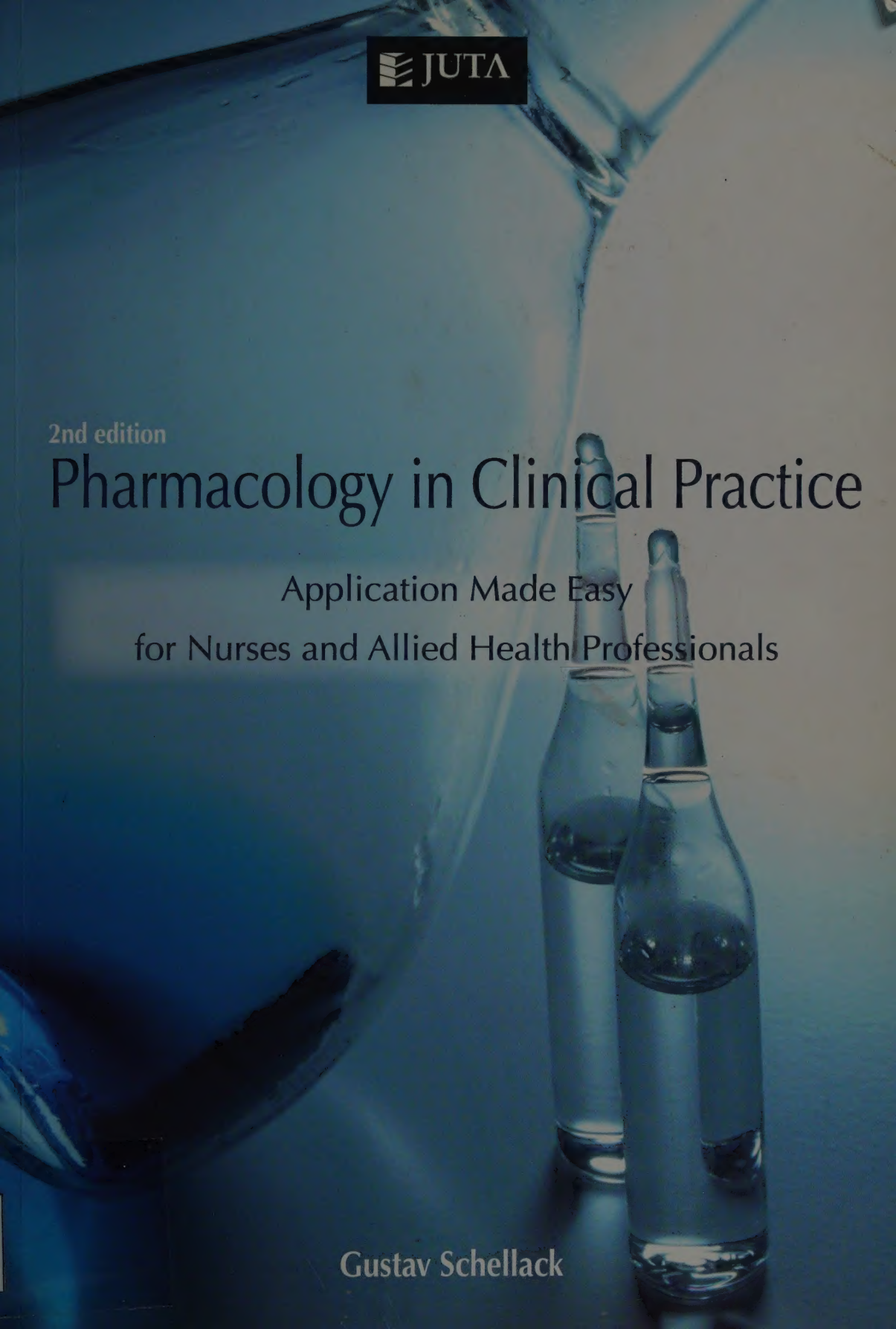

JUTA
2nd edition
Pharmacology in Clinical Practice
Application Made Easy
for Nurses and Allied Health Professionals
Gustav Schellack

