Lecture No:
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Objective: To study
Topic Outcomes: At the end of topic you should be Able to learn and understand

Hospital Pharmacy and Clinical Pharmacology :

Introduction to Hospital System

Hospital
The hospital is a complex organization utilizing combination of intricate,specialized scientific equipment, and functioning through a corps of trained people educated to the problem of modern medical science. These are all welded together in the common purpose of restoration and maintenance of good health

Hospital Pharmacy
The department or service in a hospital which is under the direction of a professionally competent, legally qualified pharmacist, and from which all medications are supplied to the nursing units and other services, where special prescriptions are filled for patients in the hospital, where prescriptions are filled for ambulatory patients and out-patients, where pharmaceuticals are manufactured in bulk, where narcotic and other prescribed drugs are dispensed, where injectable preparations should be prepared and steri

Organisation of Health Care System
health care services in the country spreads across the national level.total organisation structure of health care system can be divided into national,state,district,community,primary health care and subcentre level.

References

1) Practice of hospital ,clinical community pharmacy BY Mohd.Aqil,Elsevier a division of reed Elsevier India private limited.2013

2) Mosby's pharmacy technician principals and practice by Teresa hopper 2nd edition, Saunder's elsvier.2013

3) Hospital pharmacy by William e. Hassan ,lea and febiger:Philadelphia 1986

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Hospital Logistics
GOALS FOR HOSPITAL PHARMACY
MINIMUM STANDARD FOR HOSPITAL PHARMACY
Pharmaceutical services in institutions have numerous components,
the most prominent being
(1) The procurement, distribution, and control of all pharmaceuticals used within the facility.
(2) The evaluation and dissemination of comprehensive information about drugs and their use to the institution's staff and patients.
(3) The monitoring, evaluation, and assurance of the quality of drug use

- **health care services**
- **management of hospitals**
- **hospital pharmacy – location and layout**
- **planning,resources.**

References

1) Practice of hospital ,clinical community pharmacy BY Mohd.Aqil,Elsevier a division of reed Elsevier India private limited.2013

2) Mosby's pharmacy technician principals and practice by Teresa hopper 2nd edition, Saunder's elsvier.2013

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Functions and role-hospital pharmacy:

Functions of hospital
Proper functioning of a hospital pharmacy department is vital not only for the professional care of the patient but also for management of hospital .
Major functions of a hospital pharmacy are as follows

ROLE OF PHARMACY TECHNICIANS IN THE PHARMACEUTICAL SERVICES
The pharmacist and pharmacy technician are important professionals on the healthcare team. The primary responsibility of the pharmacist is to see that drugs are dispensed properly and used appropriately.
A few of their responsibilities include: receiving written prescriptions or requests for prescription refills from patients or their caregivers.,verifying that the information on the prescription is complete and accurate,counting, weighing, measuring, and mixing the medication,preparing prescription labels and selecting the container establishing and maintaining patient profiles ordering and stocking prescription and over-the-counter medications assisting with drug studies. taking prescriptions over the telephone, transferring prescriptions,tracking and reporting errors, "tech check tech" in preparation of medicine carts

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Hospital and therapeutic committe :

PHARMACY AND THERAPEUTICS COMMITTEE

The multiplicity of drugs available and the complexities surrounding their safe and effective use make it necessary for hospitals to have an organized, sound program for maximizing rational drug use. The pharmacy and therapeutics committee, or its equivalent, is the organizational keystone of the program. The pharmacy and therapeutics committee is an advisory group of the medical staff and serves as the organizational line of communication between the medical staff and pharmacy department. This committee is composed of physicians, pharmacists, and other health professionals selected with the guidance of the medical staff. It is a policyrecommending body to the medical staff and the administration of the hospital on matters related to the therapeutic use of drugs.

Role or purposes of committee

The primary purposes of the pharmacy and therapeutics committee are as specified in the following:
1. *Advisory*. The committee recommends the adoption of, or assists in the formulation of, policies regarding evaluation, selection, and therapeutic use of drugs in hospitals
2. *Educational*. The committee recommends or assists in the formulation of programs designed to meet the needs of the professional staff (physicians, nurses, pharmacists, and other health-care practitioners) for complete current knowledge on matters related to drugs and drug use.

Organization and Operation

Explanati**on and functions**

References

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HOSPITAL AND THERAPEUTIC COMMITTEE-FUNCTIONS:

Functions and Scope

The basic organization of the hospital and medical staffs will determine the functions and scope of the pharmacy and therapeutics committee. The following list of committee functions is offered as a guide:

1. To service in an advisory capacity to the medical staff and hospital administration in all matters pertaining to the use of drugs (including investigational drugs).
2. To develop a formulary of drugs accepted for use in the hospital and provide for its constant revision. The selection of items to be included in the formulary will be based on objective evaluation of their relative therapeutic merits, safety, and cost. The committee should minimize duplication of the same basic drug type drug entity, or drug product.
3. To establish programs and procedures that help ensure costeffective drug therapy.
4. To establish or plan suitable educational, programs for the hospital's professional staff on matters related to drug use.
5. To participate in quality-assurance activities related to the distribution, administration, and use of medications.
6. To review adverse drug reaction occurring the hospital.
7. To initiate (or both) drug-use review programs and studies and review the results of such activities.
8. To advise the pharmacy in the implementation of effective drug distribution and control procedures.
9. To make recommendations concerning drugs to be stocked in hospital patient-care areas

References

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Hospital Formulary;

THE HOSPITAL FORMULARY

Definition of formulary and formulary system

The *formulary* is a continually revised compilation of pharmaceuticals (plus important ancillary information) that reflects the current clinical judgment of the medical staff.

The *formulary system* is a method whereby the medical staff of an institution, working through the pharmacy and therapeutics committee, evaluates, appraises, and selects from among the numerous available drug entities and drug products those that are considered most useful in patient care. Only those so selected are routinely available from the pharmacy. The formulary system is thus an important tool for assuring the quality of drug use and controlling its cost. The formulary system provides for the procuring, prescribing, dispensing, and administering of drugs under either their non-proprietary or proprietary names in instances where drugs have both names

Benefits of the formulary system

The potential benefits of a formulary system are threefold:

(l) Therapeutic. (2) Economic. (3) Educational.

The therapeutic aspect of a formulary system provides the greatest benefit to the patient and physician in that only the most efficient products are listed and available.

The economic merit also has a double benefit in that the formulary eliminates duplication thus reducing inventory duplication and the opportunity for volume purchasing means lower charges to the patient. The educational benefit is also significant for the resident staff, nurses and medical students because many good formularies contain various prescribing tips and additional drug information of educational value.

Format and appearance of the formulary

The physical appearance and structure of the formulary is an important influence on its use. Although elaborate and expensive artwork and materials are unnecessary, the formulary should be visually pleasing, easily readable, and professional in appearance.

The need for proper grammar, punctuation, correct spelling, and neatness is obvious. There is no one single format or arrangement which ail formularies must follow.

A typical formulary must have the following composition:

1. Title page
2. Names and titles of the members of the pharmacy and therapeutics Committee

References :

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HOSPITAL FORMULARY AND ROLE OF HOSPITAL PHARMACIST:

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Hospital Pharmacist's Role:

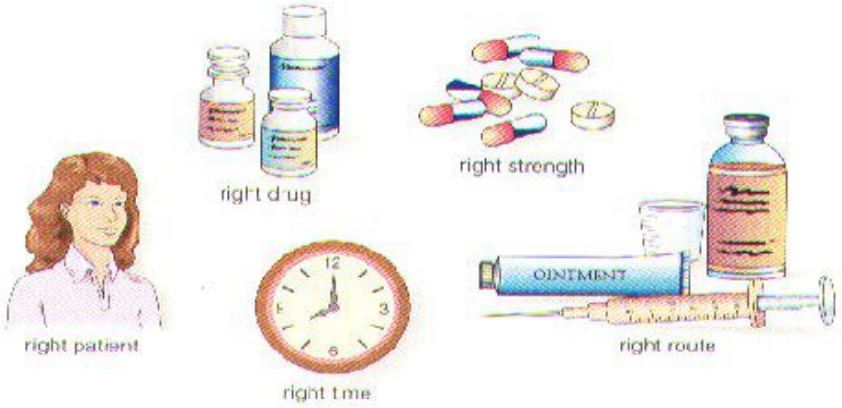
Primary duty of hospital pharmacist is to support safe,rational,economic use of medicine for benefit of patient

Hospital pharmacist use their knowledge of pharmacy to dispence drugs and advice patient about medicines that hve been prscribed.

