As we incorporate EBM into routine clinical practice, we need to evaluate our approach at frequent intervals and to decide whether we need to improve on any of the four steps discussed above. As Strauss and Sackett have suggested, we need to ask whether we are formulating answerable questions, finding good evidence quickly, effectively appraising the evidence, and integrating clinical expertise and patient's values with the evidence in a way that leads to a rational, acceptable management strategy. Formal auditing of performance may be needed to show whether the EBM approach is improving patient care.

3.12 Anatomy of a good clinical question: PICO

PICO is a mnemonic that helps one remember the key components of a well-Focused question. The question needs to identify the key problem of the patient, what treatment you are considering for the patient, what alternative treatment is being considered (if any) and what is the outcome you want to avoid or promote.

i **P = Patient or problem:** How would you describe a group of patients similar to yours? What are the most important characteristics of the patient? This may include the primary problem, disease, or co-existing conditions. Sometimes the sex,

age or race of a patient might be relevant to the diagnosis or treatment of a disease.

ii **I = Intervention, prognostic factor, or exposure:** Which main intervention, prognostic factor, or exposure are you considering? What do you want to do for the patient? Prescribe a drug? Order a test? Order surgery? What factor may influence the prognosis of the patient? Age? Co-existing problems? Has the patient been exposed to something? Asbestos? Cigarette smoke?

iii **C = Comparison:** What is the main alternative to compare with the intervention? Are you trying to decide between two drugs, a drug and no medication or placebo, or two diagnostic tests? Your clinical question does not always need a specific comparison.

iv **= Outcomes:** What can you hope to accomplish, measure, improve or affect? What are you trying to do for the patient? Relieve or eliminate the symptoms? Reduce the number of adverse events? Improve function or test scores?

Table 43: Constructing A Clinical Question

P = Patient	**I = Intervention**	**C= Comparison**	**O= Outcome**
Who?	What?	Alternative Intervention	Outcomes
"How would I describe a group of patients similar to this particular patient?"	" Which treatment, test or other intervention?"	"Compared to what other treatment, test, or perhaps compared to doing nothing"	What is the patient-oriented outcome – better prognosis? Higher rate of cure? Etc.?"

3.13 Benefits: Why Evidence Based Medicine?

The most important reason for practicing EBM is to improve quality of care through the identification and promotion of practices that work, and the elimination of those that are ineffective or harmful. EBM promotes critical thinking. It demands that the effectiveness of clinical interventions, the accuracy and precision of diagnostic tests, and the power of prognostic markers should be scrutinised and their usefulness proven. It requires clinicians to be open minded and look for and try new methods that are scientifically proven to be effective and to discard methods shown to be ineffective or harmful.

It is important that health care professionals develop key EBM skills including the ability to find, critically appraise, and incorporate sound

scientific evidence into their own practice. EBM advocates the use of up-to-date "best" scientific evidence from health care research as the basis for making medical decisions.

For supporters, EBM has three main advantages:

i It offers the surest and most objective way to determine and maintain consistently high quality and safety standards in medical practice;
ii It can help speed up the process of transferring clinical research findings into practice;
iii It has the potential to reduce health-care costs significantly.
The approach, however, is not without its opponents. These consider that EBM risks downplaying the importance of clinical experience and expert opinion, and that the conditions under which clinical trials used to define best practice take place are hard to replicate in routine practice.

3.14 LIMITATIONS OF EVIDENCE BASED MEDICINE

Although evidence-based medicine is regarded as the gold standard of clinical practice. There is however, a number of limitations to its use. According to Strauss and McAllister, the limitations are basically 3 namely:

i limitations universal to the practice of medicine
ii limitations unique to evidence-based medicine and
iii misperceptions of evidence-based-medicine

Popular limitations include;
EBM produces quantitative research, especially from randomized controlled trials (RCTs). Accordingly, results may not be relevant for all treatment situations.

Because RCTs are expensive, the priority assigned to research topics is inevitably influenced by the sponsors' interests.

There is a lag between when the RCT is conducted and when its results are published.

There is a lag between when results are published and when these are properly applied. Certain population segments have been historically under-researched (racial minorities and people with co-morbid diseases), and thus the RCT restricts generalising.

Not all evidence from an RCT is made accessible. Treatment effectiveness reported from RCTs may be different than that achieved in routine clinical practice.

Published studies may not be representative of all studies completed on a given topic (published and unpublished) or may be unreliable due to the different study conditions and variables.

Research tends to focus on populations, but individual persons can vary substantially from population norms, meaning that extrapolation of lessons learned may founder. Thus, EBM applies to groups of people, but this should not preclude clinicians from using their personal experience in deciding how to treat each patient.

3.14.1 Values: while patient values are considered in the original definition of EBM, the importance of values is not commonly emphasised in EBM training, a potential problem under current study.

3.14.2Older Professionals: As with any concept, there are disadvantages as well as advantages of applying evidence-based medicine to modern healthcare; despite the integration of evidence-based medicine in the curriculum for university medical studies courses, as a relatively new practice the number of healthcare professionals not familiar with such a routine is still fairly high. Furthermore, many of those who practiced long before the implementation of evidence-based medicine feel it undermines their clinical expertise and the value of their experience to a degree.

3.14.3 Costs: Short term cost is an obvious limitation but can be justified to some extent when considering the long-term cost-effectiveness of using evidence-based medicine. The decision related to which research program to fund raise ethical as well as economic issues but it is obviously not possible to fund research into every known illness.

3.14.4A Lack of Evidence: Critics of the evidence-based medicine system have stated that most commonly a lack of funding for research means there is a lack of sufficient evidence for treatments associated with many different illnesses, particularly those that are relatively uncommon. If no money is committed to researching certain illnesses then it is possible that no progress will ever be made concerning the treatment of that particular illness, despite advances in technology and scientific research possibilities. In addition to this, research suggests that not all data is made available for all to see, with negative trials often not published; this infers a degree of selectivity and bias.

3.14.5The Personal Touch: Whilst the evidence supporting the benefits of evidence based medicine is abundant in terms of determining effective

treatments, this concept does not account for issues such as how an individual patient feels from one day to the next; even if a drug is proven scientifically to be effective it will still affect each individual in a different way and therefore some patients may not follow the predicted course of recovery.

3.14.6Lack of Skills: Critics have expressed concern that those healthcare professionals who have not previously been specifically trained to interpret the data they receive do not have the necessary skills to do so and are therefore struggling to act in accordance with new guidelines.

Amidst these limitations and criticism, there are some advantages to its use. These include

i Patients satisfaction
ii Improved efficiency
iii With the explosion of scientific knowledge being published, it's difficult for clinicians to stay current on the latest best medical practices.
iv Improved technology enables healthcare workers to have better access to data and knowledge.
v Payers, employers, and patients are all driving the need for the healthcare industry to show transparency, accountability, and value.

4.0 CONCLUSION

In this unit, you have learnt the importance of history taking. This includes the approach to patient while taking medication history and proper documentation and possible limitation to expect in taking medication history. The second part of this unit deals with evidence-based practice as it is used in physical therapy. Students have been exposed to how to recognise the 5-step process in Evidence-Based Practice, compare and contrast arguments for and against evidence-based practice, understand the key research methods needed to locate medical evidence and have learnt how to describe strategies to apply evidence-based practice to clinical cases

5.0 SUMMARY

This unit introduces you to the importance taking detail, accurate and complete account of all prescribed and non-prescribed medications that a patient had taken or is currently taking prior to current admission or medical care. Its emphasis that without an accurate medication history, prescribers may inadvertently make incorrect decisions about a patient's treatment, causing harm if previously discontinued medicines are

restarted, or if current medicines are omitted or prescribed at the wrong dose for the patient.

Medication history help in preventing prescription errors and consequent risk to patients. It is useful in detecting drug –related pathology or changes in clinical signs that may be the result of drug therapy and it should encompass all currently and recently prescribed drugs, previous adverse drug reactions including herbal or alternative medicines and adherence to therapy for better care plan.

The need to approach the patients properly introducing yourself and purpose of interview as well as the content and tips of history taking was outlined.

Elements of client education such as encouraging patient to take ownership, educate client to bring medications from home at each appointment, and educate client to carry a list of current medications (prescription and OTC) were outlined. The Unit conclude with tips on how to wrap up medication. For example, the need to conclude with thanking the patient for their time and information and asking them if they have any other questions etc.

EBM aims to improve quality of care through the integration of best research evidence with clinical expertise and patient's and parents' preferences. In this, it has explained the five essential steps for practicing EBM, which are: formulating answerable clinical questions; searching for evidence; making a critical appraisal; assessing the applicability of the evidence; and evaluating performance.

We have discussed The Five "A" and identify each component of the PICO pneumonic:

P = patient, problem, population
I = intervention
C = comparison
O = outcome

How to ask and identify and develop a well-articulated question about either patient care issues or research issues using the PICO Worksheet. Then determine the study question category as either diagnosis, therapy/prevention, prognosis, or aetiology.

SELF ASSESSED EXERCISES

i. Explain the anatomy of a good clinical question.
ii. Discuss the limitations of Evidence Based Medicine.

6.0 TUTOR- MARKED ASSIGNMENT

1. You are asked to take a medication history. Why is it important for you to obtain a complete description of the patient's medication history?
2. Outline steps in medications
3. Tabulate a sample of Cards for Medication History Script
4. Define EBM, outline the five steps of evidence-based Model
5. what PICO? Discuss it role in patients' evidence
6. discuss the benefit and limitation evidence Based medicine

7.0 REFERENCES/FURTHER READING

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UNIT2 PHARMACOVIGILANCE/PHARMACOVIGILANCE IN PUBLIC HEALTH PROGRAMMES

CONTENTS

1.0 INTRODUCTION

Modern medicines/drugs have brought significant benefits to our lives, offering reduction in morbidity and mortality. The improving health status of increasing number of the population can be attributed to drugs. However, even though medicines are generally seen as beneficial, all medications including the excipients in medicines are capable of producing adverse or unwanted effects. Governments in several countries consider the need to ensure quality, safety, and efficacy of all medicines and health products used in their country as an important public health function. Pharmacovigilance activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems become an integral part of health care in recent times.

Ensuring Pharmacovigilance in Public Health Programmes become necessary because, many Public Health Programmes (PHPs) are involved in direct administration of medicines to large populations and communities for the prophylaxis, treatment and/or eradication of diseases The large number of patients who will receive the drugs in a systematic manner in these programmes generates the possibility of harm if unmonitored and, at the same time, an opportunity to develop systems for generating valid and valuable data that will assist in decision making. Therefore, PHPs and Pharmacovigilance (PV) can derive mutual benefits from each other; PV and adverse drug reactions monitoring in PHPs can detect rare adverse events and risk factors in patients and can have a tremendous positive impact on the implementation and success of these programmes; PHPs on the other hand can provide an opportunity to introduce PV in countries that lack a system for drug safety monitoring. Safety issues that are specific to various disease-control programmes (Chagas, HIV/AIDS, Malaria, Tuberculosis, etc.) are being addressed through different Projects.

Registers and databases are being created and used as a foundation for statistics that allow medical care providers to oversee potential risks and minimise them. The success or failure of any pharmacovigilance activity depends on the reporting of suspected adverse reactions. WHO has played a vital role in promoting the safety of medicinal products as a clinical and public health issue? Duly, the data collected through spontaneous reporting, national pharmacovigilance centres, and the WHO Programme for International Drug Monitoring has led to changes in the labelling of medicines. It has become an essential tool in providing the necessary infrastructure for drugs programmes. Furthermore, the cost of an effective pharmacovigilance system is notably smaller when compared to the national expenditure on medicines or the cost of managing ADRs.

2.0 OBJECTIVES

By the end of this, you will be able to:

- identify what is and why we Need Pharmacovigilance
- outline the goals, need and importance of pharmacovigilance
- explain origin of modern PV: Era of Safety and Efficacy
- identify working knowledge of the guides & tools for reporting
- describe tools used for causality assessment and able to
- assess severity and causality of ADRs
- describe the importance of Pharmacovigilance in Public Health Programme (PHP).
- State why PV should be integrated into PHPs
- describe practices to improve ADR reporting in PHP.

- describe strategies to strengthen functioning of the Expert Advisory Committee.

3.0 MAIN CONTENT

3.1 Definition of Terms

i. Organisations involved

WHO - World Health Organisation
CIOMS - Council of International Organisations of Medical Sciences
ICH – International Conference on Harmonisation

ii. **Pharmacovigilance:** Is define as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

iii. **Spontaneous Report:** An unsolicited communication by MAHs, healthcare professionals, or consumers that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection scheme.

iv. **Serious Adverse Event or Reaction:** Any untoward medical occurrence that, at any dose, results in death; is life threatening; requires inpatient hospitalisation or prolongs current hospitalisation; results in persistent or significant disability, incapacity, or congenital abnormality

v. **Serious Adverse Event Or Reaction :** Any untoward medical occurrence that at any dose
   a. results in death
   b. is life-threatening
   c. requires inpatient hospitalisation or
   d. prolongation of existing hospitalisation
   e. results in persistent or significant disability or incapacity
   f. results in a congenital abnormality

note on Serious adverse event or reaction

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', the following note of clarification is provided:

The term 'severe' is not synonymous with serious. In the English language, 'severe' is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as severe headache).