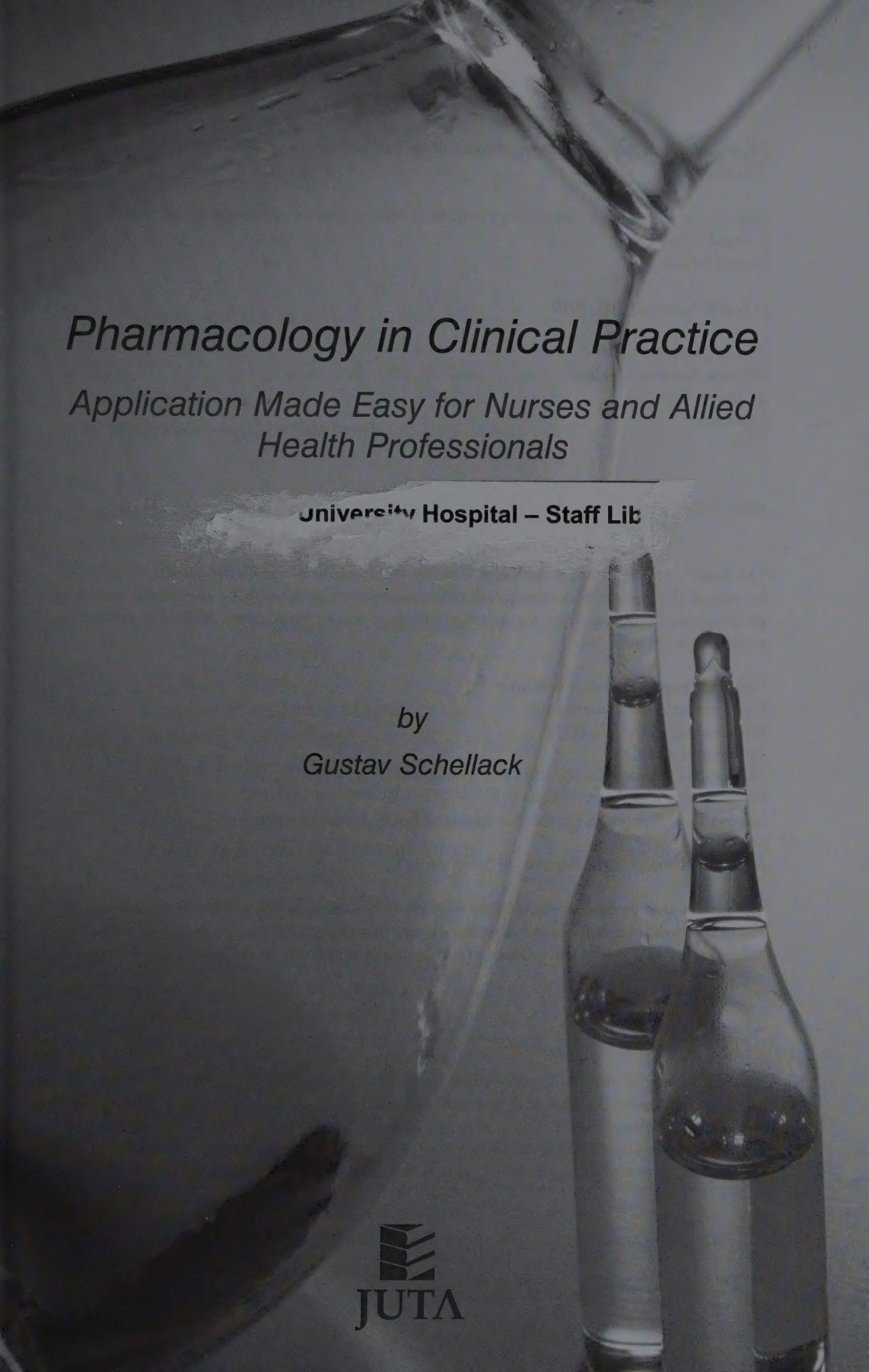
# Pharmacology in Clinical Practice

## Application Made Easy for Nurses and Allied Health Professionals



by

Gustav Schellack



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*This book is dedicated to our students.*

# Preface

It gives me great pleasure to introduce the second edition of this textbook, which has been extensively revised and updated. Students and other readers can look forward to updated and expanded information on the general aspects of pharmacology, novel drug therapies, and contemporary issues and developments in drug science. Improved features in this edition include additional information on the new drug development process, a guide to finding and interpreting drug information, and a new chapter on the nursing management of drug preparations and treatment.

This text has been prepared as a broad introduction to the fascinating science of pharmacology and to illustrate the importance and applicability of pharmacological principles to clinical practice.

The strength of this text lies in the explanation of the principles that underlie the two major subdivisions of pharmacology, namely pharmacodynamics and pharmacokinetics. Due to restrictions in the scope of this text, only the most significant and major drug groups, with relevant drug examples and clinical applications, have been addressed. The reader is advised to consult appropriate drug references for topics such as specific indications, contraindications, side-effects and dosage regimes, since this text has not been prepared to serve as a medicines formulary, treatment or prescribing guide.

Part 1 deals with the scientific principles of pharmacology.

Part 2 addresses the pharmacological aspects of drug treatment as they relate to the major organ systems of the human body. In part 3 of the text the nursing management of drug preparations and treatment is addressed, as well as the legal framework for drug prescribing and dispensing by nurses in South Africa, a contemporary and very contentious practice issue. Only generic drug names are used in this text; they have been printed in italic lettering for ease of recognition. The names of drugs that are listed in the National Department of Health's Essential Medicines List (i.e. the EML, also referred to as the EDL) for Primary Health Care have been printed in bold italic lettering.

Annexure A lists all of the drugs that are contained in the 2008 edition of the EML for Primary Health Care, classifies and contextualises each of these medicines, and cross-references these agents to the relevant sections or listings in the text. In addition, Annexure B contains notes on patient adherence, or compliance with prescribed drug therapy.

It is our sincere hope that students will find this text book to be a valuable introduction and overview of pharmacology and a useful reference to the basics of drug science and its application to various clinical practice settings.

GS
May 2010

# Acknowledgements

I wish to acknowledge the valuable contributions of the following people towards the quality and success of this edition:

- My co-authors, Natasjha Engelbrecht, Nelouise Geyer and Natalie Schellack, my dear and loving wife, for their dedication and hard work.
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- Numerous colleagues and students, past and present, for their valuable input and suggestions towards expanding and improving this edition.
- The team at Juta Health, including Hyreath Anderson, Johanna Breakey, David Merrington, Ethné Clarke, Clint MacDonald and Jeanne Cope for their patience, encouragement, perseverance and excellent management of this intricate project.
- My mentors, including Dr Marieta van Wyk and the late Prof. De Klerk Sommers, who introduced me to the wonderful and fascinating science of pharmacology.