Various roles will be discussed

Hospital – medication – patient

THE FIVE RIGHTS FOR CORRECT DRUG ADMINISTRATION



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Hospital committees-Role:

Overall functions-

To participate in quality-assurance activities related to the distribution, administration, and use of medications.

To review adverse drug reaction occurring the hospital.

To initiate (or both) drug-use review programs and studies and review the results of such activities.

To advise the pharmacy in the implementation of effective drug distribution and control procedures.

To make recommendations concerning drugs to be stocked in hospital patient-care areas.

Institutional review Board is committee that ensures that appropriate protection is provided to patient in terms of investigational drugs or procedures.

Committee compositions and functions

Informed consent

References

1. Pracite of hospital ,clinical community pharmacy BY Mohd.Aqil,Elsevier a division of reed elseveir india private limited.2013
2. Mosby'spharmacy technician principals and practice by Teresa hopper 2nd edition,saunder's elsvier.
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Practice of rational drug therapy :

Rational Drug Use

Rational drug use is defined as "patients receive medicines 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".

The requirements for rational use will be fulfilled if the process of prescribing is appropriately followed. This process includes steps in defining a patient problems (or diagnosis); in defining effective and save treatments (drugs and nondrugs); in selecting appropriate drugs; dosage and duration; in writing a prescription; in giving patients adequate information; and in planning to evaluate treatment responses

The Pillars of Rational Drug Therapy

1. Genuine indication 2. Minimum number of appropriate, familiar and inexpensive drugs of assured quality
3. Formulations having appropriate dosage form
4. Oral route-optimum duration
5. Adverse Drug Reaction: anticipation, monitoring and management
6. Adverse drug reactions – to be anticipated, monitored and managed

References

1. Pracite of hospital ,clinical community pharmacy BY Mohd.Aqil,Elsevier a division of reed elseveir india private limited.2013
2. Mosby'spharmacy technician principals and practice by Teresa hopper 2nd edition,saunder's elsvier.
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Rational drug –examples

Rational Drug Concept: Right Quantity,Right Dosage To Right Patient.

Antitubercular drugs-prevents development of resistance, dosage convenience

Combinations :

- _ Amoxycillin + Clavulinic acid (B-Lactamase inhibitor – by irreversible binding
- Suicide inhibitors) - restore activity
- _ Ampicillin + Sulbactum
- _ Imipenem + Cilastatin
- _ Pyrimethamine + Sulfadoxine
- _ Sulfamethoxazole + trimethoprim
- _ Ferrous salt + Folic acid

References

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Introduction to documentation

Hospital documentation

is important to keep data of prescription, drug information, patient medication profile, patient case report etc.

A. To ensure the documentation in the medical record meets generally accepted professional standards of documentation, specifically mandated regulatory, legal and/or accrediting standards and supports the documentation guidelines identified in the Medical Staff Rules and Regulations.

B. The purposes of the Medical Record are:

1. To serve as a detailed data base for planning patient care by all involved practitioners, nurses and ancillary personnel.

2. To document the patient's medical evaluation, treatment and change in condition during the hospital stay or during an ambulatory care or emergency visit, 3. To allow a determination as to what the patient's condition was at a specific time, 4. To permit review of the diagnostic and therapeutic procedures performed and the patient's response to treatment,

5. To assist in protecting the legal interest of the patient, hospital and practitioner responsible for the patient and to provide data for use in the areas of quality and resource management, billing, education, and research.

C. Charts will be completed. Records will be classified as per conditions.

General Requirements
Medical Record Content
History & Physical Examination
Operative reports,Final diagnosis

Discharge medications -Suspention of medical records

References

1. Pracite of hospital ,clinical community pharmacy BY Mohd.Aqil,Elsevier a division of reed elseveir india private limited.2013

2. Clinical pharmacy by peter bennet,morris j brown 11th edition Churchill living stone Elsevier 2012

3. Mosby'spharmacy technician principals and practice by Teresa hopper 2nd edition,saunder's elsvier.

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Introduction to prescription recording.

A prescription is written document by medical practitioner on a form that is used to imply an order to take certain medications Orders to patient, caretaker, nurse, pharmacistor other health care professionals

Symbol-

Filling of prescriptions

Involves various steps- prescription verification, prescription labelling

General information

Prescription filling for narcotics and non-narcotics

Examples and Importances

References

1. Pracite of hospital ,clinical community pharmacy BY Mohd.Aqil,Elsevier a division of reed elseveir india private limited.2013
2. Clinical pharmacy by peter bennet,morris j brown 11th edition Churchill living stone Elsevier 2012
3. Mosby'spharmacy technician principals and practice by Teresa hopper 2nd edition,saunder's elsvier.
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Prescription recording and analysis, Drug profile-examples

DETAILS OF PRESCRIPTION –DISCUSSSION

It is an outline or summary of the characteristics of a drug of drug family listing drug name,indications,contraindications, adverse effects- reactions, drug interactions,

Pharmacokinetics,dose,prescriptions of OTC,Dosage Forms Generic medication.

Drug name-chemical, generic, proprietary

Classification of a drug

Mechanism of action – interactions-targets

Indications- for curing

Pharmacokinetics-ADME

Adverse or side effects-

Routes of administrations

Dosage forms- examples

Contraindications- against indications

Special considerations -pregnant, nursing, childbearigng age

References

1. Pracite of hospital ,clinical community pharmacy BY Mohd.Aqil,Elsevier a division of reed elseveir india private limited.2013
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Patient Medication profile:

The patient medication profile gives pharmacy personnel an opportunity to actively participate in monitoring patient care

It contains six sections
Patient information
Allergy, diagnosis
Scheduled medications- for safety check
Non-scheduled medications ordered for one time administrations

Wardstock medications – sections handling for bulk drug order
Controlled drugs y

These items recovered from the vault sections of the pharmacy
and sterile drugs

Medications- sterile preparations.

References

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2. Mosby'spharmacy technician principals and practice by Teresa hopper 2nd edition,saunder's elsvier.
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Importance and examples -Patient Medication:

Case study is helpful to understand new and vital informations- to improve patient outcome.

It contains an abstracts and four sections

Introductions

Case presentations

Discussions

And conclusions

Examples

1. **Drug interaction of Tizanidine and Ciprofloxacin**

2. **Idiosyncratic Drug Reactions**

References

1. Pracite of hospital ,clinical community pharmacy BY Mohd.Aqil,Elsevier a division of reed elseveir india private limited.2013
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Outpatient and Inpatient Services.

HOSPITAL DRUG DISTRIBUTION SYSTEM

Traditional methods of distributing drugs in hospitals are now undergoing reevaluation.Some of the newer concepts and ideas in connection with hospital drug distribution systems are centralized or decentralized (single, or unit-dose)dispending, automated (mechanical and/or electronic) processing of medication orders and inventory control, and automated (mechanical and/or electronic) storage and delivery devices.

Distribution systems during this period of change, the following
guidelines for evaluating proposed changes or new ideas or equipments

In-Patient Services Division

1. Provide medications for all in-patients of the hospital on a 24-hour per day basis.
2. Inspection and control of drugs on all treatment areas.
3. Cooperate with medical drug research.