Seriousness (not severity) which is based on patient/event outcome or action criteria serves as guide for defining regulatory reporting obligations.

Table 44:Frequency Of Adverse Drug Reactions (Cioms):

Very common	≥1/10
Common (frequent)	< 1/10 but ≥ 1/100
Uncommon (infrequent)	< 1/100 but ≥ 1/1000
Rare	< 1/1000 but ≥ 1/10000
Very rare	< 1/10000 but

vi. **Signal:**Possible causal relationship between adverse event and drugs previously unknown or incompletely documented. More than one report is needed depending on; Quality of the information or Seriousness of the event

vii. **Causality Assessment:** The process of assessing the likelihood that the reported adverse reaction is actually due to the suspected medicine using pre-determined criteria such as the WHO causality assessment criteria.

viii. **Spontaneous Report:** A system whereby case reports of adverse drug events are voluntarily submitted by health professionals and MAHs to the National Pharmacovigilance Centre.

ix. **Health Product:** Any product, substance or a mixture of substances used or purported to be suitable for use that is manufactured or sold for use in the diagnosis, treatment, mitigation, modification or prevention of a disease, abnormal physical or mental state, or the symptoms thereof, in humans or animals; or for restoring, correcting or modifying any somatic, psychic or organic function in humans or animals. A health product can include medicines, herbal products, vaccines, antisera, biological and blood products.

x. **Health Products Regulation:** All the processes involved in the pre-marketing evaluation, marketing authorisation, and post-marketing review of medicines, vaccines, devices, and other health products to ensure compliance with established standards of quality, safety, and efficacy.

xi. **Marketing Authorisation Holder (MAH):** The holder (an individual, institute, manufacturer, company, importer, distributor, development partner/donor agency) of a marketing authorisation to market a medicinal product. For the purpose of this

policy document, the MAHs will have full responsibility and liability for their product on the market and full responsibility for ensuring that appropriate action can be taken when necessary.

xii. **Medication Errors:** Any unintended preventable events that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer. Such events may be related to professional practice, healthcare products, procedures and systems including prescribing, order communication, product labelling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use. Cosmetics, chemicals/detergents medical devices and all drinks including packaged water.

xiii. **Periodic Safety Update Report (PSUR):** A report produced by an MAH intended to provide an update of a worldwide safety experience (with some focus on Nigeria) of a medicinal product to the competent authorities at defined times post authorisation.

3.2 Pharmacovigilance

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.
Recently, its concerns have been widened to include herbals, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines etc. Other issues relevant to this science include

i. Substandard medicines
ii. Medication errors
iii. Lack of efficacy reports
iv. Use of medicines for indications that are not approved and for which there is inadequate scientific basis
v. Case reports of acute and chronic poisoning
vi. Assessment of drug-related mortality
vii. Abuse and misuse of medicines
viii. Adverse interactions of medicines with chemicals, other medicines and food'.

Pharmacovigilance is an arm of patient care. It aims at getting the best outcome of treatment with medicines. No one wants to harm patients, but unfortunately, because of many different factors, any medicine will sometimes do this.

3.2.1Origins of Pharmacovigilance: Era of Safety Monitoring

The 1st reported case of ADR occurred over 150 years ago, in 1848, a 15-year-old girl from Winlaton, north-east England, had a routine general anaesthetic while undergoing a surgical procedure for an ingrown toenail. The anaesthetic agent, chloroform, had only been introduced into clinical practice a year earlier, since it produces less nausea and vomiting than Ether. The girl died during the anaesthesia from what was probably an episode of ventricular fibrillation. The Lancet set up a commission, which invited doctors in Britain and its colonies to report anaesthesia-related deaths. Their findings were subsequently published in medical journal in 1893. Thus, **the forerunner of a Spontaneous reporting system** for suspected adverse drug reactions (ADRs) was established, at least for a time.

Another early incident of harmful effects of drug was recorded in 1937, where a formulation defect in **elixir of sulphonamide** resulted in poisoning. DEG; US 105 deaths in 1937 Federal Food, Drug and Cosmetic Act (1938) with the premarket notification requirement. Though, the sulphonamide incidence led to improvement in pharmaceutical regulations, there was no define monitoring system for drug safety until Thalidomide: 1956 – 1962 about 10,000 children were born with severe malformations, including phocomelia. In **1960** report of 2 grossly deformed infants in Germany (**thalidomide disaster**). **By 1961** 477 cases of phocomelia in paediatric clinics, and withdrawal recommended. However, a delay of one month, lead to another 50 - 100 new cases and by the time regulation was put in place, - **More than 4000 cases.**

Thurs in 1962 the World Health Assembly *(Kefauver-Harris Drug Amendment (1962) required proof of effectiveness and safety before marketing)* requested the WHO Director General to study ways to make drugs safer including ‘securing prompt transmission to national health authorities of new information
on serious side effects of pharmaceutical preparations. As a result, an international system for monitoring adverse reactions to drugs (ADRs) – ***Pharmacovigilance***, based on data from national centres was proposed. Voluntary notification scheme (1961962: Kefauver-Harris Drug Amendments

Figure 37: A child with Phocomelia. Due to thalidomide disaster (@Wikipedia
en.wikipedia.org)

passed to ensure drug efficacy and safety; first time Pharma were required to prove effectiveness before market entry After a pilot project was carried out in the USA, an international database was established at WHO headquarters in Geneva in **1971** and moved to Uppsala, Sweden in **1978**.

3.2.2 How medicine safety is assured

All drugs undergo a significant amount of testing and evaluation before marketing to ensure their effectiveness as well as safety. Marketed medicines undergo trials in animals (preclinical testing) and humans (clinical trials) to establish their efficacy, safety, and quality.

i. Pre-marketing evaluation

Pre-marketing evaluation involves animal studies and clinical trials in humans. Studies in two or more animal species are conducted to test whether the drugs are harmful and whether they may for instance induce cancer, damage an unborn child; etc. Once scientists are sure that the drug is safe, they start studies in human beings and these studies are known as Clinical Trials.

Each phase involves increasing number of patients and by the end of full pre- marketing clinical trials about 5000 patients would have taken the drug. However, when the drug is marketed millions of people will take the medicine. There is therefore the question of whether the clinical trials involving just about 5000 people will provide enough information to extrapolate the safety of a new drug to millions of people. Pre- marketing safety evaluations have two significant drawbacks:
Under – identification of adverse drug reactions: ADRs which occur infrequently are difficult to identify. Statistically, reactions with an incidence of less than 1% are frequently not identified.

Over- identification of ADRs: Many adverse drug reactions that are identified in pre- clinical studies are not proven to be related to the drug, but are nevertheless listed in the product literature as potentially causing the ADR. This provides some measure of legal protection for pharmaceutical company but is misleading to practitioners and patients, as many of these reactions are not definitely proven.

ii. Post-marketing surveillance (PMS)

It is not possible to identify all of the safety- related problems that may exist with a new drug during pre- market testing and evaluation. After drugs have been released on the market, NAFDAC, the manufacturers/importers and health care professionals are responsible for post-marketing surveillance of these products. Drugs released to the market will be used not only by more people, but also by different categories of people other than those in whom the drug was tested. The marketed drug will be used by older people, those with more serious illness, and those from different ethnic groups, pregnant women and also by children in whom drugs are rarely tested.

The medicines may also be used under many different dose regimens (not necessarily the correct and approved dose) and they could also be deliberately misused. These circumstances inevitably lead to a potential for more adverse drug reactions. For these reasons, it is obvious that the safety of a drug requires long-term surveillance after marketing.
Regulations Around the world

USA – 1962 FDA required both safety and efficacy data
UK – 1963 committee on safety of drugs, and yellow card system
1965 – Committee on safety of medicine (CSM). Medicine Act (safety, quality, efficacy requirements)
EU – 1965 EC Directives 6565
WHO – 1968 Program for international Drug monitoring?

3.6 History of Withdrawals

i. Therapeutic mishaps have catalysed medicines regulation
ii. DEG poisoning from 1937-2008, about 600 deaths in11 countries
iii. Heparin — 131 heparin-related deaths reported to FDA 1 Jan 2007 and 13 April 2008
iv. 125 products withdrawn for safety reasons over past 40 years
v. FDA Amendment Act (2007)
vi. Enhanced statutory authority regarding post-market safety of drugs

Table 45: Number of deaths in different countries

Year	Country	# of deaths reported
1937	United states	105
1985	Spain	5
1986	India	14
1987	South Africa	7
1990	Bangladesh	51
1990	Nigeria	47
1992	Argentina	7
1995/96	Haiti	88
1998	India	33
2006	Panama	123
2008	Nigeria	84
2009	Bangladesh	25

3.7 Detection of Adverse Drug Reactions

3.7.1 Mode of Reporting

In Nigeria there are two modes of reporting suspected adverse drug reaction. Voluntary and Mandatory.

i. **Voluntary:** is when a healthcare practitioner identifies suspected adverse drug reaction and report it to the National Pharmacovigilance Centre (NPC). It is voluntary for health providers & traditional herbal medicine practitioners. Although it is voluntary it is a professional duty.
ii. **Mandatory:** It is mandatory for all Marketing Authorisation Holders (MAHs). These include Manufactures and their local agents in Nigeria including public health programs to report ADR related to their product.

It should be noted that reporting does not suggest culpability. Adverse drug reaction reports shall not be tendered as evidence in a legal dispute. NAFDAC does not regulate medical practice.
The strategic methods for detection of ADR consist of the following:

3.7.2 Passive pharmacovigilance (Spontaneous reporting of ADRs)

Spontaneous reporting of adverse events identified during the use of any health product is mandatory for the manufacturer or marketing authorisation holder (MAH) of that product. Serious adverse events occurring during clinical trials conducted in Nigeria should also be mandatorily reported. Spontaneous reporting of adverse events suspected to be related to the use of a health product is an ethical responsibility for all healthcare providers. No claims of medical malpractice can be based

solely on a submitted report. Reports received by the Centre as part of spontaneous reporting shall not be made available to support any legal, administrative or any other action that may be detrimental to the reporting health professional or the patient.

3.7.3. Active pharmacovigilance.

Reporting of medication errors.
Reporting of suspected cases of substandard and counterfeit medicines and other health products.
Detection of lack of effectiveness.

Collaboration with public health programmes.

Due to the inherent limitations of passive pharmacovigilance (spontaneous reporting), the NPC shall undertake either solely or in collaboration with relevant stakeholders' active forms of pharmacovigilance when necessary. Active pharmacovigilance could be in the form of Cohort Event Monitoring, Prescription Event Monitoring, Intensive Medicines Monitoring Programme, Record Linkages, and Pregnancy Registers etc. as maybe necessary. NPC shall also put in place a process for the detection of signals of public health importance that require further evaluation through active surveillance.

3.8 Adr Reporting

3.8.1 Reporting of medication errors

The generation of information on medication errors and its dissemination minimises similar occurrence in clinical practice.

To achieve this goal, the National Pharmacovigilance Centre shall ensure:
That healthcare providers report any case of medication error to the nearest pharmacovigilance centre/NPC.

The maintenance of a database for medication errors.
The carrying out of an appropriate root cause analysis on the reported medication errors.
The dissemination of information on medication errors to prevent future occurrence.

Sources of ADR and other medicine related problems shall include:
Individuals: doctors, pharmacists, nurses, traditional herbal/alternative medicine practitioners or other healthcare providers in the public or private sector who, on their own initiative, send reports of adverse drug

reactions and other medicine related problems to the nearest pharmacovigilance centre/NPC.

Institutions: healthcare institutions, including hospitals, clinics, medical Centres, research institutes and Public Health Programmes operating in the public or private sectors.

Traditional/herbal medicinal institutions/Centres/associations.

Other units of NAFDAC such as the Drug Quality Control Laboratories, Drug Information Centres and the Consumer Affairs Division.
Manufacturers or importers/distributors (MAHs) of products covered by this policy. Any other relevant sources.

3.8.2 Who is to report?

i. Doctors, pharmacists, nurses, medical laboratory scientists and traditional herbal medicine practitioners or health care practitioners or healthcare providers working in the public, private and Non-Governmental sectors shall report adverse drug reactions and other medicine related problems to the nearest pharmacovigilance centre/NPC.
ii. Patients/ consumers are strongly encouraged to report all ADRs and medicine related problems to their healthcare providers who will in turn forward the report to the nearest pharmacovigilance centre/NPC.
iii. Importers/distributers, retailers, Marketing Authorisation Holders of pharmaceutical products, traditional/herbal medicinal products and other related products.