GS
May 2010

# Key to symbols used in this book

**Clipboard icon:** This icon has been used for information that provides you with some explanatory notes.

**Stethoscope icon:** This icon has been used to draw your attention to information concerning the effects of specific drugs on the patient or information pertinent to clinical application.

**Capsule icon:** You will see this icon when the information relates to specific groups of drugs or specific drug examples.

**Plant alkaloid:** Words that have been written in bold and underlined on their first usage are explained in the glossary.

*Codeine:* All generic drug names appear in italics.

***Amoxicillin:*** The names of drugs that are listed in the Department of Health's Essential Medicines List (EML) for Primary Health Care appear in bold italics.

**Antagonists:** Certain words and phrases appearing in bold letters are important terms or vocabulary that you should make sure you understand. Consult a reliable medical dictionary where necessary.

# Part 1


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CHAPTER ONE

# Understanding the basic principles of pharmacology

## 1.1 Introduction to the science of pharmacology

Drugs are chemical substances used to prevent, diagnose and treat disease. Pharmacology is the scientific study of drugs, where they come from and how they work.

### 1.1.1 How do drugs fit into the bigger picture?

The treatment of disease may entail a wide variety of **modalities**, aimed at removing the causative agent(s), relieving the symptoms, alleviating the suffering and bringing about a satisfactory outcome. These modalities may include invasive diagnostic procedures, surgical repair or removal of diseased tissue, and medical management through the use of drug treatment or pharmacotherapy.

As health professionals, we are faced with physical and mental illness on a daily basis. Illness, or disease, is caused by various factors, some of them **intrinsic** (i.e. from within human beings themselves, for example, genetic factors, inadequate adaptive mechanisms, age and gender), and others **extrinsic** (determined by such environmental factors as harmful chemicals, physical agents, microbes and environmental pollutants, or lack of the means to make an adequate living).

These disease-causing factors can bring about structural (anatomical), functional (physiological) and molecular (or biochemical) changes in the body, most of which are both **identifiable** and **quantifiable** by modern-day medical science. Recognising these changes helps us to develop appropriate treatment modalities for managing them.

Essential hypertension, for example, is both identifiable and quantifiable by obtaining a non-invasive arterial blood pressure reading with a stethoscope and sphygmomanometer. A reading of 175/105 mmHg is indicative of both the presence of hypertension, and of how high the blood pressure actually is. Thus, to quantify disease is to provide a measure of its **severity**.

## 1.1.2 Medical, surgical and psychiatric treatment modalities

Patients usually fall into one of three categories, namely medical, surgical or psychiatric, or a combination of these. All three categories of patients, however, may require drug treatment in some or other form. Refer to figure 1.1.