Out-Patient Services Division

1. Compound and dispense out-patient prescriptions.
2. Inspect and control all clinic and emergency service medication stations.
3. Maintain prescription records.
4. Provide drug consultation services to staff and medical students.

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Unit Dose:

Unit dose system

Unit-dose medications have been defined as:

"Those medications which are ordered, packaged, handled, administered and charged in multiples of single dose units containing a predetermined amount of drugs or supply sufficient for one regular dose application or use."

Advantages of unit dose system:

(1) Patients receive improved pharmaceutical service 24 hours a day and are charged for only those doses, which are administered to them.

(2) All doses of medication required at the nursing station are prepared by the pharmacy thus allowing the nurse more time for direct patient care.

(3) Allow the pharmacists to interpret or check a copy of the physician's original order thus reducing medication errors.

(4) Elimination excessive duplication of orders and paper work at the nursing station and pharmacy.

Unit dose dispensing Procedure

The characteristic features of centralized unit-dose dispending are that all in-patient drugs are dispensed in unit-doses and all the drugs are stored in a central area pharmacy and dispensed at the time the dose is due to be given to the patient. To operate the system effectively, electronic data processing equipment is not required, however delivery, systems such as medication carts and dumbwaiters are needed to get the unit-doses to thepatients; also suction tube system (called pneumatic tube) or other means are required to send a copy of the physician's original medication order to
the pharmacy for direct interpretation and filling.

References

1. Pracite of hospital ,clinical community pharmacy BY Mohd.Aqil,Elsevier a division of reed elseveir india private limited.2013
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DRUG DISTRIBUTION SYSTEM :

Inpatieent are those who get hospitalised for the purpose of treatment,cure of disease,disease,surgery or rehabilitations

Generally four type of system
There are four systems in general use for dispensing drugs for inpatients**.**
They may be classified as follows:
(i) *Individual Prescription Order System.*
(ii) Complete Floor Stock System.
(iii) Combination of (i) and (ii).
(iv) The unit dose method.

Individual prescription order system
As has been previously stated, this system is generally used by the small and/or private hospital because of the reduced manpower requirement and the desirability for individualized service.
Inherent in this system is the possible delay in obtaining the required medication and the increase in cost to the patient.
Advantages of this system:
(i) All medication orders are directly reviewed by the pharmacist.
(ii) Provides for the interaction of pharmacist, doctor, nurse and patient.
(iii) Provides closer control of inventory.

References

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Floor Ward Stock System :

Complete floor stock system

Under this system, the nursing station pharmacy carries both "charge" and "non-charge" patient medications. Rarely used or particularly expensive drugs are omitted from floor stock but are dispensed upon the receipt of a prescription or medication order for the individual patient.

Although this system is used most often in governmental and other hospitals in which charges are not made to the patient or when the allinclusive rate is used for charging, it does have applicability to the general hospital. Obviously, there are both advantages and disadvantages to the complete floor stock system.

Advantages of complete floor stock system:

(i) Ready availability of the required drugs.

(ii) Elimination of drug returns.

(iii) Reduction in the number of drug order transcriptions for the pharmacy.

(iv) Reduction in the number of pharmacy personnel required.

Disadvantages of complete floor stock system:

(i) Medication errors may increase because the review of medication orders is eliminated.
(ii) Increased drug inventory on the pavilions.
(iii) Greater opportunity for pilferage.
(iv) Increased hazards associated with drug deterioration.
(v) Lack of proper storage facilities on the ward may require
capital outlay to provide them.
(vi) Greater inroads are made upon the nurse's time.

References

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SATELLITE PHARMACY SERVICES, BED SIDE PHARMACY, DISTRIBUTION OF CONTROL DRUGS:

Charge floor stock drugs and non-charge floor stock drugs
Each pavilion in the hospital, regardless of its size or specialty care, has a supply of drugs stored in the medicine cabinet even though the nursing unit is serviced by a unit dose system. However, the use of floor stock medications should be minimized. In addition, research has shown that the system of drug distribution has an effect upon the incidence of adverse drug reactions. These medications may be classified under two separate headings, each of which serves a specific purpose. Drugs on the nursing station may be divided into "*charge floor stock drugs*" and "*noncharge floor stock drugs*".

Definitions

- *Charge floor stock drugs* may be defined as those medications that are stocked on the nursing station.
- *Charge floor stock drugs* represent that group of medications that are placed at the nursing station.
- It is the responsibility of the hospital pharmacist, working in cooperation with the nursing service, to develop ways and means

Combination of Individual prescription order system and complete floor stock system
Falling into this category are those hospitals which use the individual prescription or medication order system as their primary means of dispensing, but also utilize a limited floor stock. This combination system is probably the most commonly used in hospitals today and is modified to include the use of unit dose medications.

DRUG DISTRIBUTION AND CONTROL
(UNIT DOSE SECTION)
Medication distribution is the responsibility of the pharmacy. The pharmacist, with the assistance of the pharmacy and therapeutics committee and the department of nursing, must develop comprehensive policies and procedures that provider for the safe distribution of all medications and related supplies to inpatients and outpatients.
For reasons of safety and economy, the preferred method to distribute drugs in institutions is the *unit dose system*. Though the unit dose system may differ in form depending on the specific needs, resources, and characteristics of each institution, for elements are common to all.

References

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METHODS OF ASSESSMENT OF COMPLIANCE:

Compliance

This is a term that has been established to describe a patient's degree of conformity with the advice and recommendations given by health professionals. The term *non-compliance* was used to describe significant failure to conform with the advice and recommendations to an extent that it interferes with achieving the patient outcomes planned. Since this term has a negative nuance for the patient and overrides the concept that the patient may have a problem with the medication or recommendations, the term non-compliance is not very much supported today.The concept of compliance seems to denote a relationship in which the patient has a passive role and is expected to follow the doctor's orders. Since the term does not emphasise patient participation, there has been a shift towards the use of 'adherence' as a term instead.

Adherence

As opposed to the concept of compliance, adherence seems to denote a relationship in which the patient has an active role and is expected to contribute to the establishment of the treatment to be followed. In the concept of adherence the patient is free to decide whether or not to adhere to recommendations by health professionals and failure to do so should not be a reason to blame the patient. Health professionals have a responsibility to facilitate adherence.

Concordance

This term is used to denote the degree to which the patient and the health practitioner agree about the nature of the illness and the need for management, and the relative risks and benefits of the proposed line of treatment. In the concept of concordance, the patient's views are taken into account during the prescribing phase in order to increase the likelihood of better compliance.

Categories of non-adherence

References

- Pracite of hospital ,clinical community pharmacy BY Mohd.Aqil,Elsevier a division of reed elseveir india private limited.2013
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Topic Outcomes: At the end of topic you should be Able to learn and understand

REASON FOR PATIENT NONCOMPLIANCE:

Classification of non-adherence

• The ideal situation – adherence achieved
• Few errors (0–15%) – partial adherence
• Major default (_15%) – partial/non-adherence.

It is still hard to quantify the consequences of poor adherence to medication. There is no consensus as to the quantification of partial adherence (number of missed doses).

Measurement of non-adherence

• *Direct methods:* observation of ingestion of the drug or by detecting its presence in body fluids
• *Indirect methods:* assume ingestion based on proxy evidence such as patient's self-reporting, number of dosages remaining, number of dosages removed from a container through data recorded in medication compliance aids.

These include:

– tablet counts: counting number of units left in container
– patient diary cards: reporting by patient
– electronic monitors: incorporation of electronic devices into the medicine container recording time and date of usage
– clinicians' estimates and therapeutic outcomes
– patient self-reporting on health status and how the condition has improved.