3.8.3 What is to be reported

All response to medicines used in humans which are harmful and unintended

i. No improvement after treatment
ii. Medication error
iii. Overdose
iv. Misuse and/or abuse of a medicine
v. Counterfeit or substandard medicine
vi. Case reports of acute and chronic poisoning
vii. Assessment of drug-related mortality
viii. Abuse and misuse of medicines
ix. Adverse interactions of medicines with chemicals, other medicines and food

3.8.4. When Do I Report?

At the stage of Pharmacovigilance development that Nigeria is in, we need to report all safety issues of concern. By the time we would have developed our capacity in detecting, reporting and assessing of adverse effects of medicines then we would be in a position to report only serious ADR's.

3.8.5 How to Report

Report Serious adverse event or reaction

i. A serious ADE or ADR is any untoward medical occurrence that at any dose:
ii. Results in death;
iii. Results in inpatient hospitalisation or prolongation of existing hospitalisation;
iv. Results in persistent or significant disability or incapacity;
v. Is life-threatening;
vi. Is a congenital anomaly/birth defect.

NB: The term "SEVERE" is not synonymous with "SERIOUS". While severe is used to describe the intensity (severity) of a specific event (as in mild, moderate or severe); the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) which is based on the outcome of the event on the patient or action criteria serves as the guide for defining regulatory reporting obligations.

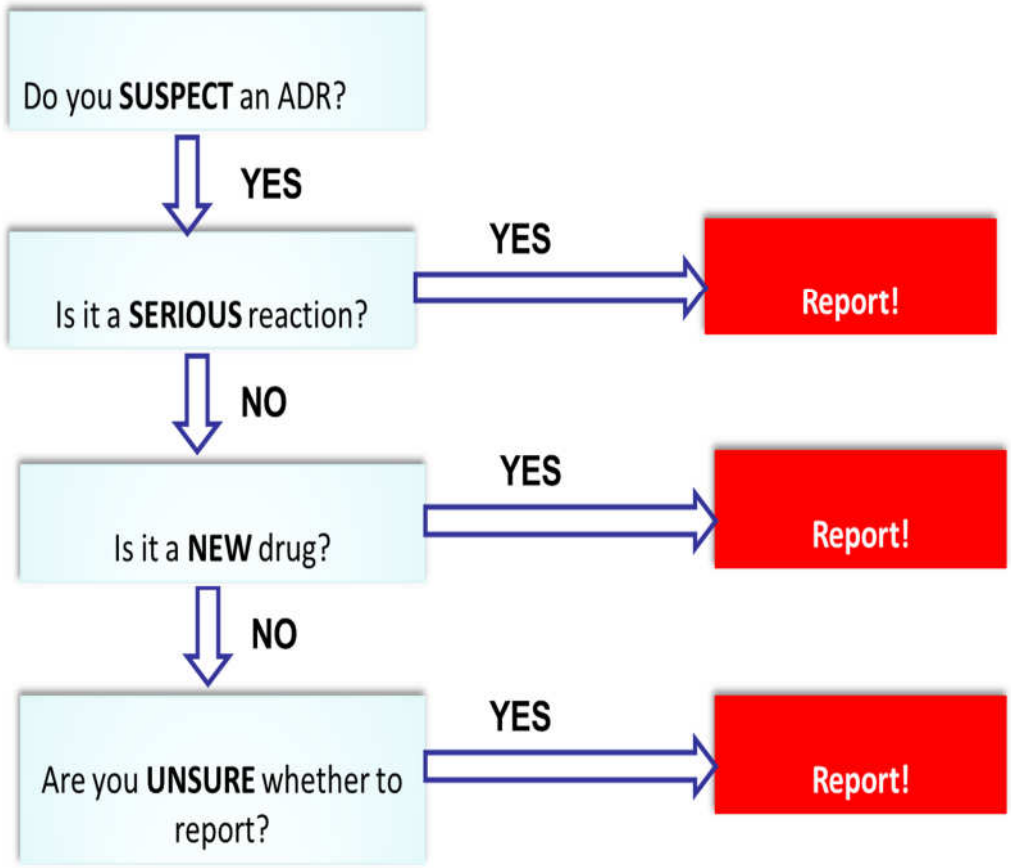

Figure 38: How to report adverse drug reaction (@NAFDAC Nigeria PhV training slides)

3.9 Causality Assessment and Signal Generation

Causality assessment is the **assessment** of relationship between a drug treatment and the occurrence of an adverse event. It is also used to evaluate and to check that the particular treatment is the cause of an observed adverse event or not. It is an essential part of ADR report and important task, conducted by National Pharmacovigilance Programme in each country.

3.9.1Objectives of Causality Assessment are to

i. Provide relationship between the drug and events.
ii. Signal detection (“a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously".)
iii. Provide better evaluation of the benefit/harm profiles of drugs.
iv. Play as an essential part of evaluating ADR reports in early warning systems and for regulatory purpose

In order to assess the likelihood that the suspected adverse reaction is actually due to the medicine, a list of causality assessment criteria for deciding on the contribution of the medicine towards the adverse event.

3.9.2 How the Causality Assessment is performed

Many researchers developed various methods of causality assessment by using different criteria like

v. Chronological relationship between the administration of the drug and the occurrence of the ADR,
vi. Screening for drug and non-drug related causes,
vii. Confirmation of the reaction by in vivo or in vitro test,
viii. Previous information on similar events etc.

But there is no universally accepted method for assessing causality of ADRs

3.9.3 Methods of causality

Causality is broadly classified under three broad categories

i. **Expert Judgement/ Global Introspection**

- Swedish method by Wilholm et al.
- World Health Organisation (WHO) - Uppsala Monitoring
- Centre (UMC) causality Assessment criteria.

i. **Algorithms:** It consists of a problem-specific flow chart with step-by-step instruction on how to arrive at an answer. Actually, its form contains some questionnaire, whose answers provide the causality of particular ADR. It gives structured and standardized methods of assessment in a systematic approach. Assessment of ADRs based on parameters such as **t**ime to onset of the ADR or temporal sequence, Previous drug/adverse reaction history, Dechallenge and Rechallenge

Types of Algorithms Method

There are many algorithmic methods of causality assessment but no single algorithm is accepted as the "gold standard", because of many shortcomings. Important Algorithmic Methods are-

i. Dangaumou's French method
ii. Kramer et al. method
iii. Method Naranjo scale (Naranjo et al (9181)

iv. Balanced assessment method (Lagier et al.1983)
v. Summary time plot (Castle et al.1984)
vi. Ciba geigy method (Venulet et al. 1980)
vii. Roussel Uclaf causality assessment method (RUCAM)
viii. Maria and Victorino (M and V) scale
ix. Drug Interaction Probability Scale (DIPS)

Naranjo Algorithms -Naranjo et al. method (Naranjo scale)

Widely accepted method. The method used to determine the causal link between drug and clinical event. Likelihood of whether an adverse drug reaction is actually due to the drug rather than the result of other factors.
It is a systematic causality assessment consists of ten questions that are answered as "yes", "no", "unknown" (don't know)
These answers are assigned via a score termed Definite, Probable, Possible or Doubtful. Definite- when a total score of ≥ 9. Probable- when a total score of 5–8. Possible- when a total score of 1–4. Doubtful- when a total score of ≤ 0.

Table 46: The Naranjo ADR Probability Scale

Questions	**Yes**	**No**	**Don't Know**
1) Are there previous conclusive reports on this reaction?	+1	0	0
2) Did the ADR appear after the suspected drug was administered?	+2	-1	0
3) Did the ADR improve when the drug was discontinued?	+1	0	0
4) Did the ADR appear with re-challenge?	+2	-1	0
5) Are there alternative causes for the ADR?	-1	+2	0
6) Did the reaction appear when placebo was given?	-1	+1	0
8) Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9) Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0
10) Was the ADR confirmed by any objective evidence?	+1	0	0

The Naranjo Probability Scale
The score: -
> 8 = highly (Definite) probable
5-8 = probable
1-4 = possible

0 = doubtful
Limitation-:

- Method only explains the causality of one individual drug
- Not explains the causality occur due to drug interactions

Probabilistic or Bayesian Approaches

i. Australian method
ii. Bayesian Adverse Reactions Diagnostic Instrument (BARDI)
iii. MacBARDI spreadsheet
Causality assessment based on study of prior probability and posterior probability. i. **The prior probability** is calculated from epidemiological information.
ii. **The posterior probability** combines this pedological background information with the evidence in the individual case.
This method allows the simultaneous assessment of multiple causes.
iii. Bayesian Adverse Reactions Diagnostic Instrument (BARDI)
iv. BARDI is used to calculate the odds in favour of a particular drug causing an adverse event compared with an alternative cause (posterior odds)
v. The posterior odds factor is calculated by considering six assessment subsets: one deals with background epidemiologic or clinical trials information (the prior odds) and the other five deal with case specific information (the likelihood ratios).

$$PsO = PrO \times LR(Hi) \times LR(Ti) \times LR(Ch) \times LR(De) \times LR(Re)$$

i. Pro (the prior odds) - epidemiologic or clinical trials information
ii. The five likelihood ratios (LRs) deal with any information of differential diagnostic value under
iii. patient history (Hi)
iv. timing of the adverse event with respect to drug administration (Ti)
v. characteristics of the adverse event (Ch)
vi. drug dechallenge (De)
vii. drug rechallenge (Re)

3.9.4 Causality Assessment of Vaccine Related Adverse Events

i. Vaccines are administered on large scale to healthy individuals, children, infants and neonates. So, vaccines must meet with high degree of safety.
ii. Method developed by the Advisory Committee on Causality Assessment (ACCA) in Canada.

iii. ACCA is composed of specialist in paediatrics, epidemiology, infectious diseases, immunology, neurology, pathology, adverse event surveillance, and microbiology

iv. They review individual cases in a systematic stepwise manner to categorize them on a specially designed causality assessment form.

v. This causality assessment form consists of seven sections. Section one, Section two, Section three, Section four, Section five, Section six and Section seven

Section one-: Section one relates to the reason for reporting and whether the committee agreed with both the diagnosis that was made and the statement of severity.

Section two-: Section two takes the evaluators through several important factors like frequency of occurrence of adverse events, similar events known to occur with other diseases, vaccine-event interval compatible with event, similar symptoms in past, concomitant drugs or other conditions; for assessment of causality.

Section three-: Section three relates to causality assessment by using **WHO-UMC criteria.**

Section four-: Section four permits brief summary of case with important elements and **discussion** which contributed to the final assessment of causality.

Section five-: Section five permits recommendations for improving immunization or case reporting procedures to be written.

Section six-: Section six considers whether the case could be useful for **Educational purpose**

Section seven-: Section seven considers whether the case could be useful **for publication.**

3.9.5 Expert Judgement/Global Introspection

It is a process in which an expert expresses judgement about possible drug causation by considering all available data relevant to a suspected ADR.

i. Assessment of ADR is either done by single expert evaluator or by a group of expert evaluators.

ii. As evaluation and assessment of ADR by these experts is purely based on their respective knowledge and experience about the subject of interest.

Two methods based on expert opinion or global introspection.

i. Swedish method by Wilholm et al.
ii. World Health Organisation (WHO) - Uppsala Monitoring Centre (UMC) causality assessment criteria

World Health Organisation (WHO) - Uppsala Monitoring Centre (UMC) causality assessment criteria. Widely and globally accepted method.
WHO-UMC system provides practical tool for assessment of case reports for International drug monitoring and **s**system is used to detect unknown and unexpected adverse drug reaction.

Assessment is based on following four criteria-:

iii. Time relationships between the drug use and the adverse event.
iv. Absence of other competing causes (medications, disease process itself).
v. Response to drug withdrawal or dose reduction (de-challenge).
vi. Response to drug re-administration (re-challenge).

The level of causal association is grouped into four categories which are based on a number of the above criteria being met.

3.9.6 WHO Causality Categories

i. C1 – Certain
ii. C2 – Probable
iii .C3 – Possible
iv C4 – Unlikely
v. C5 – Unclassifiable

WHO Causality Categories

Certain causality: a clinical event (including laboratory test abnormality) occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals; re-administration of the drugs causes a similar reaction

Probable or likely causality: a clinical event occurs within a reasonable time sequence to drug administration and is unlikely to be due to any concurrent disease or other drug administration

Possible causality: a clinical event occurs within a reasonable time sequence to drug administration, but could be explained by concurrent disease or another drug administration

Unlikely: a clinical event, including laboratory test abnormality, occurs with no temporal relationship to drug administration and which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations
Conditional/unclassified: a clinical event, including laboratory test abnormality, reported as an adverse reaction in which more data is essential for a proper assessment, or the additional data is under examination.