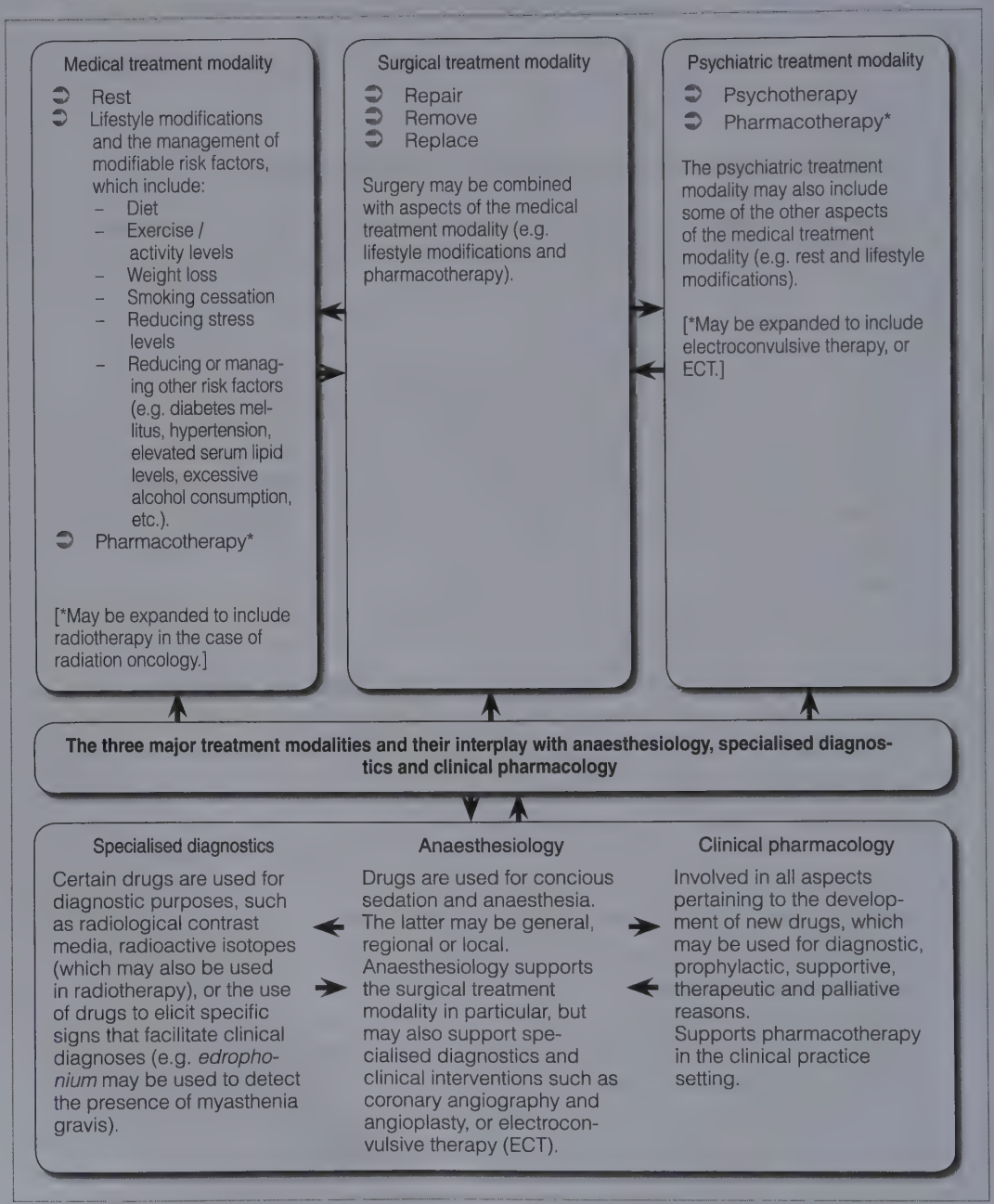



**Figure 1.1 Medical, surgical and psychiatric treatment modalities**

The structural changes brought about by disease are often managed or treated through surgical intervention, whereas the functional and molecular changes may respond to chemical intervention. **Pathology** is the scientific study of disease and disease-causing factors.

Typically, patients requiring **surgery** will receive drugs to calm them during the preoperative phase of treatment and to augment the general anaesthetics that they will receive in theatre; analgesics to manage their postoperative pain; and drugs to prevent or manage postoperative complications, including antimicrobials for prophylaxis against bacterial infections and *heparin* for the prevention of venous thrombi.

**Medical** patients, on the other hand, usually require a combination of drug treatment regimens, lifestyle changes and some form of rest that will promote remission or recovery, while **psychiatric** patients may be in need of extensive psychotherapy, electroconvulsive therapy (ECT) or therapeutic interactions and conversation, augmented by psychiatric drug therapy.

Therefore, it comes as no surprise that many authorities view drug treatment, also referred to as **pharmacotherapy**, as the backbone of all treatment modalities (i.e. the quantitative chemical influencing of physical or mental illness, or the adjunctive influencing of invasive procedures, once suitable clinical treatment goals have been set), whether medical, surgical or psychiatric in nature. **In other words, drugs may be used to treat illness, or to support and strengthen any other therapeutic interventions.**

## 1.2 What are drugs?

Physiological or mental changes brought about by disease may be favourably influenced with an array of chemical substances called drugs.

**Drugs** are chemical substances that influence physiological (including biochemical) or mental processes in the body. When used with discretion and vigilance, drugs will display their beneficial biological effects in the presence of physical or mental illness. Some drugs may even be used to prevent or diagnose disease.

The term 'drug', however, is also associated with the use and abuse of so-called recreational substances that affect the central nervous system (CNS) in some or other way and, in doing so, cause chemical dependency or addiction. For the purposes of this book, however, the term will only be applied to drugs that are used for medicinal purposes (i.e. 'medical drugs').

Drugs usually require special preparation to make them suitable for administration to our patients. This may include compounding them, adding colorants, flavourings and preservatives, preparing suitable **dosage forms** (e.g. tablets, capsules, mixtures, elixirs, suppositories, etc.) and deciding on the most suitable dosing schedule.

**Note 1.1 Dosage forms**

Common dosage forms encountered in clinical practice include (but are not limited to):

| | |
|---|---|
| Aerosols | Pastes |
| Capsules | Pessaries (vaginal suppositories) |
| Creams | Powders |
| Elixirs | Skin patches for transdermal administration |
| Emulsions | Solutions |
| Gels | Sponges impregnated with drugs |
| Granules | Suppositories |
| Lotions | Suspensions |
| Mixtures | Syrups |
| Ointments | Tablets |
| Ophthalmic and aural preparations | Volatile liquids and gases |
| Parenteral preparations for injection | |

The art and science of drug preparation and the design of dosage forms is known as **pharmaceutics**. Drugs that have been pharmaceutically prepared are called **medicines**. A medicine may therefore contain one, two or many different drugs (as active substances) within a suitable base (of pharmaceutically inactive substances known as **excipients**).

**Biopharmaceutical agents** constitute a group of therapeutic agents that do not fit the traditional definition of drugs. In contrast to the chemical substances mentioned above, which are also referred to as small-molecule drugs or 'traditional' pharmaceuticals, the biopharmaceutical agents are much bigger macromolecules produced through **biotechnology**, as opposed to simple extraction (i.e. direct extraction from a biological source) or chemical sourcing and manufacturing (i.e. chemical synthesis).