Causes of non-adherence

• *Therapy-related factors:* type of dosage
• *Condition-related factors:* non-adherence particularly noted in conditions where patient is not seeing benefit from drug therapy (e.g. hypertension), in conditions that are associated with a social stigma (e.g. psychiatric disorders, HIV), where patients may not be ready to accept medications for the condition (denial of illness or of need for medications)
• *Patient-related factors:* patient's knowledge, beliefs about and attitudes towards medicine and disease state
• *Health-system factors:* relationships with the healthcare team, ability to get prescription and medicines, inadequate patient education
• *Social and economic factors:* social factors such as lack of patient support and income, problems with living conditions and problems at home, level of education and literature

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STRATEGIES TO IMPROVE COMPLIANCE:

Strategies to improve patient adherence

• Labelling: large (font size), clean (printed), simple, specific

• Packaging: while taking into account stability of the product, ensure patient accessibility and acceptance of product appearance
• Compliance aids: use of devices that can be used to remind patient to take medication, dispensing medication in blister pack according to dosage regimen, preparing medicine reminder charts, administration devices (e.g. eye-drop applicators)
• Review patient prescriptions and medications: to reduce dosing frequency and multiple drug therapy where relevant
• Improve patient–pharmacist–doctor rapport
• Ensure effective patient information
Maintain patient contact and regular pharmacist follow-ups

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PATIENT COUNSELLING and PRECAUTION AND DIRECTIONS FOR MEDICATION:

Patient counselling

1. Maintain patient contact and regular pharmacist follow-ups
2. On discharge • At outpatient clinics • In rehabilitation settings.
3.

Objectives of patient counseling by pharmacists

1. To ensure that patients are adequately informed about their medication
2. To predict any problems which might cause loss of efficacy of the drug or be detrimental to health of patient
3. To identify any drug-related or health-related problems.

Pharmacist counselling process

1. Recognising the need for counselling: extent of counselling required varies from one individual to another.
2. Assessing and prioritising the needs: what points need to be emphasised?
3. Checking assessment methods: to identify outcomes and follow-up counselling process.
4. Environment in pharmacy: must be conducive to privacy and to induce patients to ask for professional advice from the pharmacist.
5. Professional appearance of pharmacist: to project a professional appearance that enables individuals, including those who feel that they have a very sensitive issue to discuss, to address the pharmacist with confidence.

Recognising the need for counselling

• *Is it a repeat medication*
• *Polytherapy:*
• *Complex instructions:*
• *Narrow therapeutic index drugs:*
• *Patient characteristics:*

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Counselling -Administration Instructions:

Assessing and prioritizing needs

Patient needs vary according to a number of factors. The counselling process has to be developed according to each individual patient's needs. Patient priorities in life (e.g. lifestyle) should be taken into consideration during the counselling session if maximum patient benefit is expected. Information about patients that will help to prioritise the needs
Includes:

a. educational background
b. available support
c. sight or hearing problems
d. Pregnancy and breast-feeding.

Follow-up counseling sessions

Administration instructions

- **Route**
- **Dosage**
- **Drug Interactions**

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ADVERSE DRUG REACTIONS

Epidemiology,Classification

Adverse drug reactions are unwanted effects caused by normal therapeutic doses. Drugs are great mimics of disease, and adverse drug reactions present with diverse clinical signs and symptoms. The classification proposed by Rawlins and Thompson (1977) divides reactions into type Aand type B

Type A reaction – an extension of the pharmacology of the drug, dose related, and accounts for most adverse reactions (e.g. β-adrenoreceptor antagonist-induced
bradycardia or AV block).

• *Type B reaction* – idiosyncratic reaction to the drug, not dose related, rare but severe (e.g. chloramphenicolinduced aplastic anaemia).

• Other types of drug reaction (much rarer):

type C reaction – continuous reactions due to longterm use: analgesic nephropathy;

type D reaction – delayed reactions of carcinogenesis or teratogenesis;

type E reaction – drug withdrawal reactions (e.g. benzodiazepines).

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RISK FACTORS-ADR

Risk factors and systems

Rare (and often severe) adverse drug events may not be detected in early drug development but only defined in

the first few years post marketing (phase IV of drug development).

• Be aware of and participate in the MHRA yellow card

system for reporting suspected adverse drug reactions.

• Constant vigilance by physicians for drug-induced

disease, particularly for new drugs, but also for more established agents, is needed.

Classification of immune-mediated adverse drug reactions:

• *Type I* – urticaria or anaphylaxis due to the production of IgE against drug bound to mast cells, leading to massive release of mast cell mediators locally or systemically (e.g. ampicillin skin allergy or anaphylaxis).

• *Type II* – IgG and IgM antibodies to drug which, on contact with antibodies on the cell surface, cause cell

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Mechanism –ADR:

Classification of immune-mediated adverse drug reactions:

• *Type III* – circulating immune complexes produced by drug and antibody to drug deposit in organs, causing

drug fever, urticaria, rash, lymphadenopathy, glomerulonephritis, often with eosinophilia (e.g.

co-trimoxazole, β-lactams).

• *Type IV* – delayed-type hypersensitivity due to drug forming an antigenic conjugate with dermal proteins and sensitized T cells reacting to drug, causing a rash (e.g. topical antibiotics).

Mechanism of adverse drug reactions

Pharmacodynamic and Pharmacokinetics

Oxidant and Antioxidant

Glutathiol reactions

Cellular and molecular mechanism

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Monitoring, Detecting and reporting of ADR :

It is often difficult to decide whether a clinical event is drug related, and even when this is probable, it may be difficult to determine which drug is responsible, as patients are often taking multiple drugs. One or more of several possible approaches may be appropriate.
1. A careful drug history is essential. The following considerations should be made to assess causality of theeffect to the drug: did the clinical event and the timecourse of its development fit with the duration of suspected drug treatment and known adverse drug effects Did the adverse effect reverse upon drug withdrawal and, upon rechallenge with the drug, reappear? Were other possible causes reasonably excluded? A patient's drug history may not always be conclusive because, although allergy to a drug implies previous exposure, the antigen may have occurred in foods (e.g. antibiotics are often fed to livestock and drug residues remain in the flesh), in drug mixtures or in some casual manner. 2. Provocation testing. This involves giving a very small amount of the suspected drug and seeing whether a reaction ensues, e.g. skin testing, where a drug is applied as a patch, or is pricked or scratched into the skin or injected intradermally. Unfortunately, prick and scratch testing is less useful for assessing the systemic reaction to drugs than it is for the more usual atopic antigens (e.g. pollens), and both false-positive and false-negative results can occur. Patch testing is safe, and is useful for the diagnosis of contact sensitivity, but does not reflect systemic reactions and may itself cause allergy. Provocation tests should only be undertaken under expert guidance, after obtaining informed consent, and with resuscitation facilities available. 3. Serological testing and lymphocytes testing. Serological testing is rarely helpful, circulating antibodies to the drug do not mean that they are necessarily the cause of the symptoms. The demonstration of transformation occurring when the patient's lymphocytes are exposed to a drug ex vivo suggests that the patient's T-lymphocytes are sensitized to the drug. In this type of reaction, the hapten itself will often provoke lymphocyte transformation, as well as the conjugate. 4. The best approach in patients on multiple drug therapy is to stop all potentially causal drugs and reintroduce them one by one until the drug at fault is discovered. This should only be done if the reaction is not serious, or if the drug is essential and no chemically unrelated alternative is available.

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Types, General Considerations :

• There are three main types of adverse interaction:

– PHARMACEUTICAL;

– PHARMACODYNAMIC;

– PHARMACOKINETIC.