Unassessable/unclassifiable: a report suggesting an adverse reaction that cannot be judged because information is insufficient or contradictory and cannot be supplemented or verified

3.9.7 Assessment of Relationship and Causality

Assessment of each event 1
Initially, what we are really doing is assessing the strength of the

relationship between the drug and the event.
We can seldom say without any doubt that a specific drug caused a specific reaction
We work with imperfect data and our conclusions are those of probability.

Assessment of each event 2

Relationship assessment is an essential discipline. *It ensures*:
i. careful review of report details
ii. standardised assessment
iii. an in-depth understanding of the data
iv. standardised data for later evaluation
v. the ability to sort reports by quality

Relationship Categories

1. Certain
vi. Event with plausible time relationship
vii. No other explanation -*disease or drugs*
viii. Event definitive -*specific problem*
ix. Positive dechallenge
x. Response to withdrawal plausible
Key feature: Positive rechallenge

2. Probable

i. Event with plausible time relationship to drug intake
ii. No other explanation
iii. Response to withdrawal (dechallenge) clinically reasonable
iv. No rechallenge, or result unknown

Key feature: Positive dechallenge

3. Possible

v. Event with plausible time relationship to drug intake
vi. Could also be explained by disease or other medicines
vii. Information on drug withdrawal lacking or unclear

Key feature: other explanations for the event are possible

4. Unlikely

viii. Event with a duration to onset that makes a relationship improbable
ix. Diseases or other drugs provide plausible explanations
x. Event does not improve after dechallenge

Key feature: several factors indicate strongly that the event is not a reaction.

3.9.8 Uses and Limitation of Causality Assessment.

What it can do:

xi. Decrease disagreement between accessor.
xii. Classify uncertainty
xiii. Mark individual case reports
xiv. Improve the scientific basis of assessment

What it cannot do;

xv. Give and accurate quantitative measurement of the likelihood of a relationship.
xvi. Distinguish valid from invalid cases
xvii. Quantify the contribution of a drug to the development of an adverse event
xviii. Change uncertainty to certainty

3.10 Pharmacovigilance In Public Health Programmes

3.6.1 Goals and objectives of pharmacovigilance in Public health Programmes

xix. the rationale and safe use of drugs

xx. to contribute to the assessment and communication of benefit, harm, effectiveness and risk of medicines,

i. identification of risk factors and possible mechanisms underlying ADRs

ii. educating and informing patients

Specific objectives

i. early detection of hitherto unknown ADRs
ii. detection of increases in frequency of known ADRs
iii. estimation of benefit/risk
iv. dissemination of information
v. to improve patient care and safety
vi. to improve public health and safety
vii. to promote education and clinical training
viii. to promote effective communication to the public
ix. to promote rational and safe use of medicines

3.10.2 Types of Public Health Programmes

Education, Lifestyle and behavioural changes, Environmental modifications, Nutritional interventions and Drug administration programmes (Mass control programmes, case control programmes and individual treatment programmes)

3.10.3 Characteristics of Public Health Programmes

1. Vertical and intensive programmes

x. Vaccination, préventive treatment (Ivermectine, Albendazole, antibiotic and antiparasitic prophylaxis…)
xi. Artémisinine dérivatives against malaria, ARVs, Tuberculoses, Schistosomiasis.
xii. Lymphatic filariasis, Trachomatis, Leprosy, poliomyelitis elimination programmes…Involve - Drug and vaccines.
xiii. Procurement agency
xiv. In 2009 delivered over 2.4 million patients' treatment
xv. In 2011 brought up to 60,000 additional MDR-TB patients' treatment.

3.10.4 Current situation in Public Health Programmes

Pharmacovigilance in Public health Programme and medicinal products

i. Accelerated access the use of new drugs in new environment, which are mostly devoid of pharmacovigilance activities for priority disease
ii. Faster large-scale ups of public health programmes due to available new funding's from major donors such as Global fund, World Bank, PEPFAR, PMI etc.
iii. Mass distribution of medicines with often presumptive treatment
iv. New drug is reaching developing countries in greater numbers and more quickly because of new funding's from several donors including Bill and Melinda gates foundations
v. Often there is rarely records adverse drug reactions
vi. In most in setting pharmacovigilance and public health programmes operate in isolation, as independent vertical programmes.

3.10.6 Why PV should be integrated into PHPs

PHPs definition range and changed over time to include disease prevention, and health promotion through organized efforts amongst the population as a whole. It focusses on entire population not individuals and disease and involves healthy as well as sick people, with the goal to reduce morbidity and mortality due to major and common disease. Pharmacovigilance into Public Health Programme because;

vii. Old medinas in different populations combination and indication
viii. Integration can increase public trust in programme are being dispense
ix. Infection collected can be provided to the public increasing compliance
x. Integration can help take appropriate measures and communicate effectively in a crisis.
xi. Integration can help strengthen existing national pharmacovigilance or provide leverage for setting up a pharmacovigilance where it does not exist.

3.10.7Challenges of pharmacotherapy in PHPs

One key challenge that has emerged is the issue of monitoring the safe use of medicines in countries with no active regulatory or safety monitoring system in place. In this scenario, the use of medicines in specific communities, such as the treatment of diseases like malaria, leishmaniasis

and schistosomiasis, or HIV/AIDS and tuberculosis, becomes a matter of great concern and the subject of coordinated efforts to reduce the risks.

xii. may use agencies and staff with a wide variety of skills and patients may not be seen by a physician insufficient diagnosis and follow up large numbers exposed, may include special populations i.e. pregnant & breast-feeding mothers
xiii. use of new drugs with limited experience, i.e. ARVs, ACTs; use of substandard drugs; incorrect use of drugs; counterfeit drugs
xiv. weak health care systems, often poor drug control/legislation

3.10.3 Strengths of PHPs

xv. Well established programmes using a limited number of drugs or vaccines
xvi. Operate according to standard guidelines
xvii. Well-funded with international support
xviii. Monitoring and evaluation procedures
xix. Quality of product can be assured
xx. Good databases
xxi. Expertise in assessment of drug safety
xxii. training in benefit/risk assessment
xxiii. Good international support, WHO, UMC

Public health programmes (PHP) are well established and organised. PHP use limited number of medicines as 1st& 2nd lines, this may not be same with other health conditions where choice of medicines may be less restricted. Ensuring the quality of those limited products is an issue of public health importance, hence the WHO has the prequalification scheme for such products. Large, defined populations are involved in PHP, example ART/TB/Malaria/Immunisation, etc. and data is more readily available. There is stricter use of STGs in PHP. There is extensive international support in PHP programmes through PEPFAR, Global funds and others.

3.10.9 Weaknesses of PHPs

xxiv. No direct contact with a Physician
xxv. Diagnosis may not be well diagnosed/presumptive
xxvi. lack experience in drug safety monitoring, insufficient follow -up
xxvii. drugs used in PHPs considered safe
xxviii. lack of coordination between PHPs, duplication
xxix. may cover special populations
xxx. relatively new concept
xxxi. role not well recognised
xxxii. poorly funded, considered a luxury

xxxiii. not seen as a component of PHPs

Ensuring rational use of medicines can be very challenging in PHP. In PHP, it may not always be possible to tailor medicines to individual patient needs to reflect co-morbid conditions, nutritional status or for pregnant women, nursing mothers, Paediatrics, and elderly. Even with the attention to quality, widespread use of generics and multisource products still makes it challenging to ensure quality. Drug resistance may quickly manifest as in HIV/AIDS/TB/Malaria, at times aided by drug interactions and poor adherence.

3.10.10 Opportunities

Together, PV and PHPs may greatly benefit each other.

I. PV will assist in the early identification and prevention of ADRs and product quality problem.
ii. Improve compliance thereby reduce drug resistance
iii. PHPs may provide resources, reliable
iv. PV can improve knowledge and there improve patients care
v. Databases, M and E tools leading to …….

The importance of PhV to PHP is reflected in the fact that both are mutually beneficial to each other. PHP can serve as pathfinders for PhV in RLS particularly in introducing or strengthening spontaneous reporting, and the initiation of active surveillance activities. PHP also have large cohorts of patients which is very beneficial in the conduct of PhV studies. PhV can support PHP in providing important outcome data on toxicity and safety of PHP medicines. Such data can be used to address safety scares or spurious claims when they arise and improve acceptability of the programs. PhV also ensures rational use since safety risk factors identified through PhV studies can be used to inform better patient management.

3.10.11 Threat to Pharmacovigilance Public Health Programmes

i. Lack of political/public support
ii. funding shortfalls
iii. misunderstanding of each other’s roles
iv. The malaria PV project – an update

4.0 CONCLUSION

This unit exposes the you to the understand what is and why we Need Pharmacovigilance as a science and activity relating to assessment, detection and reporting adverse drug reactions. It describes the goals, need and importance of pharmacovigilance and how the origin of modern

PV (Era of medicine safety and efficacy) developed. The course discussed thetools used for causality assessment and able to assess severity and causality of ADRs. The importance of Pharmacovigilance in Public Health Programme (PHP) and why PV should be integrated into PHPs including the strategies to strengthen functioning PV in PHP.

5.0 SUMMARY

Pharmacovigilance (PV): Is a science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. The origins of pharmacovigilance dates back to the 1st reported case of ADR occurred over 150 years ago, in 1848, when a 15-year-old girl, had a routine general anaesthetic while undergoing a surgical procedure for an ingrown toenail. The anaesthetic agent, chloroform, had only been introduced into clinical practice a year earlier. That become, the forerunner of a spontaneous reporting system for suspected adverse drug reactions (ADRs) was established, at least for a time. There was no define monitoring system for drug safety until Thalidomide in 1960 report of 2 grossly deformed infants in Germany (thalidomide disaster). By 1961 477 cases of phocomelia in paediatric clinics, and withdrawal recommended.

There exist strategic methods for detection of ADR consist of the following: 1. Passive pharmacovigilance (spontaneous reporting of ADRs), Active pharmacovigilance. Active pharmacovigilance could be in the form of (Cohort Event Monitoring, Prescription Event Monitoring, Intensive Medicines Monitoring Programme, Record Linkages, and Pregnancy Registers etc. as maybe necessary), Reporting of medication errors, Reporting of suspected cases of substandard and counterfeit medicines and other health products, and Detection of lack of effectiveness.

Causality assessment is the assessment of relationship between a drug treatment and the occurrence of an adverse event. Many researchers developed various methods of causality assessment by using different criteria like

1. Chronological relationship between the administration of the drug and the occurrence of the ADR, 2. Screening for drug and non-drug related causes, 3 Confirmation of the reaction by in vivo or in vitro test, 4Previous information on similar events etc. But there is No universally accepted method for assessing causality of ADRs

Causality is broadly classified under three broad categories 1. Algorithms, 2. Probabilistic Methods and 3. Expert Judgement/ Global Introspection. The level of causal association is grouped into four

categories which are based on a number of the above criteria being met. WHO Causality Categories C1 – Certain, C2 – Probable, C3 – Possible, C4 – Unlikely and C5 – Unclassifiable?

Good progress made in early implementation with key personnel in place and active. Need: to scale up activities with stimulation of reporting and data collection

The potential benefits of a public health programme aimed at reducing or eliminating a specific condition will depend on the health burden due to that condition, which is a function of the seriousness of the condition and its frequency, as well as the likely efficacy of the programme in reaching its goals. The present article has outlined an approach to pharmacovigilance for such a donor-funded programme, using pharmacovigilance in leishmaniasis as an example.

SELF ASSESSED EXERCISES

Justify the importance of pharmacovigilance in Public Health Practice.
What is the role of pre-marketing evaluation and post marketing surveillance in Determining drug safety?

6.0 TUTOR MARKED ASSIGNMENT

1. Exercise: Using WHO Criteria determine the causality relationship of the events

i. An event with:
- a plausible time to onset
- no dechallenge information
- other medicines could have caused the event
- **Relationship =.....**

ii. An event with:
- a plausible time to onset
- no other obvious causes of the event
- positive dechallenge & rechallenge
- **Relationship =.....**

iii. An event with:
- a plausible time to onset
- no other obvious causes of the event
- event resolved on dechallenge
- a rechallenge was undertaken, but the result is not known
- **Relationship =.....**

iv. An event with:

- unknown duration to onset
- positive dechallenge
- rechallenge not stated
- no other obvious cause
- **Relationship =.....**

vi. An event with:

- a plausible time to onset
- no other obvious cause
- event outcome 'death'
- cause of death was a known reaction to the medicine
- **Relationship =.....**

vii. An event with:

- a plausible time to onset
- no other obvious causes of the event
- a dechallenge was undertaken**, but the event did not resolve**
- **Relationship =.....**

2. A 24years pregnant woman with normal LFTs was commenced on lamivudine, zidovudine, and nelfinavir at 16 weeks gestation.
event -jaundice leading to liver failure

- onset after 13 weeks (29weeks Gestation)
- outcome: recovered completely after drug stopped and
- commenced on: Efavirenz, Emtricitabine, tenofovir
- well at 12 months

What is the Causality Relationship = ……?

i.Discuss advantages, opportunities and of Pharmacovigilance integrated in Public Health Programmes

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UNIT 3 RATIONAL USE OF MEDICINES/DRUG DEPENDENCE AND SUBSTANCE ABUSE

CONTENTS

1.0 INTRODUCTION

Rational use of medicines requires that patients receive medications appr opriate to their clinical needs, in doses that meet their requirements, for a n adequate period of time, and at the lowest cost to them and their comm unity. Unfortunately, more than 50% of all medicines are prescribed, dis pensed, or sold inappropriately on a global basis and 50% of patients fail to take their medicines correctly according to estimates based on various ad hoc reviews. Common types of inappropriate medicines use include, Polypharmacy (the use of too many medicines per patient), overuse ofinjections, inappropriate use of antimicrobials, failure to prescribe in a ccordance withclinical guidelines, and inappropriate self-medication, often with prescription-only medicines. Inappropriate use of medicines is harmful for patients in terms of poorpatientclinical outcomes and avoi dable adverse drug reactions. Overuse of antimicrobialsexerts pressure to increase rates of antimicrobial resistance. Non-sterile injections contribute to the transmission of hepatitis, HIV/AIDS and other blood borne diseases. Inappropriate medicines use wastes scarce economic resources that could be used for food or other necessities. Unnecessary overuse of medicines can stimulate inappropriate patient demand and lead to medicine stockouts and loss of patient confidence in the health system.