The use of biotechnology implies that living organisms or components such as cultured cells and tissues of such organisms, and so-called genetic engineering are involved in the manufacturing process. Biopharmaceutical agents include monoclonal antibodies (refer to note 12.2), recombinant human ***insulin***, certain vaccines, clotting factors VIII and IX, enzymes, hormones and **cytokines**. Examples include *infliximab, bevacizumab,* human growth hormone *(somatropin), filgrastim* (granulocyte colony-stimulating factor, or *G-CSF*) and tissue plasminogen activator, or t-PA *(alteplase).*

Novel biopharmaceutical agents are being developed at an extraordinary pace and are already helping to shape the way in which various serious illnesses are being treated today. These include, but are by no means limited to, rheumatoid arthritis, cancer, haemophilia, ulcerative colitis, multiple sclerosis, etc.

Note that the 'older' term, **biological agent**, was originally aimed at blood products, biological poisons and all of the biological products used to bring about

either passive or active immunity in the person receiving them, including toxoids, immunoglobulins, antitoxins and most other vaccines. Thus, the 'older' biological agents are produced through simple, or direct, extraction from a biological source (hence the name) and do not involve modern-day biotechnology or genetic engineering. Examples of biological agents include *equine gamma globulin, human plasma albumin, human immunoglobulin,* live attenuated virus vaccines and ***diphtheria, tetanus*** and ***pertussis toxoid*** vaccines.

It should be noted, however, that the term 'biopharmaceutical' is also used in pharmaceutics (the art and science of drug preparation and the design of dosage forms) when referring to the so-called biopharmaceutical properties of drugs, i.e. those factors that determine the net **bioavailability** (also refer to paragraph 2.2.3) of a drug from the time that the drug molecules are released from the relevant dosage form until they enter the systemic blood circulation. Therefore, the biopharmaceutical properties of drugs will include all aspects related to their release, dissolution and stability in body fluids, their ability to cross plasma membranes and other biological barriers, the resultant absorption, and the rate and extent of their presystemic elimination (i.e. their metabolism in the gastrointestinal tract and liver before they eventually reach the systemic circulation). These factors are most applicable to orally administered drugs.

Lately some authors have begun to use the term **biotechnology drugs** when referring to the abovementioned biopharmaceutical agents as a more descriptive means of differentiating between the older biological agents, the novel biotechnologically derived agents, and the biopharmaceutical properties of drugs.

Another interesting development is the advent of generic versions of biotechnology drugs. These generic biotechnology drugs are referred to as follow-on biologics (FOBs) or **biosimilar** agents. These biosimilar agents are considered to be *similar* to the innovator or branded products, but *not* exactly the same. The reason for this is that the generic manufacturer (i.e. the manufacturer of the biosimilar agent) will not necessarily have access to the exact same strain of living organism or cell culture that is used by the innovator company (i.e. the manufacturer that originally discovered and developed the product).

## 1.3 Naming drugs and medicines

Generic names are usually recognised internationally, while trade names are unique to the manufacturers of specific medicines. Thus, it could also be said that drugs have generic names and medicines have trade names.

The well-known β-blocker ***atenolol***, for example, is sold under a variety of **trade names**. Each individual trade name is registered as, or constitutes, a trademark belonging to the manufacturer in question. Manufacturers use these registered trade names to promote and sell their products.

**Generic names**, on the other hand, identify the actual drug or drugs contained in the manufacturer's product. Sometimes one specific drug is combined with one or more other drugs in a single product. ***Atenolol***, for instance, may be found in combination with the diuretic *chlorthalidone*. Therefore, it makes sense to study the pharmacology of drugs by using the appropriate generic names.

There are, however, a few cases where generic names differ from one country to another – even from one English-speaking country to another. When studying texts from the United States, for instance, readers will note that *acetaminophen* is the generic, or non-proprietary, name given to a drug that is known in South Africa and the United Kingdom as ***paracetamol***. Similarly, the generic drug which is called *epinephrine* in the United States is known in our country as ***adrenaline***.

To summarise, generic (or non-proprietary) names identify the various **drugs** that we use in clinical practice. These drugs are made into a variety of **medicinal products** that carry their manufacturers' registered trade names, under which they will be marketed and sold to distributors, retailers and end-users (i.e. patients or consumers).

## 1.4 What is pharmacology?

To enable us to use and administer drugs (or medicines) effectively, we need to know what to expect from them and what will happen to them once they are introduced into the human body.

**Pharmacology** is the scientific study of drugs, where they come from, their nature, their chemical composition, their expected actions, their wanted and unwanted effects and their uses. Pharmacology, or **drug science**, has two major subdivisions, namely **pharmacodynamics** and **pharmacokinetics**.

The two major subdivisions of pharmacology answer the two most fundamental questions that may be posed wherever drug therapy is concerned. These questions are:

- What will the drug do to the body?
- What will the body do to the drug?

Pharmacodynamics provides us with answers to the former question, while pharmacokinetics answers the latter one.

**Pharmacodynamics** describes the physiological effects that drugs have on living cells or organisms (such as the human body) and shows how drugs influence body functions through biochemical changes in body fluids and tissues. Pharmacodynamics therefore describes a drug's **mechanism of action** and its **therapeutic effects**. Pharmacodynamics also gives us an indication of how the **drug concentration** (or dosage) is related to the subsequent extent of its therapeutic effects.