• Pharmaceutical interactions are due to in vitro incompatibilities, and they occur outside the body (e.g. when drugs are mixed in a bag of intravenous solution, or in the port of an intravenous cannula).• Pharmacodynamic interactions between drugs with a similar effect (e.g. drugs that cause drowsiness) are common. In principle, they should be easy to anticipate, but they can cause serious problems (e.g. if a driver fails to account for the interaction between an antihistamine and ethanol).
• Pharmacokinetic interactions are much more difficult to anticipate. They occur when one drug influences the way in which another is handled by the body: (a) *absorption* (e.g. broad-spectrum antibiotics interfere with enterohepatic recirculation of
oestrogens and can cause failure of oral contraception);
(b) *distribution* – competition for binding sites seldom causes problems on its own but, if combined with an effect on elimination (e.g. amiodarone/digoxin or NSAID/methotrexate), serious toxicity may ensue;
(c) *metabolism* – many serious interactions stem from enzyme induction or inhibition. Important inducing agents include ethanol, rifampicin, rifabutin, many of the older anticonvulsants, St John's wort, nevirapine and pioglitazone. Common inhibitors include many antibacterial drugs (e.g. isoniazid, macrolides, co-trimoxazole and metronidazole), the azole antifungals, cimetidine, allopurinol, HIV protease inhibitors; (d) *excretion* (e.g. diuretics lead to increased reabsorption of lithium, reducing its clearance and predisposing to lithium accumulation and toxicity).
MECHANISM OF DRUG INTERACTINS: Drug interactions may be clinically useful, trivial or adverse.• Many interactions that occur in vitro (e.g. competition for albumin) are unimportant in vivo because displacement of drug from binding sites leads to increased elimination by metabolism or excretion and hence to a new steady state where the total concentration of displaced drug in plasma is reduced, but the concentration of active, free (unbound) drug is the same as before the interacting drug was introduced. Interactions involving drugs with a wide safety margin (e.g. penicillin) are also seldom clinically important.Adverse drug interactions are not uncommon, and can have profound consequences, including death fromhyperkalaemia and other causes of cardiac dysrhythmia, unwanted pregnancy, transplanted organ rejection, etc.

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Introduction to clinical trial :

History, terminologies, types of clinical research, phases of clinical research,

Many years before Christ, humans discovered that certain plants influence the course of disease. Primitive tribes used extracts containing active drugs such as **opium**, **ephedrine**, **cascara**, **cocaine**, **ipecacuanha** and **digitalis**. These were probably often combined with strong psychosomatic therapies and the fact that potentially beneficial agents survived the era of magic and superstition says a great deal about the powers of observation of those early 'researcher Many useless and sometimes deleterious treatments also persisted through the centuries, but the desperate situation of the sick and their faith in medicine delayed recognition of the harmful effects of drugs. Any deterioration following drug administration was usually attributed to disease progression, rather than to adverse drug effects. There were notable exceptions to this faith in medicine and some physicians had a short life expectancy as a consequence.

Over the last 100 years, there has been an almost exponential growth in the number of drugs introduced into medicine. Properly controlled clinical trials, which are the cornerstone of new drug development and for which the well-organized vaccine trials of the Medical Research Council (MRC) must take much credit, only became widespread after the Second World War. Some conditions did not require clinical trials (e.g. the early use of **penicillin** in conditions with a predictable natural history and high fatality rate). (Florey is credited with the remark that 'if you make a real discovery, you don't need to call in the statisticians'.) Ethical considerations relating to the use of a 'nontreatment' group in early trials were sometimes rendered irrelevant

by logistic factors such as the lack of availability of drugs. It was not until the 1960s that the appalling potential of

drug-induced disease was realized world-wide. **Thalidomide** was first marketed in West Germany in 1956 as a sedative/ hypnotic, as well as a treatment for morning sickness.

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INTRODUCTION OF NEW DRUGS AND CLINICAL TRIALS

'the safe hypnotic'. However, in 1961, it became clear that its use in early pregnancy was causally related to rare congenital abnormality, phocomelia, in which the long bones fail to develop.

The **thalidomide** tragedy stunned the medical profession, the pharmaceutical industry and the general public. In 1963, the Minister of Health of the UK established a Committee on the Safety of Drugs, since it was clear that some control over the introduction and marketing of drugs was necessary. These attempts at regulation culminated in the Medicines Act (1968).

Role of clinical trial in new drug developments

Discovery

• Screening

• Preclinical testing

• Phase I (usually healthy volunteers)

• Phase IIa

• Phase IIb

• Phase III *(1000–5000 patients)*

* Registration

• Phase IV

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Principle of regulatory:

Requirements, responsible conduct, supervision of ethics

Ethical & Safety Considerations

Ethical Principles

All research involving human subjects should be conducted in accordance with the ethical principles contained in the current revision of Declaration of Helsinki should respect three basic principles, namely justice, respect for persons, beneficence (to maximize benefits and to minimize harms and wrongs) and non malaficence (to do no harm) as defined by "Ethical Guidelines for Biomedical Research on Human Subjects" issued by the Indian.Council of Medical Research and any other laws and regulations of the country, which ensure a greater protection for subjects.

The following principles are to be followed:

a. **Principles of essentiality** whereby, the research entailing the use of human subjects is considered to be absolutely essential after a due consideration of all alternatives in the light of the existing knowledge in the proposed area of research and after the proposed research has been duly vetted and considered by an appropriate and responsible body of persons who are external to the particular research and who, after careful consideration, come to the conclusion that the said research is necessary for the advancement of

knowledge and for the benefit of all members of the human species and for the ecological and environmental well being of the planet.

b. **Principles of voluntariness, informed consent and community agreement**

whereby, Study Subjects are fully apprised of the Study and the impact and risk of such Study on the Study Subjects and others; and whereby the research subjects retain the right to abstain from further participation in the research irrespective of any legal or other obligation that may have been entered into by them or by someone on their behalf, subject to only minimal restitutive obligations of any advance consideration received and outstanding.

c. **Principles of non-exploitation** whereby as a general rule, research subjects are remunerated for their involvement in the research or experiment; and, irrespective of the social and economic condition or status, or literacy or educational levels attained by the research subjects kept fully apprised of all the dangers arising in and out of the research so that they can appreciate all the physical and psychological risks as well as moral implications of the research whether to themselves or others, including those yet to be born.

d. **Principles of privacy and confidentiality**

e. **Principles of precaution and risk minimisation**

f. **Principles of professional competence**

f. **Principles of accountability and transparency**

h. **Principles of the maximisation of the public interest and of distributive justice** whereby, the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged; and in particular, the research subject themselves.

i. **Principles of institutional arrangements** whereby, there shall be a duty on all persons connected with the research to ensure that all the procedures required to be complied with and all institutional

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arrangements required to be made in respect of the research and its subsequent use or application are duly
made in a bonafide and transparent manner; and to take all appropriate steps to ensure that research reports, materials and data connected with the research are duly preserved and archived.

j. **Principles of public domain**
k. **Principles of totality of responsibility**
l. **Principles of compliance**

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Informed Consent, Institutional Review Board:

Informed Consent Process

Format

Informed Consent of Subject :

Prior to the beginning of the Study the Investigator(s) should obtain the Ethics Committee's approval for the written informed consent form and all information being provided to the Subjects and / or their legal representatives or guardians as well as an impartial witness. None of the oral and written information concerning the Study, including the written informed consent form, should contain any language that causes the Subject(s) or their legal representatives or guardians to waive or to appear to waive their legal rights, or that releases or appears to release the Investigator, the Institution, the Sponsor or their representatives from their liabilities for any negligence. The information should be given to the Subjects and / or their legal representatives or guardians in a language and at a level of complexity that is understandable to the Subject(s) in both written
and oral form, whenever possible.

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Class:

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

Responsibilities

An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

Role Responsibility,Members and auditing

The Nuremberg Code

RESPONSIBILITIES

Sponsor:

Investigator and Institution Selection:

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THE BELMONT REPORT :

THE BELMONT REPORT ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH

Part A: Boundaries Between Practice & Research

Part B: Basic Ethical Principles

Part C: Applications

References

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Concept.-basic in GCP :

Importance, GCP guidelines.