About 275 million people worldwide, which is roughly 5.6 per cent of the global population aged 15-64 years, used drugs at least once during 2016. Some 31 million of people who use drugs suffer from drug use disorders, meaning that their drug use is harmful to the point where they may need treatment. Initial estimations suggest that, globally, 13.8 million young people aged 15-16 years used cannabis in the past year, equivalent to a rate of 5.6 per cent. Roughly 450,000 people died as a result of drug use in 2015, according to WHO. Of those deaths, 167,750 were directly associated with drug use disorders (mainly overdoses). The rest were indirectly attributable to drug use and included deaths related to HIV and hepatitis C acquired through unsafe injecting practices.

Opioids continued to cause the most harm, accounting for 76 per cent of deaths where drug use disorders were implicated. PWID - some 10.6 million worldwide in 2016 - endure the greatest health risks. More than half of them live with hepatitis C, and one in eight live with HIV.

The headline figures for drug users have changed little in recent years, but this stability masks the striking ongoing changes in drug markets. Drugs such as heroin and cocaine that have been available for a long time increasingly coexist with NPS and there has been an increase in the non-medical use of prescription drugs (either diverted from licit channels or illicitly manufactured). The use of substances of unclear origin supplied

through illicit channels that are sold as purported medicines but are destined for non-medical use is also on the increase. The range of substances and combinations available to users has never been wider.

Psychoactive drugs are substances that, when taken in or administered into one's system, affect mental processes, e.g. perception, consciousness, cognition or mood and emotions. Psychoactive drugs belong to a broader category of psychoactive substances that include also alcohol and nicotine. “Psychoactive” does not necessarily imply dependence-producing, and in common parlance, the term is often left unstated, as in “drug use”, “substance use” or “substance abuse”.

Production, distribution, sale or non-medical use of many psychoactive drugs is either controlled or prohibited outside legally sanctioned channels by law. Psychoactive drugs have different degrees of restriction of availability, depending on their risks to health and therapeutic usefulness, and classified according to a hierarchy of schedules at both national and international levels. At the international level, there are international drug conventions concerned with the control of production and distribution of psychoactive drugs: the 1961 Single Convention on Narcotic Drugs, amended by a 1972 Protocol; the 1971 Convention on Psychotropic Substances; the 1988 Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.

Note: Public health practitioners have attempted to look at substance use from a broader perspective than the individual, emphasizing the role of society, culture, and availability. Some health professionals choose to avoid the terms alcohol or drug "abuse" in favour of language they consider more objective, such as "substance and alcohol type problems" or "harmful/problematic use" of drugs.

2.0 OBJECTIVES

By the end of this unit, you will to be able to:

- define rational use of medicines and identify the magnitude of the problem
- state the problems of irrational drug use
- outline the reasons underlying irrational use
- identify factors which influence the behavior of prescribers and patients
- explain the role of HCPs in promoting rational drug use
- describe strategies and interventions to promote rational use of medicines
- define of various terms used in substance abuse
- classify drug of abuse and its management

- list factors responsible for substance abuse
- analyse pharmacological and harmful effects of substance abuse.

3.0 MAIM CONTENT

3.1 Definition of Terms

i. **Rational Use of Medicines:** The rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community. *(WHO conference of experts Nairobi 1985)*

ii. **Irrational Use of Medicines**
Irrational (inappropriate, improper, incorrect) use of medicines is when one or more of these conditions is not met. The use of drugs when no drug therapy is indicated, the use of wrong drugs for a specific condition requiring drug therapy, the use of drugs with doubtful or unproven efficacy, the use of drugs of uncertain safety status, failure to prescribe available, safe, & effective drugs or incorrect administration, dosages, or duration

iii. **Meaning of Appropriate Use**: The term "appropriate drug use" means different things to different people. When a patient received correctly prescribed, dispensed or sold medicines and take their medication as prescribed or dispensed. This is opposite irrational use which may take many different forms, for example, polypharmacy, over-use of antibiotics and injections, failure to prescribe in accordance with clinical guidelines and inappropriate self-medication.

iv. **Medical definition of Abuse** is defined by the WHO Expert Committee on Drug Dependence as “persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice”. The term “abuse” is sometimes used disapprovingly to refer to any drug use at all, particularly of illicit drugs.

v. **Analgesic** is a medicine that reduces pain.

vi. **Controlled medicines** are medicines containing controlled substances.

vii. **Drug** includes any substance or mixture of substances manufactured, sold or advertised for use in the diagnosis, treatment, mitigation or prevention of any diseases or disorder, abnormal physical state or symptoms thereof, in man or in animals; restoring, correcting or modifying organic functions in man or animal’s disinfection or the control of vermin, insects, pests or contraception.

viii. **Drug abuse** is an intense desire to obtain increasing amounts of a particular substance.

ix. **Drug dependence** is the body's physical need, or addiction, to a specific agent. Over the long term, this dependence results in physical harm and behavior problems which causes tolerance and cross tolerance. Thus, it creates a vicious cycle.

x. **Dependence** is defined by the WHO Expert Committee on Drug Dependence as "A cluster of physiological, behavioural and cognitive phenomena of variable intensity, in which the use of a psychoactive drug takes on a high priority. The necessary descriptive characteristics are preoccupation with a desire to obtain and take the drug and persistent drug-seeking behaviour.

xi. **Hard drug (lead to severe physical addiction):** – Drug that is generally considered to be more dangerous, with a higher risk of dependence that soft drugs. E.g.: Heroin, methamphetamine, cocaine.

xii. **Medicine:** Any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient.

xiii. **Misuse** (of a controlled substance) for the purposes of these guidelines, is defined as the nonmedical and non-scientific use of substances controlled under the international drug control treaties or under national law.

xiv. **Narcotics** are derived from the opium and its derivatives which include morphine and codeine. They are also derived from cannabis and coca leaf plants. Also included are synthetic Narcotics, such as Pethidine, Fentanyl, and Methadone. Legally they are substances contained in Schedule I, II, III and IV of the UN Single Convention on Narcotics as amended 1961. The differences in the scheduling relate only to the control measures to be applied. The medicines are indispensable for the relief of pain and the convention seeks to make them adequately available for medical and scientific purposes only.

xv. **Opioids** means literally "opium-like substance". It can be used in different contexts with different but overlapping meanings: **Opioids Substitution Therapy r**efers to treatment Opioids Substitution Therapy refers to treatment of opioids dependence with relatively stable doses of the long acting agonists (usually methadone or buprenorphine) prescribed over prolonged periods of

time (usually more than six months), which allows stabilisation of brain functions and prevention of craving and withdrawal.

xvi. **Precursor**s are raw materials which when used in the production of a drug become part of a finished product. Reagent and Solvents are also listed as precursors but usually not a part of the finished product. They are however used in the manufacture and processing of some Narcotic drugs and psychotropic substances. Examples are ephedrine used in the manufacture of methamphetamine; sulphuric acid is a reagent and acetone are a solvent.

xvii. **Psychotropic Substances** are drugs that alter the central nervous system such as sedatives, hypnotics, hallucinogens and stimulants. Under the UN Convention on Psychotropic Substances of 1971, these substances are listed under Schedules I, II, III, and IV. Some of these medicines are employed in anaesthesia for surgical procedures (such as thipopentone and midazolam), essential in emergency obstetrics (ergometrine) or used as anxiolytics and hypnotics (benzodiazepines) or as antiepileptics (phenobarbital and benzodiazepines).

xviii. **Rational drug use** requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time and at the lowest cost to them and their community. This implies rational prescribing; good this implies rational prescribing, good dispensing practices and concordance.

xix. **Soft drug (do not cause physical addiction):** – While they do not cause physical addiction, some of them may still lead to psychological dependency. Psychological dependency is a dependency of the mind. This means that people feel better when they have the drug. E.g.: lysergic acid diethylamide (LSD), Cannabis.

xx. **Street drug:** Drug that is taken for non-medicinal reasons (usually for mind-altering effects); drug abuse can lead to physical and mental damage and (with some substances) dependence and addiction. e.g.: Alcohol, heroin, methamphetamine, crack, cocaine and marijuana (Cannabis).

xxi. **Tolerance is defined** as a person's diminished response to a drug that is the result of repeated use. People can develop tolerance to both illicit drugs and prescription medications. As stated above, tolerance is a physical effect of repeated use of a drug, not necessarily a sign of addiction. For example, patients with chronic

pain frequently develop tolerance to some effects of prescription pain medications without developing an addiction to them.

3.2 Rational Use of Medicines

The rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community. *(WHO conference of experts Nairobi 1985)*

Criteria' for Using Medicine

i. correct drug
ii. appropriate indication
iii. appropriate drug considering efficacy, safety, suitability for the patient, and cost
iv. appropriate dosage, administration, duration
v. no contraindications
vi. correct dispensing, including appropriate information for patients
vii. patient adherence to treatment.

3.3 Irrational Use of Medicines

Irrational drug use consists of poly pharmacy, use of drugs that are not related to diagnosis, or unnecessarily expensive, inappropriate use and irrational self-medication, with many insufficient quantities' consumption of drugs.

3.3.1 Examples of Common Inappropriate Prescribing Practices

i. The overuse of antibiotics and antidiarrhoeals for nonspecific childhood diarrhea
ii. Indiscriminate use of injections
iii. Multiple or over-prescription
iv. Wrong Diagnosis
v. Use of antibiotics for mild, non-bacterial infection, e.g., common cold URI
vi. Tonics and multivitamins for malnutrition
vii. Unnecessary use of expensive antihypertensives
viii. Adequacy of diagnostic process

Inappropriate antibiotic use

Overuse and misuse of antibiotics is a particularly serious global problem. Established and newly emerging infectious diseases are increasingly threatening the health of populations. If antibiotics become ineffective, these diseases will lead to increased morbidity, health-care use and eventually premature mortality. Furthermore, antibiotics are required for other treatments (taken for granted in developed countries), such as surgery and cancer chemotherapy, which would become unavailable with the disappearance of effective antibiotics. Unfortunately, while resistance to older antibiotics is increasing, the development of new generations of antibiotic medicines is stalling. Therefore, efficient use of existing antibiotics is needed to ensure the availability in the long term of effective treatment of bacterial infections. Efficient use includes both restrictive and appropriate use. However inappropriate and incorrect use of antibiotics occurs in both developing and developed countries. Doctors prescribe antibiotics to patients who do not need them, while patients do not adhere to their treatment causing the risk of antibiotic resistance. Two thirds of all antibiotics are sold without prescription, through unregulated private sectors. Even in those European countries where over-the-counter delivery of antibiotics is not allowed, patients use antibiotics without prescription. Low adherence levels by patients are common, many patients taking antibiotics in under-dose or for shortened duration — 3 instead of 5 days.

Since there is very little information on medicines use for chronic diseases or on the use of over-the-counter (OTC) medicines in developing countries, the focus of this discussion would mainly on use of prescription-only medicines in acute disease, particularly antibiotics, although mention will be made of treatment of chronic diseases, especially in terms of adherence to medication.