**Pharmacokinetics** describes the **absorption**, **distribution**, **metabolism** (or **biotransformation**) and **elimination** (through excretion) of drugs, in other words, the effects of body processes on drug molecules, as a function of time (i.e. as measured over time). Some authors refer to the four highlighted processes as the 'ADME' processes, however, some substitute elimination with excretion.

Pharmacology also includes, but is in no way limited to, the following specialised areas of study:

- **Pharmacotherapeutics:** The science of drug usage in the treatment of disease. **Pharmacotherapy** refers to a patient's actual drug treatment programme. This is closely linked to, and often used interchangeably with, **clinical pharmacology**, which studies the actual therapeutic use of drugs, and involves the entire drug development process from laboratory to real-world clinical practice. Refer to paragraph 1.10. The goal of clinical pharmacology is to optimise a patient's drug therapy (or pharmacotherapy) to deliver maximal therapeutic benefit (i.e. effectiveness, or efficacy) with minimal harm or detriment (i.e. optimal safety).
- **Comparative pharmacology:** Comparisons are drawn between findings and results obtained from animal trials versus human trials. Comparative pharmacology has to establish whether findings or predictions related to a specific drug's performance in animals may be applied to humans.
- **Molecular pharmacology:** The study of the interaction between drug molecules and the biological molecules of living organisms.
- **Pharmacogenetics:** The area of drug science that studies the genetic susceptibility of individuals to specific drugs. A certain individual's genetic make-up may, for instance, determine the rate at which drugs will be metabolised (or biotransformed) in his or her body. Also, a specific individual's response to a certain drug may be significantly altered in the presence of a genetic defect.
- **Pharmacoeconomics:** As part of health economics, the cost and economic benefit of drug treatment plays an important role in determining which treatments constitute the best value for money, especially when weighing the high cost of novel drug therapies against the budgetary constraints of many healthcare systems.
- **Pharmacoepidemiology:** Epidemiological methods and processes may be employed to analyse the use of a drug treatment at population level, and to draw comparisons between populations, as well as individual responses within a population, as a measure of variability and the possible utilisation of such a drug in a real-world setting.
- **Toxicology:** The study of toxins or poisons and their antidotes. In pharmacology, toxicology also deals with the toxic (or poisonous) effects of drugs in overdose, as well as the treatment of poisoning and overdose.

**Toxicity** refers to the **poisonous qualities** of chemical substances such as drugs. Refer to paragraph 1.11.

Pharmacology is constantly evolving and new and highly specialised areas of study, such as **pharmacogenomics** (regarded by some as a sub-speciality of pharmacogenetics, which is evolving from our ever-increasing understanding of the human genome) and gene therapy, and the use of cutting-edge biotechnology and genetic engineering in the development of **biopharmaceutical agents**, will help to shape drug science in the not-too-distant future.

## 1.5 Basic principles of pharmacotherapy

Drug therapy should be well thought out, safe, and convenient, and promote good patient compliance.

### 1.5.1 General aspects of drug therapy

Drug treatment should always be tailored to patients' specific requirements and needs. Due to significant **inter-individual variation**, for example, not all patients will exhibit the same rate of drug biotransformation.

The decision to opt for drug therapy should always be a sound and **rational** one. The outcome that the treatment plan is aiming for should be realistic and take into consideration what the available drugs, under the specified conditions, may be reasonably expected to do when given to the patient in question. Sometimes drugs may only be of partial benefit to the patient, or the possible benefits may be outweighed by the cumbersome side-effects, more serious safety concerns, or toxicity of a particular drug or treatment regimen.

Many different factors determine the choice and possible outcomes of drug therapy. These factors include:

- Age and gender
- Physical characteristics (e.g. size and body mass index)
- Diet and nutritional status
- Gene pool and genetic factors
- Previous responses and reactions to drug treatment (including allergic reactions and anaphylaxis)
- Other drugs already in use, which may give rise to drug interactions, including **over-the-counter (OTC)** medicines and herbal remedies
- The influence of current and pre-existing illness
- Health status and general standards of living
- Unwanted and toxic effects of the drugs in question
- Fertility, pregnancy and lactation

- Patient compliance

Drug treatment should always be carefully adjusted to the particular needs and responses of the patients in question. Biotransformation may vary significantly between individuals (i.e. there is **inter-individual variation**), making standard dosages undesirable. The inter-individual variation is the product of genetic differences among humans. Furthermore, patients who are well informed tend to display higher levels of compliance with their treatment regimens.

### 1.5.2 Advantages and disadvantages of drug use

Most drugs will exhibit **unwanted** effects in addition to the therapeutic effects that they are meant to produce.

Drugs alter physiological and biochemical processes in the body, but cannot create new body functions. Drug treatment is therefore limited to the quantitative influencing of the altered physiology associated with illness. At the correct dosages drugs may be expected to exert their therapeutic effects on the body with relative safety. A drug's **efficacy** is the maximal response that it is able to deliver.