Good Clinical Practice is a set of guidelines for biomedical studies which encompasses the design, conduct, termination, audit, analysis, reporting and documentation of the studies involving human subjects. The fundamental tenet of GCP is that in research on man, the interest of science and society should never take precedence over considerations related to the well being of the study subject. It aims to ensure that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical substances under investigation are properly documented. The guidelines seek to establish two cardinal principles: protection of the rights of human subjects and authenticity of biomedical data generated. These guidelines have been evolved with consideration of WHO, ICH, USFDA and

European GCP guidelines as well as the Ethical Guidelines for Biomedical research on Human Subjects issued by the Indian Council of Medical Research. They should be followed for carrying out all biomedical research in India at all stages of drug development, whether prior or subsequent to product registration in India.

The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects**,** including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty. subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

References

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1. Clinical pharmacy by peter bennet,morris j brown 11th edition Churchill living stone Elsevier 2012

GCP GUIDELINES :

NORMS AND GUIDELINES

" a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected." (ICH GCP)

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ICH guidelines

<u>International Conference on Harmonization (ICH): 88</u>

- **Objectives of ICH guidelines**
- **Provide a unified standard**
- **EU; US; Japan**
- **To facilitate mutual acceptance of clinical data**

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Objective: To study
Topic Outcomes: At the end of topic you should be Able to learn and understand

- **Developed in accordance with existing standards in US, EU, Australia, Canada, Nordic Countries, and WHO**
- **Principles of ICH GCP**
- **Conduct trials according to GCP**
- **Weigh risks vs. benefits**
- **Protect the subjects**
- **Have adequate information to justify trial**
- **Write a sound protocol**
- **Receive IRB/IEC approval**
- **Use qualified physicians**

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Bioavailability, bioequivalence and Therapeutic Drug Monitoring-

Drugs must enter the circulation if they are to exert a systemic effect. Unless administered intravenously, most drugs are absorbed incompletely There are three reasons
for this:
1. the drug is inactivated within the gut lumen by gastric
acid, digestive enzymes or bacteria;
2. absorption is incomplete; and
3. presystemic ('first-pass') metabolism occurs in the gut
wall and liver.
Together, these processes explain why the bioavailability of an orally administered drug is typically less than 100%. Bioavailability of a drug formulation can be measured experimentally by measuring concentration vs. time curves following administration of the preparation via its intended route (e.g. orally) and of the same dose given intravenously (i.v.).
Bioavailability _ AUCoral/AUCi.v. _ 100%

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Topic Outcomes: At the end of topic you should be Able to learn and understand

Many factors in the manufacture of the drug formulation influence its disintegration, dispersion and dissolution in the gastrointestinal tract. Pharmaceutical factors are therefore important in determining bioavailability. It is important to distinguish statistically significant from clinically important differences in this regard. The former are common, whereas the latter are not. However, differences in bioavailability did account for an epidemic
of **phenytoin** intoxication in Australia in 1968–69. Affected patients were found to be taking one brand of **phenytoin**: the excipient had been changed from calcium sulphate to
lactose, increasing **phenytoin** bioavailability and thereby precipitating toxicity. An apparently minor change in the manufacturing process of digoxin in the UK resulted in reduced potency
due to poor bioavailability. Restoring the original manufacturing conditions restored potency but led to some confusion, with both toxicity and underdosing. These examples raise the question of whether prescribing should be by generic name or by proprietary (brand) name.
When a new preparation is marketed, it has a proprietary name

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Organisation - Bioavailability, bioequivalence and Therapeutic Drug Monitoring-

Determining the plasma concentrations of drugs in order to adjust therapy is referred to as therapeutic drug monitoring. It has distinct but limited applications.
• Therapeutic drug monitoring permits dose individualization and is useful when there is a clear relationship between plasma concentration and
pharmacodynamic effects.
• The timing of blood samples in relation to dosing is crucial. For aminoglycosides, samples are obtained for measurement of peak and trough concentrations. To guide chronic therapy (e.g. with anticonvulsants), sufficient time must elapse after starting treatment or changing dose for the steady state to have been achieved, before sampling.
• Drugs which may usefully be monitored in this way include digoxin, lithium, aminoglycosides, several anticonvulsants, methotrexate, theophylline, several
anti-dysrhythmic drugs (including amiodarone) and ciclosporin.
• Individualization of dosage using therapeutic drug monitoring permits the effectiveness of these drugs to be maximized, while minimizing their potential toxicity

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TDM- clinical application

Drug response differs greatly between individuals. This variability results from two main sources:
1. variation in absorption, distribution, metabolism or elimination (pharmacokinetic);
2. variation at or beyond tissue receptors or other macromolecular drug targets (pharmacodynamic).
Monitoring of drug therapy by biological response encompasses
Measurement of drug concentrations is sometimes a useful complement to clinical monitoring to assist in selecting the best drug regimen for an individual patient. Accurate and convenient assays are necessary. Measurements of drug concentrations in plasma are most useful when:
1. There is a direct relationship between plasma concentration and pharmacological or toxic effect, i.e. a therapeutic range has been established. (Drugs that work via active metabolites, and drugs with irreversible actions,
are unsuited to this approach. Tolerance also restricts the usefulness of plasma concentrations.)
2. Effect cannot readily be assessed quantitatively by clinical observation.
3. Inter-individual variability in plasma drug concentrations from the same dose is large (e.g. **phenytoin**). 4. There is a low therapeutic index (e.g. if the ratio of toxic concentration/effective concentration is 2).

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ANTERIOR PITUITARY HORMONES- INTRODUCTION

Hormones of anterior pituitary gland:

Anterior Growth hormone (GH) (somatotropin):

Somatotropin is a large polypeptide that is released by the anterior pituitary in response to growth hormone (GH) releasing hormone produced by the hypothalamus. Secretion of GH is inhibited by another pituitary hormone, somatostatin. GH is released in a pulsatile manner, with the highest levels occurring during sleep. With increasing age, GH secretion decreases, being accompanied by a decrease in lean muscle mass. Human GH is produced synthetically by recombinant DNA technology. GH from animal sources is ineffective in humans. Somatotropin influences a wide variety of biochemical processes; for example, through stimulation of protein synthetic processes, cell proliferation and bone growth are promoted. Increased formation of hydroxyproline from proline boosts cartilage synthesis.

Prolactin:

Prolactin is a peptide hormone similar in structure to GH, and is also secreted by the anterior pituitary. Its secretion is inhibited by dopamine acting at D_2 receptors. Its primary function is to stimulate and maintain lactation. In addition, it decreases sexual drive and reproductive function.

Adrenocorticotropic hormone (ACTH, Corticotropin): It is a 210 amino acid, two chain glycoprotein (22"k sugar), MW 30000.

Thyroid stimulating hormone (TSH, Thyrotropin): TSH stimulates thyroid to synthesize and secrete thyroxine (T4) and triiodothyronine (T3)

Gonadotropins-Follicle stimulating hormone (FSH) and Luteinizing hormone (LH). The gonadotropins are glycoproteins that are produced in the anterior pituitary. The regulation of gonadal steroid hormones depends on these agents. They find use in the treatment of infertility in men and women. Menotropins are obtained

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from the urine of menopausal women and contain FSH and luteinizing hormone LH. Chorionic gonadotropin (hCG) is a placental hormone and an LH agonist, to which it is structurally related. It is also excreted in the urine.

ANTERIOR PITUITARY HORMONES- PHARMACOLOGY

Adrenocorticotropic hormone (corticotropin)

The target organ of ACTH is the adrenal cortex, where it binds to specific receptors on the cell surfaces. The occupied receptors activate G protein coupled processes to increase cyclic adenosine monophosphate (cAMP), which in turn stimulates the rate-limiting step in the adrenocorticosteroid synthetic pathway. This pathway ends with the synthesis and release of the adrenocorticosteroids and the adrenal androgens.