Absolutely Irrational Use

i. Injudicious use of antimicrobials: Antibiotics in Viral fever and diarrhoea
ii. Unnecessary combinations
iii. Use of drugs not related to diagnosis
iv. Incorrect route
v. Incorrect dosing – under or overdose
vi. Incorrect duration – prolong or short-term use
vii. Unnecessary use of expensive medicines
viii. Unsafe use of corticosteroids
ix. Polypharmacy

3.3.2 Example of Over the Counter (OTC) Drugs

i. **Topical anti-bacterial, anti-fungal OTC drugs:** - Bacitracin, Clotrimazole (vaginal, topical use) Miconazole 2% ointment etc.
ii. **Pain reliever OTC drugs:** Acetaminophen, Aspirin, NSAIDs, Ibuprofen, Naproxen etc.
iii. **Smoking cessation OTC drugs:** Nicotine patch
iv. **Topical Dermatological (skin, scalp) OTC drugs:** Capsaicin, Doak tar distillate oil, Hydrocortisone, Permethrin, Pyrethrin, Zinc oxide ointment.
v. **Diabetes OTC drugs:** Insulin OTC vials (Humulin 50/50 vial, Humulin N, Humulin R, Novolin 70/30 vial, Novolin R vial etc) Glucose chewable tablet.
vi. **Digestion OTC Drugs Anti-diarrheal drug:** - Loperamide
vii. **Anti-ulcer drugs:** Cimetidine, Famotidine, Ranitidine Nizatidine.
viii. **Proton pump inhibitors:** -Omeprazole Laxatives &Cathartics: - Bisacodyl, Docusate, Glycerine, Psyllium, Sorbitol.
ix. **Other digestion drugs: -**Aluminium hydroxide gel, Antacid liquid suspension, Calcium antacid tablets, Simethicone drops etc.
x. **OTC Vitamins: -** Calciferol, Ergocalciferol drops, Calcium carbonate, Calcium carbonate 600mg+vit. D, Calcium citrate, Ferrous fumarate, Ferrous gluconate, Ferrous sulfate, Magnesium oxide, Multivitamins etc.
xi. **Eye care OTC drugs**: -Artificial tears, Refresh tears, liquate (15ml or 30ml bottle only), Sodium chloride 5% drops, ointment, Systane etc.
xii. **Cough/Cold/allergy OTC drugs Anti –histamine:** Cetirizine tab, Cetirizine-D tab, Cetirizine sol., Diphenhydramine, Loratadine, Loratadine-D,
xiii. **Anti-histamine/DecongestantCombinations**: - Brompheniramine- Pseudoephedrine elixir.
xiv. **Other drugs**: - Nasal spray, Pseudoephedrine

3.3.2 Examples of Irrational Drug Combinations

i. If the combination of drugs is illogical in terms of plasma half-life and pharmacokinetics of the drug, the combination should be termed as irrational drug combination. Large numbers of such irrational drug combinations are available in the market which unnecessarily increase the cost of medication and add to the side effects of the therapy.

ii. **Ampicillin + Cloxacillin Ampicillin** is effective against Gram negative bacilli but Cloxacillin is an Anti-staphylococcal penicillin and not effective against Gram negative bacilli. Mixed Gram negative and Staphylococcal (Gram positive) infection rarely

coexists. So, in a patient with a single infection, one of the drugs of the combination would be useless. In addition to the cost of therapy it would add to adverse side effects and resistance of bacteria to the drug. On the other hand, the combination would reduce the dose of effective drug to the half and the patient would need longer course of therapy.

iii. **Antibacterial + Antiamoebic Combinations:** Ciprofloxacin + Metronidazole, Norfloxacin + Tinidazole and Ofloxacin + Ornidazole are such commonly available fixed dose drug combinations. In bacterial diarrhoea only anti-bacterial drug is effective and antiamoebic drug is useless. Similarly, in intestinal amoebiasis only antiamoebic drug is effective while antibacterial drug is useless. Amoebiasis and bacterial diarrhoea rarely coexist. The therapy should be based on the diagnosis to reduce the cost of treatment since in a given case, only one drug of the combination would be effective and the other one would be useless.

iv. **NSAIDs Combinations**: Nimesulide, diclofenec, ibuprofen and Paracetamol are some non-steroidal anti-inflammatory drugs (NSAIDs). There is no justification in combining one NSAID (nimesulide, diclofenec, ibuprofen) with another NSAID (paracetamol) having same pharmacological actions. The increased risk of hepatotoxicity has been reported due to the use of combination of nimesulide with paracetamol. There is increased risk of nephrotoxicity with NSAIDs combinations.

v. **H2 Blocker + Domperidone:** Ranitidine and Famotidine are H2 blockers. H2
blockers reduce gastric acid production in peptic diseases and give symptomatic relief. The combination of these drugs with antiemetic drug (Domperidone) is an irrational drug combination as peptic ulcer is not always associated with vomiting. Even in gastro-oesophageal reflux disease (GERD), the domperidone is less effective as compared to metoclopramide, so combining H2 blockers with domperidone seems to be an irrational choice.

vi. **H2 Blocker (Ranitidine) + Antispasmodic Drug (Dicyclomine):** The pain of peptic ulcer is due to high level of gastric acid but not due to spasm of smooth muscles and will subside only with reduction in gastric acid in stomach by use of H2 blocker (Ranitidine) or proton pump inhibitor drugs (Omeprazole, Pantoprazole or Lansoprazole). So, there is no justification in combining H2 blocker (Ranitidine) with antispasmodic drug (Dicyclomine).

vii. Mucolytic Agent + Antibacterial Ambroxol + Ciprofloxacin or Cefadroxil or Roxithromycin.: Ambroxol is a mucolytic agent used to liquefy thick respiratory secretions. There is no justification in combining mucolytic agent with antibacterial, as thick secretions in respiratory tract are always not due to respiratory infections. Also, the antibacterial therapy always does not require an associated dose of mucolytic agent.

ix. **Metformin + Glimepiride + Pioglitazone**: Metformin is indicated drug in obese type -2 diabetes mellitus whereas Sulfonylurea (Glimepiride) is indicated drug in non-obese type-2 diabetes mellitus. As per pharmacological principle, another drug should be added only when monotherapy fails. Metformin (biguanide) is to be administered after meal whereas Glimepiride (sulfonylurea) drug is to be administered before meal, therefore even when both the drugs are required, it would be better to administer them separately. Pioglitazone is indicated in suspected cases of insulin resistance. So, the combination of all these drugs in one formulation is an irrational drug combination.

ix. Codeine+NSAID (paracetamol): This combination is used to treat severe pain or to inhibit pain perception but these combinations can cause excessive sedation which can be dangerous. Needs further examination. Multi vitamin preparations Multivitamin combination is considered to be irrational. Excessive use may lead to several side effects.

x. **Expectorant central cough suppressants:** antihistaminics + bronchodilator mucolytic agent Bromhexine Hydrochloride 8 mg + Terbutaline sulphate 2.5 mg + Guaiphenesin 100 mg + Menthol 5 mg, this combination of expectorants is a costlier way of helping a condition which is often self- resolving. Expectorant given in effective doses are often not tolerated and produce adverse drug reaction.

3.3.4 Obstacles/Reasons Irrational Use Continue

Very few low- and middle-income countries regularly monitor drug use and implement effective nation-wide interventions - because…

i. They have insufficient funds or personnel?
ii. Lack of objective information & of continuing education & training in pharmacology.
iii. There is insufficient knowledge of concerning the cost-effectiveness of interventions? They lack of awareness about the funds wasted through irrational use?

iv. Presence of large number of drugs in the market & the lucrative methods of promotion of drugs employed by pharmaceutical industries.
v. Lack of well-organised drug regulatory authority & supply of drugs.
vi. The prevalent belief that "every ill has a pill.

3.3.5 Factors Underlying Irrational Use of Drugs

There is strong interrelationship of factors and as problems rarely have single cause

i. **Patients:** drug misinformation, misleading beliefs and inability to communicate problems
ii. **Prescribers:** lack of education and training, lack of drug information, heavy patient load, pressure to prescribe, generalisation of limited beliefs and misleading beliefs about efficacy
iii. **Drug Supply:** inefficient management and non-availability of required drugs
iv. **Industry:** promotion or misleading claims
v. **Drug Regulation:** availability of unsafe drugs, informal prescribers etc.
vi. **Adverse drug events are the** 4-6th leading cause of death in the USA, estimated costs from drug-related morbidity & mortality 30 million-130 billion US$ in the USA, 4-6% of hospitalisations in the USA & Australia. commonest, costliest events include bleeding, cardiac arrhythmia, confusion, diarrhoea, fever, hypotension, itching, vomiting, rash, renal failure.

3.3.6 Impact of Inappropriate Use of Drugs

i. **Reduced quality of therapy** – Ineffective & unsafe treatment, over-treatment of mild illness, inadequate treatment of serious illness and exacerbation or prolongation of illness leading to increase morbidity & mortality
ii. **Waste of resources -** Reduced availability & increased cost. Irrational use is wasteful and can be harmful for both the individual and the population.
iii. **Risk of unwanted effects** - adverse reactions & bacterial resistance; Antimicrobial resistance is dramatically increasing worldwide in response to antibiotic use much of its inappropriate overuse (and is causing significant morbidity and mortality. It has been estimated that antimicrobial resistance costs annually US$ 4000–5000 million in the USA and €9000 million in Europe.
iv. **Psycho-social impacts** - patients rely on unnecessary drugs

v. **Adverse drug events** –commonest, costliest consequences of inappropriate use of medicines. These includes include bleeding, cardiac arrhythmia, confusion, diarrhoea, fever, hypotension, itching, vomiting, rash, renal failure. A 4-6th leading cause of death in the USA, ADR is estimated costs from drug-related morbidity & mortality 30 million-130 billion US$ in the USA. Adverse medicines events cause significant morbidity and mortality and rank among the top 10 causes of death in the United States of America. They have been estimated to cost £466 million annually in the United Kingdom of Great Britain and Northern Ireland and up to US$ 5.6 million per hospital per year in the USA. (Source: Review by White et al, Pharmacoeconomics, 1999, 15(5):445-458)

vi. The use of unsterile injections is associated with the spread of blood borne infections, such as hepatitis B and C and HIV/AIDS. Although evidence-based medicine has gained importance the use of both diagnostic and treatment guidelines is sub-optimal and could be greatly improved.

3.4 The Role of Hcps in Promoting Rational Drug Use Objectives

Thing to Ponder: Case Report - A 20yrs. female student, suffering from tonsillitis, was seen by an OPD doctor in a 600-bed hospital. She obtained a drug from the hospital pharmacy and took it as instructed. She felt very weak after taking the drug. 3 days later she became severely comatose and was admitted to the same hospital. She took chlorpropamide 250 mg four times a day as dispensed to her at the Pharmacists. The OPD doctor claimed that he prescribed chloromycetine 4x250 mg daily for her tonsillitis. The patient eventually died two weeks after hospital admission. ***Discuss possible cause of Death – Identify any system failure***

3.5 Changing A Drug Use Problem: An Overview of The Process

i. **Examine:** measure existing practice (Descriptive Quantitative studies) improve diagnosis

ii. **Diagnosis:** Identify specific problems and causes (in-depth qualitative and qualitative studies)

iii. **Treat:** Design and implement intervention (Data collect data to measure outcome

iv. **Follow up:** measure changes in outcomes (qualitative and evaluation)

3.5.1 Steps of rational drug use

Step: - I Identify the patient's problem based on symptoms & recognise the need for action

Step: - II Diagnosis of the disease – define the diagnosis

Step: - III List possible intervention or treatment (drug or no drug) – Identify the drug

Step: - IV Start the treatment by writing an accurate & complete prescription e.g. name of drugs with dosage forms, dosage schedule & total duration of the treatment.

Step: -V Give proper information, instruction & warning regarding the treatment given e.g. side effects (ADR), dosage schedule & dangers/risk of stopping the therapy suddenly

Step: -VI Monitor the treatment to check, if the particular treatment has solved the patient's problem.

i. **Passive monitoring** – done by the patient himself. Explain him what to do if the treatment is not effective or if too many side effects occurs
ii. **Active monitoring** - done by physician and he make an appointment to check the response of the treatment

3.6 Strategies to Improve Use of Drugs

3.6.1. Educational Strategies: Goal: to inform or persuade

i. Training for Providers

Undergraduate education
Continuing in-service medical education (seminars, workshops)
Face-to-face persuasive outreach e.g. academic detailing
Clinical supervision or consultation

ii. Printed Materials

Clinical literature and newsletters
Formularies or therapeutics manuals
Persuasive print materials

iii. Media-Based Approaches
Posters
Audio tapes, plays
Radio, television

3.6.2. Training for prescribers: *The Guide to Good Prescribing*
WHO has produced a Guide for Good Prescribing - a problem-based method?

Developed by Groningen University in collaboration with 15 WHO offices and professionals from 30 countries Field tested in 7 sites Suitable for medical students, post grads, and nurses widely translated and available on the WHO medicines website

3.6.3. Managerial strategies: *Goal: to structure or guide decisions*

i. Changes in selection, procurement, distribution to ensure availability of essential drugs. - Essential Drug Lists, morbidity-based quantification, kit systems
ii. Strategies aimed at prescribers - targeted face-to-face supervision with audit, peer group monitoring, structured order forms, evidence-based standard treatment guidelines
iii. Dispensing strategies - course of treatment packaging, labelling, generic substitution

3.6.4. Economic strategies: *Goal: to offer incentives to providers a consumer*
iv. **P**romotes positive financial incentives and also eliminating perverse
v. incentives for prescribers.
vi. Implements significant changes in service providers' reimbursement
vii. schemes or disallowing prescribers to sell medicines themselves
viii. Removes the financial motivation for over-prescribing are economic
i. interventions that may be used.