In addition to their therapeutic effects, most drugs will, however, also influence certain processes or functions that do not form part of the desired clinical treatment plan. Such unwanted, or adverse, effects may be categorised as follows:

- **Side-effects:** These effects are attributable to the drug's mechanism of action. They occur in addition to the effects that the drug was meant to elicit in the first place and are associated with **normal therapeutic dosages**. Lowering the dosage or changing the drug regimen to include a more target-specific (selective) drug will reduce these unwanted effects. In some instances, though, drugs may even be administered for the specific **utilisation** of their side-effects. The attributable or expected side-effects of a drug or medicinal preparation can be found in the accompanying package insert, however, unexpected adverse reactions may also occur and need to be detected and reported appropriately.
- **Toxic effects:** Thorough research during a new drug's development process leads to the **predictability** of its toxic effects, which are **dosage-dependent** and often manifest during over-dose (intended or accidental). Accidental overdose may occur in patients with impaired hepatic or renal function, leading to impaired biotransformation and excretion of drugs. Toxic effects may lead to tissue, organ or organ-system damage, and may prove harmful to an unborn child:

- **Toxicity towards tissues, organs and organ systems:** The liver, kidneys, lungs, gastrointestinal tract, cardiovascular system, nervous system, bone marrow and integument (skin) are particularly sensitive to the toxicity of drugs. Organ failure, bone marrow suppression with resultant aplastic anaemia, cardiac dysrhythmias, peptic ulceration and photosensitivity are but a few examples of the effects of drug toxicity.
- **Toxicity during pregnancy:** Drugs may be toxic to the developing embryo and foetus. The first trimester of pregnancy (i.e. the stage of embryonic development and **organogenesis**) is of particular importance, since the **teratogenic** effects of certain drugs will influence normal development. A **teratogen** is a drug (or other chemical substance) that may affect normal embryonic development and cause recognisable congenital (birth) defects. During the second and third trimester, drugs usually only affect the growth and maturation of the foetus, since organogenesis is completed by the end of the embryonic period, although the development of the external genitalia continues into the second trimester and the development of the central nervous system is an ongoing process for the duration of the pregnancy (and beyond). During the very early stages of pregnancy the expectant mother may not even be aware of the fact that she is carrying a developing embryo. She may unknowingly harm her unborn child through the careless or indifferent use of drugs. Therefore, this is an important topic to include in pre-conception care.
- **Mutagenic effects:** Drugs in general should also be viewed as being potentially **mutagenic**. **Mutagens** cause genetic defects by affecting developing germ cells during the reproductive years. Here too, as in pregnancy, extreme caution should be exercised when deciding on appropriate drug treatment for disease or mental illness. Teenagers and young adults who are sexually active, females of childbearing potential, and even males of any age who are capable of fathering children, should be cautioned about the harmful effects that drugs, including *ethanol*, may have on sperm cells, ova or pregnancy.

➲ **Meta-reactions:** These reactions are **unexpected** and may occur **irrespective of the dosage** or toxicity profile of the drug in question. Meta-reactions include:

- **Drug allergies:** Due to the small size of average drug molecules, they usually act as **haptens** during allergic reactions. The biological and biopharmaceutical agents will, however, act as **allergens** when they elicit allergic reactions due to their molecular size (they are polypeptides or proteins). Haptens are small, incomplete allergens that become complete and recognisable by the immune system once they bind to body proteins. An allergic reaction ensues, with plasma cells releasing antibodies, and

mast cells and basophils releasing their chemical mediators (including histamine, bradykinin, serotonin, the prostaglandins, leukotrienes, etc.). A relatively slow and often insignificant primary response (on first exposure) is followed by secondary responses (on subsequent exposures to the same allergen) that escalate in their acuity and severity. Allergic reactions to drugs include **immediate hypersensitivity reactions** (including anaphylaxis, bronchospasm and urticaria), so-called **serum sickness** (a combination of skin rash, lymphadenopathy, fever and inflammatory changes, with a delayed onset of up to two weeks) and **delayed hypersensitivity reactions** (including skin rashes, **exfoliative dermatitis** and **toxic epidermal necrolysis**).

- **Genetic defects that result in meta-reactions:** When some drugs are administered to individuals with certain genetic defects that alter the biochemistry of specific metabolic processes in the body, meta-reactions such as drug-elicited **porphyria**, gout and malignant hyperthermia may ensue.
- **Paradoxical drug action:** It is well known that certain central nervous system depressants sometimes cause actual stimulation of the CNS in children and the elderly. Examples include the benzodiazepines and the multipotent antihistamines and phenothiazines (for example, *trimeprazine*, which is often prescribed to children for its calming effects during the preoperative phase of the surgical treatment modality). On the other hand, attention-deficit hyperactivity disorder, or ADHD, may respond to CNS stimulants such as *methylphenidate* (a drug that is used in these 'hyperactive' children for its known paradoxical effect). These meta-reactions are called **paradoxical** because the reactions that these drugs elicit are the actual opposites of those that may readily be expected from their mechanisms of action.