Growth hormone:

Although many physiologic effects of GH are exerted directly at its targets, others are mediated through the somatomedins insulin-like growth factors I and II (IGF-I and IGF-II).

Thyroid stimulation hormone:

The TSH receptor present on thyroid cells is a G protein coupled receptor which utilizes the adenylyl cyclase-cAMP transducer mechanism to produce its effects In human thyroid cells high concentration of TSH also induces PIP2 hydrolysis The resulting increase in cytosolic Ca2+ and protein kinase C activation may also mediate TSH actions. TSH induces hyperplasia and hypertrophy of thyroid follicles and increases blood supply to the gland, promotes trapping of iodide by thyroid, promotes organification of trapped iodine and its incorporation into T3 and Ta by increasing peroxidase activity,

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enhances endocytotic uptake of thyroid colloid by the follicular cells and proteolysis of thyroglobulin to release more of T3 and T4.

Gonadotropins: Human menopausal gonadotropin, follicle-stimulating hormone, and human chorionic gonadotropin
Urofollitropin is FSH obtained from menopausal women and is devoid of LH. Follitropin beta is human FSH manufactured by recombinant DNA technology.

Prolactin
Prolactin is a peptide hormone. Its secretion is inhibited by dopamine acting at D_2 receptors. Its primary function is to stimulate and maintain lactation. It decreases sexual drive. The hormone enters a cell, where it activates a tyrosine kinase to promote tyrosine phosphorylation and gene activation.

POSTERIOR PITUITARY HORMONES- INTRODUCTION

The posterior pituitary gland consists largely of the terminals of nerve cells that lie in the *supraoptic* and *paraventricular* nuclei of the hypothalamus. Their axons form the *hypothalamic-hypophyseal tract*, and the fibres terminate in dilated nerve endings in close association with capillaries in the posterior pituitary gland. Peptides, synthesised in the hypothalamic nuclei, pass down these axons into the posterior pituitary, where they are stored and eventually secreted into the bloodstream. The two main hormones of the posterior pituitary are oxytocin and ADH (vasopressin).

Oxytocin
Oxytocin, originally extracted from animal posterior pituitaries, is now chemically synthesized. Its only use is in obstetrics, where it is employed to

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stimulate uterine contraction to induce or reinforce labor or to promote ejection of breast milk. To induce labor, the drug is administered intravenously. However, when used to induce milk let-down it is given as a nasal spray. Oxytocin causes milk ejection by contracting the myoepithelial cells around the mammary alveoli.

Vasopressin

Vasopressin (antidiuretic hormone), is structurally related to oxytocin. The chemically synthesized nonapeptide has replaced that extracted from animal posterior pituitaries. Vasopressin has both antidiuretic and vasopressor effects. In the kidney, it binds to the V_2 receptor to increase water permeability and resorption in the collecting tubules. Thus, the major use of vasopressin is to treat diabetes insipidus. It also finds use in controlling bleeding due to esophageal varices or colonic diverticula. Other effects of vasopressin are mediated by the V_1 receptor, which is found in liver, vascular smooth muscle, and other tissues.

POSTERIOR PITUITARY HORMONES- PHARMACOLOGY

Antidiuretic hormone

Regulation of secretion and physiological role: Antidiuretic hormone released from the posterior pituitary has a crucial role in the control of the water content of the body through its action on the cells of the distal part of the

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nephron and the collecting tubules in the kidney. The hypothalamic nuclei that control fluid balance lie close to the nuclei that synthesise and secrete ADH.

Antidiuretic hormone receptors

There are three classes of receptor for ADH: V_1, V_2 and V_3. V_2 receptors, which are coupled to adenylate cyclase, mediate its main physiological actions in the kidney, whereas the V_1 and V_3 receptors are coupled to the phospholipase C/inositol trisphosphate system.

Pharmacological actions:

Renal actions: Antidiuretic hormone binds to V_2 receptors in the basolateral membrane of the cells of the distal tubule and collecting ducts of the nephron. Its main effect in the collecting duct is to increase the rate of insertion of water channels into the lumenal membrane, thus increasing the permeability of the membrane to water. It also activates urea transporters and transiently increases Na^+ absorption, particularly in the distal tubule.

Other non-renal actions: Antidiuretic hormone causes contraction of smooth muscle, particularly in the cardiovascular system, by acting on V_1 receptors. The affinity of these receptors for ADH is lower than that of the V_2 receptors, and smooth muscle effects are seen only with doses larger than those affecting the kidney. ADH also stimulates blood platelet aggregation and mobilisation of coagulation factors.

Oxytocin

Action on the uterus. Oxytocin contracts the uterus. Oestrogen induces oxytocin receptor synthesis and, consequently, the uterus at term is highly sensitive to this hormone.

Other actions. Oxytocin contracts myoepithelial cells in the mammary gland, which causes 'milk let-down'-the expression of milk from the alveoli and ducts. It also has a vasodilator action. A weak antidiuretic action can result in water

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retention, which can be problematic in patients with cardiac or renal disease, or preeclampsia.

CORTICOSTEROIDS- INTRODUCTION AND CLASSIFICATION

- The adrenal gland consists of the cortex and the medulla. The latter secretes epinephrine, whereas the cortex, synthesizes and secretes two major classes of steroid hormones the adrenocorticosteroids, and the adrenal androgens.
- The adrenal cortex is divided into three zones that synthesize various steroids from cholesterol and then secrete them.
- The outer zona glomerulosa produces mineralocorticoids (for example, aldosterone), which are responsible for regulating salt and water metabolism. Production of aldosterone is regulated primarily by the renin-angiotensin system.
- The middle zona fasciculata synthesizes glucocorticoids (for example, cortisol), which are involved with normal metabolism and resistance to stress.
- The inner zona reticularis secretes adrenal androgens (for example, dehydroepiandrosterone).
- Secretion by the two inner zones and, to some extent, the outer zone is controlled by pituitary corticotropin adrenocorticotropic hormone, which is released in response to the hypothalamic corticotropin-releasing hormone. Glucocorticoids serve as feedback inhibitors of corticotropin and CRH secretion.
- Hormones of the adrenal cortex are used in replacement therapy; in the treatment and management of asthma as well as other inflammatory diseases, such as rheumatoid arthritis; in the treatment of severe allergic reactions; and in the treatment of some cancers.

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CORTICOSTEROIDS- PHARMACOLOGY

Glucocorticoids

Metabolic actions

- *Carbohydrates*: decreased uptake and utilisation of glucose accompanied by increased gluconeogenesis; this causes a tendency to hyperglycaemia.
- *Proteins*: increased catabolism, reduced anabolism.
- *Lipids*: a permissive effect on lipolytic hormones and a redistribution of fat, as observed in Cushing's syndrome.

Regulatory actions

- *Hypothalamus and anterior pituitary gland*: a negative feedback action resulting in reduced release of endogenous glucocorticoids.
- *Cardiovascular system*: reduced vasodilatation, decreased fluid exudation.
- *Musculoskeletal*: decreasing osteoblast and increasing osteoclast activity.
- *Inflammation and immunity*:
    - *acute inflammation*: decreased influx and activity of leucocytes
    - *chronic inflammation*: decreased activity of mononuclear cells, decreased angiogenesis, less fibrosis

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- *lymphoid tissues*: decreased clonal expansion of T and B cells, and decreased action of cytokine-secreting T cells.

- *Mediators*:
  - decreased production and action of cytokines, including interleukins, tumour necrosis factor-a and granulocyte macrophage colony-stimulating factor
  - reduced generation of eicosanoids
  - decreased generation of IgG
  - decrease in complement components in the blood
  - increased release of anti-inflammatory factors such as interleukin-10 and annexin 1.
- *Overall effects*: reduction in the activity of the innate and acquired immune systems, but also decreased healing and diminution in the protective aspects of the inflammatory response.