3.6.5 Avoid perverse financial incentives
ix. prescribers' salaries from drug sales
x. insurance policies that reimburse non-essential drugs or incorrect doses
xi. flat prescription fees that encourage polypharmacy by charging the same amount irrespective of number of drug items or quantity of each item
xii. (reverse – Quebec, dispensing fee is given even if pharmacist does not dispense for good reason)

xiii. Reimburse without treatment guidelines (ceftriaxone as an OPD medicine)

3.6.6 Regulatory strategies: Goal: to restrict or limit decisions

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

Only work if the regulations are enforced

3.7 Drug Dependence and Substance Abuse

3.7.1Introduction:

Public health practitioners have attempted to look at substance use from a broader perspective than the individual, emphasizing the role of society, culture, and availability. Some health professionals choose to avoid the terms alcohol or drug "abuse" in favour of language they consider more objective, such as "substance and alcohol type problems" or "harmful/problematic use" of drugs. The Health Officers Council of British Columbia — in their 2005 policy discussion paper, A Public Health Approach to Drug Control in Canada — has adopted a public health model of psychoactive substance use that challenges the simplistic black-and-white construction of the binary (or complementary) antonyms "use" vs. "abuse". This model explicitly recognizes a spectrum of use, ranging from beneficial use to chronic dependence.

3.7.2 Causes of Substance Use Disorders

The cause of substance use disorders is still unknown, though genetics are thought to account for 40% to 60% of a person's risk. Substance use often starts as a way to feel good or out of curiosity in childhood or early adolescence. Repeated use of the substance and increased tolerance pave the way to substance use disorder and addiction. Some adults who develop a substance use disorder have a co-occurring mental illness, such as depression, anxiety, or bi-polar disorder, and begin using drugs or alcohol to cope with their symptoms. Other risk factors that may lead to a substance use disorder include:

i. **Family history of addiction:** Drug addiction is more common in some families and likely involves genetic predisposition to mental health disorder.
ii. **Peer pressure:** This is most common reason among young adults and teenagers. They start to use drugs because they want to fit in. Being rebellious as a teenager or young adult is very common. In a lot of cases, young adults and teenagers don't fully understand the severity of drug use and addiction.
iii. **Sleep problems & Chronic pain:** In many cases, substances like Alcohol, Marijuana and prescription painkillers act as a gateway to drugs that have a more intense and mind-altering effect. Currently, the Opioid epidemic is forcing people to turn to street drugs, like Meth or Heroin, when their doctor stops writing refills for their prescriptions.
iv. **Experimenting:** Mind-altering substance, like Cocaine and Alcohol, promise to heighten experience and that experience is worth exploring. Unfortunately, there are drugs like Heroin, Ecstasy, and Meth that are so addictive that the person will begin a pattern of abuse, which can eventually lead to an addiction.
v. **Self- Medications:** Self-medicating is the top reason people abuse drugs and Alcohol. Stress, anxiety, reoccurring pain, undiagnosed mental illnesses, severe depression, loneliness, trauma; these are all reasons why people would self-medicate with mind-altering substances to cope with what they are feeling or what they do not want to feel.
vi. **Also,** Financial difficulties, Divorce or the loss of a loved one, Tense home environment, Lack of parental attachment in childhood, Relationship issues, Long-term tobacco habit etc.
vii. None of these risk factors guarantees that a person will develop a substance abuse disorder, but a combination of factors plus repeated substance use significantly increases the likelihood of addiction.

3.7.3 Classification of Drug Dependence/Substance Abuse

The commonly types of drugs of abuse and dependence

viii. **CNS Stimulants:** methamphetamine (Desoxyn: meth, ice, crank, chalk, crystal, fire, glass, go fast, speed), Amphetamines (Biphetamine, Dexedrine: bennies, black beauties, crosses, hearts, LA turnaround, speed, truck drivers, uppers), Cocaine (Cocaine hydrochloride: blow, bump, C, candy, Charlie, coke, crack, flake, rock, snow, toot), Methphenidate and Khat etc.
ix. **CNS Depressant:** Alcohol, Disulfiram, Naltrexone, Benzodiazepines, Barbiturates

x. **Cannabinoids:** Hashish (Boom, gangster, hash, hash oil, hemp), Marijuana. (Blunt, ganja, grass, green, trees, weed etc.) 3. Bango.

xi. **Opioids:** Heroin (Diacetylmorphine: smack, horse, brown sugar, dope, H, junk, skag, skunk, white horse, China white; cheese (with OTC cold medicine and antihistamine)), Opium, (Laudanum, paregoric: big O, black stuff, block, gum, hop), Morphine, Codeine and Codeine-containing cough sedatives and Methadone, Buphrpnorphine.

i. **Hallucinogens:** (Psychedelic); LSD, Anticholinergics and Mescaline etc.

ii. **Club Drugs:**

MDMA (Methylenedioxymethamphetamine): Ecstasy, Adam, clarity, Eve, lovers' speed, Molly, peace, uppers

Flunitrazepam: Rohypnol (date rape drug): forget-me pill, Mexican Valium, R2, roach, Roche, roofies, roofinol, rope, rophies

GHB: Gamma-hydroxybutyrate: G, Georgia home boy, grievous bodily harm, liquid ecstasy, soap, scoop, goop, liquid X

iii. **DISSOCIATIVE DRUGS;**

Ketamine: Ketalar SV: cat Valium, K, Special K, vitamin K**,** PCP and Analogs:**Phencyclidine:** angel dust, boat, hog, love boat, peace pill**.**

Salvia Divinorum: Salvia, Shepherdess's Herb, Maria Pastora, magic mint, Sally-D**.**

iv. **Dextromethorphan (DXM):** Found in some cough and cold medications: Robot ripping, Robo, Triple C.

OTHER COMPOUNDS:

Anabolic Steroids: Anadrol, Oxandrin, Durabolin, Depo-Testosterone,

Equipoise: roids, juice, gym candy, pumpers

Inhalants: Solvents (paint thinners, gasoline, glues); gases (butane, propane, aerosol propellants, nitrous oxide); nitrites (isoamyl, isobutyl, cyclohexyl): laughing gas, poppers, snappers, whippets

Caffeine: Whether consuming caffeine in large amounts can increase perinatal risk is unclear. Consuming caffeine in small amounts (e.g. 1 cup of coffee/day) appears to pose little or no risk to the fetus. Some data, which did not account for tobacco or alcohol use, suggest that consuming

large amounts increases risk of stillbirths, preterm deliveries, low birth weight & spontaneous abortions

Smoking: Carbon monoxide & nicotine - hypoxia & vasoconstriction, increasing risk of spontaneous abortion, fetal growth restriction, abruptio placentae, placenta previa, premature rupture of membranes, preterm birth, chorioamnionitis & stillbirth, Anencephaly, congenital heart defects, orofacial clefts, sudden infant death syndrome, deficiencies in physical growth & intelligence & behavioral problems, Smoking during pregnancy - childhood asthma

3.7.4 Diagnosis of Drug Dependence / Substance Abuse

Most of substances known to be amenable for abuse and dependence (Addiction) can be grouped into the following classes

i. **CNS Stimulants: Cocaine**: An alkaloid derived from cocoa leaves or synthesised from ecgonine or its derivative. Cocaine is one of the most addictive of commonly abused substances and one of the most dangerous. Various street names of cocaine, is referred to as crack, snow, cock, girl and lady etc. It is a ***white powder that is inhaled, smoked or injected***.

Effect of cocaine on CNS: Cocaine is a psychoactive stimulant. Its primary pharmacological action is related to its competitive blockade of dopamine reuptake by dopamine transporters. This leads to marked elevation of dopamine in synaptic clefts. Cocaine has powerful addictive qualities. Psychological dependence on cocaine can develop after a single use.

Withdrawal symptoms of cocaine: Withdrawal symptoms are mild compared to those of opioids. They include depressed mood, dysphonia, fatigue, hyper somnolence. Suicidal ideations may occur. Symptoms persist for a few days up to one week. Craving is very strong.

Over dose of cocaine Intoxication by high doses is associated with delirium, seizures, cerebrovascular diseases and myocardial infarction which may lead to death.
Psychiatric disorders with cocaine abuse they include: psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorder.

ii. **CNS Depressant:** Alcohol, Disulfiram, Naltrexone, Benzodiazepines and Barbiturates.

Alcohol: These are a large group of organic compounds derived from hydrocarbons and containing one or more hydroxyl (OH) group. Ethanol

is one of these class of compounds and it is the main psychoactive ingredient in alcoholic beverages. Non-beverage alcohol includes methanol, isopropyl alcohol and ethylene glycol are also occasionally consumed alcohol e.g. Disu. 90% of USA population are using alcohol, whereas only 12% or 18% have abuse or dependence problem, respectively

Effects on Pregnancy: Causes vasoconstrictor leading to increased risk of

i. spontaneous abortion with decrease birth weight by ~1 to 1.3 kg, if regular drinking, Binge drinking in particular - fetal alcohol syndrome
ii. Dysmorphic facial features (all 3 are required) - Small palpebral fissures, thin vermilion border & smooth philtrum
iii. Prenatal and/or postnatal growth impairment 3. CNS abnormalities (1 required)
iv. Structural: head size < 10th percentile, significant brain abnormality on imaging
v. Neurological:

Effect of alcohol on the brain: Alcohol is a CNS suppressant. It exerts this suppressant effect in a descending manner, where higher cortical centres are inhibited first, resulting in euphoria and then disinhibition. In larger doses, lower vital centres are inhibited, leading to hypotension and respiratory depression. Also, functional such as global cognitive or intellectual deficits, functional deficits in at least three domains

Effect of alcohol on neurotransmitters: It is found that ion channel activities associated with acetyl choline, serotonin and GABA receptors are enhanced by alcohol. Ion channel activities associated with glutamate receptors are inhibited. Death is due to central respiratory depression or inhalation of vomitus.

Alcohol-Related Disorders: Alcohol abuse and dependence, Alcohol withdrawal, Alcohol induced dementia, Alcohol induced amnestic disorders, Alcohol induced psychotic disorders and Alcohol related mood disorders.

Alcohol withdrawal: the classic signs of alcohol withdrawal are due to sympathetic over activity and tendency to develop epileptic convulsions. Symptoms include tremulousness, sweating, restlessness and even excitement. They may include psychotic symptoms (such as delusions and hallucinations). Seizures and symptoms of delirium tremens may eventually develop.

Foetal alcohol syndrome: It occurs when foetuses are exposed in utero to alcohol by their mothers' drinking alcohol. This syndrome is the leading cause of mental retardation in the United States. Women with alcohol related disorders have a 35 percent risk of having a child with deficits.

Cannabinoids: Hashish (Boom, gangster, hash, hash oil, hemp), Marijuana. (Blunt, ganja, grass, green, trees, weed etc.), Bango.

iii.**CANNABINOIDS (Cannabis):** A generic term used to denote the several psychoactive preparations of the marijuana (hemp) plant, Cannabis Sativa. The psychoactive compound in cannabinoids is delta-9tetrahydrocannabinol (THC). Cannabinoids are usually smoked, but may be taken orally and are sometimes mixed with tea or food.
Common forms of Cannabinoids include marijuana leaf (in street jargon: grass, pot, dope, weed or reefers), bhang (BHO), Hashish (derived from the resins of the flowering heads of the plant) and hashish oil.

THC is lipid soluble and rapidly absorbed after inhalation. It is redistributed from blood into other tissues. It is then released from its adipose tissue stores into the blood stream. This explains the prolonged effects of THC after acute intake

Effect of cannabinoids: Cannabinoids exert many of their actions by influencing several neurotransmitter systems. These include acetylcholine, dopamine, gammaamino-butyric acid (GABA), histamine, serotonin, norepinephrine, opioid peptides, and prostaglandins.

Cannabis intoxication
Acute Effects: Euphoria; relaxation; slowed reaction time; distorted sensory perception; impaired balance and coordination; increased heart rate and appetite; impaired learning, memory; anxiety; panic attacks and psychosis.
.
Cannabis withdrawals have been described in association with the use of high doses in the form of: Irritable or anxious mood, Tremor, Perspiration, Nausea and Sleep disturbances.
Health Risks: Cough; frequent respiratory infections; possible mental health decline; addiction.