Mineralocorticoids

The main endogenous mineralocorticoid is aldosterone. Its chief action is to increase Na^+ reabsorption by the distal tubules in the kidney, with concomitant increased excretion of K^+ and H^+. An excessive secretion of mineralocorticoids, as in Conn's syndrome, causes marked Na^+ and water retention, with a resultant increase in the volume of extracellular fluid, hypokalaemia, alkalosis and hypertension.

CORTICOSTEROID ANTAGONISTS- INTRODUCTION AND CLASSIFICATION

Several substances have proven to be useful as inhibitors of the synthesis of adrenal steroids:

- Metyrapone
- Aminoglutethimide
- Ketoconazole
- Trilostane

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- Spironolactone
- Eplerenone
- Mifepristone

Five pharmacologic agents are useful inhibitors of adrenocortical secretion. *Mitotane*, an adrenocorticolytic agent.

- The other inhibitors of steroid hormone biosynthesis—*metyrapone, aminoglutethimide, ketoconazole,* and *trilostane*.
- Metyrapone, aminoglutethimide, and ketoconazole inhibit cytochrome P450 enzymes involved in adrenocorticosteroid biosynthesis.
- Differential selectivity of these agents for the different steroid hydroxylases provides some degree of specificity to their actions.
- Trilostane is a competitive inhibitor of the conversion of pregnenolone to progesterone, a reaction catalyzed by 3-hydroxysteroid dehydrogenase.
- All of these agents pose the common risk of precipitating acute adrenal insufficiency; thus, they must be used in appropriate doses, and the status of the patient's HPA axis must be carefully monitored.

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CORTICOSTEROIDS ANTAGONISTS- PHARMACOLOGY

Metyrapone: Metyrapone interferes with corticosteroid synthesis by blocking the final step in glucocorticoid synthesis, leading to an increase in 11-deoxycortisol as well as adrenal androgens and the potent mineralocorticoid 11-deoxycorticosterone. The adverse effects encountered with metyrapone include salt and water retention, hirsutism, transient dizziness, and g.i. disturbances.

Aminoglutethimide: This drug acts by inhibiting the conversion of cholesterol to pregnenolone. As a result, the synthesis of all hormonally active steroids is reduced. Aminoglutethimide has been used therapeutically in the treatment of breast cancer to reduce or eliminate androgen and estrogen production. In these cases, it is used in conjunction with dexamethasone. However, it increases the clearance of dexamethasone. Aminoglutethimide may also be useful in the treatment of malignancies of the adrenal cortex to reduce the secretion of steroids. Recent studies indicate it is an aromatase inhibitor.

Ketoconazole: Ketoconazole is an antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis. It is used in the treatment of patients with Cushing's syndrome.

Trilostane: Trilostane reversibly inhibits 3Î²-hydroxysteroid dehydrogenase and, thus, affects aldosterone, cortisol, and gonadal hormone synthesis. Its side effects are gastrointestinal.

Mifepristone: At high doses, mifepristone is a potent glucocorticoid antagonist as well as an antiprogestin. It forms a complex with the glucocorticoid receptor, but the rapid dissociation of the drug from the receptor leads to a faulty translocation into the nucleus. Its use is presently limited to the treatment of inoperable patients with ectopic ACTH syndrome.

Spironolactone: This antihypertensive drug competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney. It can also antagonize aldosterone and testosterone synthesis. It is effective against hyperaldosteronism. Spironolactone is also useful in the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle.

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Eplerenone: Eplerenone specifically binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist. This specificity avoids the side effect of gynecomastia that is associated with the use of spironolactone. It is approved as an antihypertensive.

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THYROID HORMONES- CLASSIFICATION AND PHARMACOLOGY

The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues that is optimal for their normal function. The two major thyroid hormones are triiodothyronine (T3; the most active form) and thyroxine (T4). Although the thyroid gland is not essential for life, inadequate secretion of thyroid hormone (hypothyroidism) results in bradycardia, poor resistance to cold, and mental and physical slowing. If, however, an excess of thyroid hormones is secreted (hyperthyroidism), then tachycardia and cardiac arrhythmias, body wasting, nervousness, tremor, and excess. Heat production can occur.

A. Thyroid hormone synthesis and secretion

The thyroid gland is made up of multiple follicles that consist of a single layer of epithelial cells surrounding a lumen filled with colloid (thyroglobulin), which is the storage form of thyroid hormone.

Regulation of synthesis: Thyroid function is controlled by a tropic hormone, thyroid-stimulating hormone (TSH; thyrotropin). TSH is a glycoprotein, structurally related to LH and FSH, which is synthesized by the anterior pituitar. TSH generation is governed by the hypothalamic thyrotropin-releasing hormone (TRH). TSH action is mediated by cAMP and leads to stimulation of iodide (I^-) uptake. Oxidation to iodine (I_2) by a peroxidase is followed by iodination of tyrosines on thyroglobulin. Condensation of two diiodotyrosine residues gives rise to T4, whereas condensation of a monoiodotyrosine residue with a diiodotyrosine residue generates T3, which is still bound to the protein. The hormones are released following proteolytic cleavage of the thyroglobulin.

Regulation of secretion: Secretion of TSH by the anterior pituitary is stimulated by the hypothalamic TRH. Feedback inhibition of TRH occurs with high levels of circulating thyroid hormone. Most of the hormone (T3 and T4) is bound to thyroxine-binding globulin in the plasma.

Mechanism of action

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Both T4 and T3 must dissociate from thyroxine-binding plasma proteins prior to entry into cells, either by diffusion or by active transport. In cell, T4 is enzymatically deiodinated to T3, which enters nucleus and attaches to specific receptors. The activation of these receptors promotes the formation of RNA and subsequent protein synthesis, which is responsible for the effects of T_4.

ANTITHYROID DRUGS- CLASSIFICATION AND PHARMACOLOGY

These are drugs used to lower the functional capacity of the hyperactive thyroid gland.

Inhibit hormane synthesis (Antithyroid drugs): Propylthiouracil,Methimazole, Carbimazole.

Inhibit iodide trapping (Ionic inhibitors): Thiocyanates (-SCN), Perchlorates (-ClO4), Nitrates (-NO3).

Inhibit harmone release: Iodine, Iodides of Na and K, Organic iodide.

Destroy thyroid tissue: Radioactive iodine (^{131}I,^{125}I,^{123}I).

Inhibition of thyroid hormone synthesis: The thioamides, propylthiouracil (PTU) and methimazole, are concentrated in the thyroid, where they inhibit both the oxidative processes required for iodination of tyrosyl groups and the coupling of iodotyrosines to form T3 and T4. PTU can also block the conversion of T4 to T3. The thioamides are well absorbed from the gastrointestinal tract, but they have short half-lives. Several doses of PTU are required per day, whereas a single dose of methimazole suffices due to the duration of its antithyroid effect.

Inhibit iodide trapping (Ionic inhibitors): Î²-Blockers that lack sympathomimetic activity, such as propranolol, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. Intravenous administration is effective in treating thyroid storm. An alternative in patients

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suffering from severe heart failure or asthma is the calcium-channel blocker, diltiazem. Other agents used in the treatment of thyroid storm include PTU iodides, and glucocorticoids.

Blockade of hormone release: A pharmacologic dose of iodide inhibits the iodination of tyrosines, but this effect lasts only a few days. What is more important, iodide inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood. Today, iodide is rarely used as the sole therapy. However, it is employed to treat potentially fatal thyrotoxic crisis (thyroid storm) or prior to surgery, because it decreases the vascularity of the thyroid gland. Iodide is not useful for long-term therapy, because the thyroid ceases to respond to the drug after a few weeks. Iodide is administered orally.