Hazards of cannabinoids - Chronic cannabinoids use is associated with poor social and vocational functioning due to the development of Amotivational Syndrome. A number of psychiatric disorders such as bipolar mood disorder, anxiety, depersonalisation, and dissociative episodes are reported as a consequence of cannabinoids abuse. Affective disorders and paranoid symptoms may be exacerbated after cannabinoids abuse.

iv. **Opioids:** This generic term applies to alkaloids from opium poppy (Paperver Somniferum) Opioids are highly addicting**.**

Natural Opioids alkaloids (Morphine and Codeine) and their semi synthetic derivatives includes Semi synthetic opioids: hydromorphone, it is also known as dihydromorphinone diacetyl morphine (diamorphine, heroin), Hydrocodone is chemically altered codeine. Oxycodone which derived from thebaine. Other examples are oxymorphone, ethyl morphine and buprenorphine.

Fully synthetics opioids: fentanyl, pethidine, levorphanol, methadone, tramadol, tapentadol and dextropropoxy.
Acute Effects: Euphoria; drowsiness; impaired coordination; dizziness; confusion; nausea; sedation; feeling of heaviness in the body; slowed or arrested breathing Health Risks: Constipation; endocarditis; hepatitis; HIV; addiction; fatal overdose

Nervous system suppressants (endogenous opioids receptors). Their effects include: Analgesia, Mood changes, "Mental clouding", Sedation, Central nausea and vomiting, gastrointestinal effects, pupillary constriction and Respiratory depression.

Over dose of opiates Severe intoxication is diagnosed by the triad of: ***Coma, Pinpoint pupils and Respiratory depression.*** It is a medical emergency that requires immediate attention.

Opioids Withdrawal Syndrome; Time of onset differs according to the half-life of the drug used: e.g. 4-6 hours after the last use of heroin but up to 36 hours after the last use of methadone. Severity varies with the dose and duration of drug use. Early findings may include tachycardia, hypertension, pupillary dilatation, and diffuse muscular-skeletal pain.
Central nervous system symptoms include restlessness, irritability andinsomnia Gastrointestinal symptoms are anorexia, vomiting, abdominal colics, and diarrhoea Cutaneous and mucocutaneous symptoms includes lacrimation, rhinorrhoea and piloerection, also known as "gooseflesh" Opioids Craving.

v. **Hallucinogens**: Agents that induce a state of marked perceptual alterations. They are CNS stimulants. Examples are: lysergic acid diethylamide (LSD) and amphetamines. They have both an antagonist and an agonist effect on serotonergic system

vi. **Lysergic acid diethylamide (LSD):** LSD is synthetic derivative of ergot fungus. It is extremely potent and is effective in extremely low doses. It is ingested orally or through other mucous membranes (sublingual, orally or corneal). Tolerance quickly

develops, leading to ingestion of larger doses or increased frequency of use. It is not highly addicting.

Hazards of hallucinogen use;

i. A drug precipitated psychosis may continue following the cessation of hallucinogen use.
ii. Flashbacks are brief spontaneous recurrences of perceptual changes, such as experienced while using hallucinogens. They have been reported days, months or years after drug use.
i. **Amphetamines is Pegnancy (Cat C). Causes** Defects in Oral clefts, Cardiovascular abnormalities: Phencyclidine (PCP, angel dust) - Possible malformations & behavioral disturbances
ii. **Benzodiazepines (BDZ):** Benzodiazepines are psychoactive depressant drugs that are used to control anxiety and epilepsy and in induction of anaesthesia. Tolerance to benzodiazepines is common. Benzodiazepines are widely used in combination with heroin, cocaine, alcohol and stimulants.

Intoxication of BDZ, includes somnolence and behavioural disinhibition. In higher doses, they cause hypotension and central respiratory depression, particularly if taken with another depressant drug (e.g., alcohol)

Withdrawal of BDZ symptoms include rebound anxiety, restlessness, agitation, hypertension, and d tachycardia. Epileptic seizure is a serious emergency and may be fatal. Hospitalisation and gradual withdrawal of benzodiazepines are the main lines of treatment of benzodiazepine addiction. Prevention of seizures by antiepileptics may be needed

vi. **Nicotine**: Nicotine, in mild to moderate doses, is a central nervous system stimulant. It enhances central cholinergic receptors (activated by acetyl choline). The dependence-producing effects of nicotine appear to be modulated by dopamine (nicotinic-cholinergic receptors lie on dopamine neurons, nicotine increases dopamine)

3.7.5 Principles of Effective Treatment

Addiction is a complex but treatable disease that affects brain function and behaviour. No single treatment is appropriate for everyone.

i. Treatment needs to be readily available.
ii. Effective treatment attends to multiple needs of the individual, not just his or her drug use or misuse.
iii. Remaining in treatment for an adequate period of time is critical.

iv. Behavioural therapies—including individual, family, or group counselling—are the most commonly used forms of drug use disorder treatment.
v. Medications are an important element of treatment for many patients, especially
vi. when combined with counselling and other behavioural therapies.
vii. An individual's treatment and services plan must be assessed continually and modified as necessary to ensure that it meets his or her changing needs.
viii. Many drug-addicted individuals also have other mental disorders.
ix. Medically assisted detoxification is only the first stage of addiction treatment and by itself does little to change long-term drug use and misuse.
x. Treatment does not need to be voluntary to be effective.
xi. Drug use during treatment must be monitored continuously, as lapses during treatment do occur.
xii. Treatment programs should test patients for the presence of HIV/AIDS, Hepatitis B and C, tuberculosis, and other infectious diseases, provide risk-reduction counselling, and link patients to treatment if necessary.

3.7.6 Management of Substance Abuse/Dependence

Management of Substance Abuse/Dependence

Two major goals: the first is abstinence from the substance; the second is physical, psychiatric, and psychosocial well-being of the patient. Management of Substance Abuse/Dependence. Inpatient or outpatient settings, Detoxification, and Rehabilitation.

Throughout treatment, individual, family, and group therapies (alcoholic & narcotic anonymous) can be effective. Any underling psychiatric disorder should be

xiii. **Pharmacological Treatment of Substance Abuse:** Because substance abuse/dependence is in part a neuropharmacological phenomenon, there is at present an aggressive search for agents that may; decrease the reinforcing properties of substances (block the drug euphoric effect), decrease craving associated with substances or function as replacements for the drug of abuse.

xiv. **Naltrexone** (an opiate receptor blocking agent) decreases alcohol consumption and relapse in alcoholic patients, also in opiate abuse.
xv. **Nicotine** replacement using nicotine gum, patch, spray and inhalation have been used with successful results in nicotine dependence.

i. **Methadone** - an opiate receptor agonist proved to be highly effective in abstinence from opiate use

4.0 CONCLUSION

In this section you have learnt about definitions of rational use of medicines and identify the magnitude of the problemof irrational drug use. Also, the reasons underlying irrational use and factors which influence the behavior of prescribers and patients. The strategies and interventions to promote rational use of medicines were also explained to you. In the second part of the units the definition of drug of abuse/ substance abuse, which is using chemicals for nontherapeutic effects on the body or mind and that excessive use or misuse of drugs or alcohol for intoxicating or mind-altering effects. Other various terms used in substance abuse was defined, the factors responsible for substance abuse and classification of drug of abuse and its management was discussed.

5.0 SUMMARY

Rational use of medicines requires that patients receive medications appr opriate totheir clinical needs, in doses that meet their requirements, for an adequate period oftime, and at the lowest cost to them and their community. Unfortunately, more than 50% of all medicines are prescribed, dispensed, or sold inappropriately on a global basis and 50% of patients fail to take their medicines correctly according to estimates based on various ad hoc reviews. Common types of inappropriate medicines use include, Polypharmacy (the use of too many medicines per patient), overuse ofinjections, inappropriate use of antimicrobials, failure to prescribe in a ccordance withclinical guidelines, and inappropriate self-medication, often with prescription-onlymedicines. Inappropriate use of medicines is harmful for patients in t erms of poorpatientclinical outcomes and avoidable adverse drug reactio ns. Unnecessary overuse ofmedicines can stimulate inappropriate patient demand and lead to medicinestockouts and loss of patient confidence in the health system.

Examples of common inappropriate prescribing practices includes; the overuse of antibiotics and antidiarrhoeals for nonspecific childhood diarrhea, indiscriminate use of injections, multiple or over-prescription, wrong Diagnosis, use of antibiotics for mild, non-bacterial infection, e.g., common cold URI, tonics and multivitamins for malnutrition, unnecessary use of expensive antihypertensives and aadequacy of diagnostic process. Examples of irrational drug combinations; Antibacterial + Antiamoebic Combinations: Ciprofloxacin + Metronidazole, Norfloxacin + Tinidazole and Ofloxacin + Ornidazole are such commonly available fixed dose drug

combinations. In bacterial diarrhoea only anti-bacterial drug is effective and antiamoebic drug is useless. Similarly, in intestinal amoebiasis only antiamoebic drug is effective while antibacterial drug is useless. Amoebiasis and bacterial diarrhoea rarely coexist. The therapy should be based on the diagnosis to reduce the cost of treatment since in a given case, only one drug of the combination would be effective and the other one would be useless. NSAIDs Combinations: Nimesulide, diclofenec, ibuprofen and Paracetamol are some non-steroidal anti-inflammatory drugs (NSAIDs). There is no justification in combining one NSAID (nimesulide, diclofenec, ibuprofen) with another NSAID (paracetamol) having same pharmacological actions. The increased risk of hepatotoxicity has been reported due to the use of combination of nimesulide with paracetamol. There is increased risk of nephrotoxicity with NSAIDs combination. Impact of inappropriate use of drugs includes, reduced quality of therapy with exacerbation or prolongation of illness leading to increase morbidity & mortality, Waste of resources - reduces availability & increased cost. Adverse drug events –commonest, costliest consequences of inappropriate use of medicines. These includes include bleeding, cardiac arrhythmia, confusion, diarrhoea, fever, hypotension, itching, vomiting, rash, renal failure.

The cause of substance use disorders is still unknown, though genetics are thought to account for 40% to 60% of a person's risk. Substance use often starts as a way to feel good or out of curiosity in childhood or early adolescence. Repeated use of the substance and increased tolerance pave the way to substance use disorder and addiction. Some adults who develop a substance use disorder have a co-occurring mental illness, such as depression, anxiety, or bi-polar disorder, and begin using drugs or alcohol to cope with their symptoms. Other risk factors that may lead to a substance use disorder include; Family history of addiction, Peer pressure, Sleep problems & Chronic pain, experimenting mind-altering substance, like Cocaine and Alcohol, promise to heighten experience and that experience is worth exploring, self- Medications to allay Stress, anxiety, reoccurring pain, undiagnosed mental illnesses, severe depression, loneliness, trauma; these are all reasons why people would self-medicate with mind-altering substances to cope with what they are feeling or what they do not want to feel. Financial difficulties, divorce or the loss of a loved one, tense home environment, lack of parental attachment in childhood, relationship issues and, long-term tobacco habit.

The commonly types of drugs of abuse and dependence are; 1. CNS Stimulants e.g. Methamphetamine, Amphetamines 2. CNS Depressant like Alcohol, disulfiram, Benzodiazepines, 3. Cannabinoids: 1. Hashish, Marijuana.4. Opioids e.g. Morphine, Codeine and Codeine-containing cough sedatives, 5. Hallucinogens Psychedelic); LSD, Anticholinergics and Mescaline, Club Drugs like MDMA

(Methylenedioxymethamphetamine, Flunitrazepamand 7. dissociative drugs, ketamine, dextromethorphan (DXM), 8. other compounds such as Anabolic Steroids, Inhalants: and Caffeine etc.

Addiction is a complex but treatable disease that affects brain function and behaviour. No single treatment is appropriate for everyone. Effective treatment attends to multiple needs of the individual, not just his or her drug use or misuse etc.

Pharmacological management of Substance Abuse/Dependence is divided into two major goals: the first is abstinence from the substance; the second is physical, psychiatric, and psychosocial well-being of the patient. Throughout treatment, individual, family, and group therapies (alcoholic & narcotic anonymous) can be effective. Any underling psychiatric disorder should be managed appropriately.

Common drugs use includes Naltrexone (an opiate receptor blocking agent) decreases alcohol consumption and relapse in alcoholic patients, also in opiate abuse, Nicotine replacement using nicotine gum, patch, spray and inhalation have been used with successful results in nicotine dependence and Methadone - an opiate receptor agonist proved to be highly effective in abstinence from opiate use.

SELF ASSESSED EXERCISES

I. Explain the following terms: a) Dependence b) Pyschotropic drugs
   c) Narcotics d) Tolerance.
ii. What is the criteria for using medicines?

6.0 TUTOR -MARKED ASSIGNMENT

1. Identify the magnitude and nature inappropriate drug utilization in your facility with life examples
2. Describe the reasons underlying irrational use by prescribers/patients in your facilities
3. Outline the adverse impacts of inappropriate use of drugs
4. Discuss strategies and interventions to promote rational use of medicines in Nigeria.
5. List the five most common substances of abused

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