- **Drug dependency:** Some individuals develop an urge to repeatedly use psychoactive drugs because of their pleasurable effects and the altered mental state that they produce. Dependency may be both physical and psychological. Physical dependency is responsible for withdrawal symptoms when the use of the drug is discontinued. Psychological dependency produces the so-called drug craving that strengthens the ongoing use and abuse of the drug.
- **Tolerance:** Drug tolerance is said to have developed when it has become necessary to increase a drug's dosage in order to achieve the same level of therapeutic effect as was achieved when the drug was first introduced. Tolerance may accompany drug dependency, or may be of special pharmacotherapeutic significance when it is **pharmacodynamic** (involving reduced receptor responsiveness) or **pharmacokinetic** (involving an increased

rate of biotransformation). An **acute tolerance** for the effects of a drug, due to a rapidly developing pharmacodynamic cause, is termed **tachyphylaxis**.

Whenever new drugs or medicines are being developed, the aim is always to produce products with the best possible efficacy, at the smallest possible dosage, and with the fewest possible unwanted effects. Unfortunately, this goal may not always be fully attainable.

Remember that drug therapy should always be in a patient's best interest and that the potential benefits of such therapy should always outweigh the perceived risks (i.e. the potential 'harm' to the patient).

### 1.5.3 Special patient populations

Certain precautions and adaptations are required when prescribing and administering drugs to certain populations of patients that are particularly vulnerable to the effects of this form of chemical 'manipulation' on their body processes.

**Vulnerable patients**, who require special adaptations and precautionary measures in their drug-treatment regimens, include:

- **Infants and children:** Due to their smaller size and the higher percentage of body water, infants and children need adapted dosages that should also take their age and developmental stage into consideration. Liver biotransformation, for example, is slower in the neonate, but an increased metabolic rate is found in children. The neonate also displays a slower rate of renal elimination of certain drugs. Premature babies have an even higher percentage of body water than neonates do. Various **formulas** have been proposed to calculate paediatric drug dosages, but experience and the precise recommendations of the manufacturer should offer even greater accuracy in clinical practice. Three formulas that are often encountered are **Augsburger's Rule**, **Clark's Rule** and **Catzel's Percentage Method**. All three methods have their strengths and weaknesses, and should be used with discretion. Children cannot simply be viewed as 'mini-adults', paediatric dosages should never be calculated based on the child's age alone, and should never exceed those administered to adult patients.
- **Pregnant and lactating mothers:** The effects of teratogens and mutagens on the unborn child were highlighted in paragraph 1.5.2. For the duration of pregnancy, the placenta acts as a barrier between the circulatory systems of mother and child. This barrier, however, is not very efficient when it comes to drug molecules. All lipid-soluble drugs are capable of crossing the placental barrier through simple diffusion. Most water-soluble drugs can cross the placenta as well, because of the relative inefficiency of the barrier. *Heparin* is an exception.

During lactation, drugs may pass from the bloodstream to the breast milk, especially if they are lipid-soluble or basic drugs (basic drugs will tend to ionise in the breast milk since it is more acidic than blood), or if they are water-soluble molecules with a relative molecular mass of less than 100 **daltons**.

**Note 1.2 Calculating paediatric dosages**

**Augsburger's Rule:**

Dosage to be administered, as a percentage of the adult dosage = (child's weight in kg × 1.5) + 10, **or** (child's age in years × 4) + 20.

**Clark's Rule:**

Dosage to be administered = (child's weight in kg ÷ 70 kg)* × the adult dosage in mg.

**Catzel's Percentage Method:**

Dosage to be administered, as a percentage of the adult dosage = (child's body surface area** in $m^2$ ÷ 1.76 $m^2$)* × 100.

* An average adult male weighing 70 kg should have an average body surface area of 1.76 $m^2$.

** There are many different formulas for calculating body surface area (BSA) of which Mosteller's formula is a well-known example:
BSA ($m^2$) = $\sqrt{[\text{height (cm)} \times \text{weight (kg)}] \div 3\,600}$

We have limited data at our disposal on the actual safety profiles of many drugs during pregnancy and lactation. Drugs should therefore always be used with caution. It is of great importance to consult a suitable drug reference when prescribing medicines to pregnant or lactating mothers. Known teratogens should be avoided during pregnancy. However, situations may arise where the benefits of treating the mother with a certain drug may outweigh the possible harm that the drug may or may not do.

Well-known examples of teratogenic drugs include: *isotretinoin* (used in the treatment of severe forms of acne), *methotrexate* (an antineoplastic and immunosuppressant agent), the antiepileptic agents, ***phenytoin*** and ***valproate***, the antiretroviral agent, ***efavirenz***, and *warfarin* (an oral anticoagulant). Using *ethanol* (drinking alcohol) during pregnancy may cause foetal alcohol syndrome. There are many more examples.

➲ **Patients with hepatic and renal impairment:** Both the liver and the kidney play an important role in the termination of drug action in the body. Drug dosages will require careful adjustment in the case of impaired hepatic or

renal function, since delayed biotransformation or slowed excretion may lead to the accumulation of drugs in the body and subsequent toxicity. Drug dosages may be decreased, or the dosage intervals increased.

- **The elderly:** These patients often have impaired liver and kidney function due to the effects of ageing or primary pathology on these organs, or secondary to conditions such as congestive cardiac failure, diabetes mellitus and other chronic diseases. A particular characteristic of drug use in the elderly is **polypharmacy** (the simultaneous use of multiple drugs). The multiple pathological processes that affect many elderly patients also require a variety of different drugs to be used concomitantly. Elderly patients also tend to visit numerous medical practitioners, keep on repeating prescriptions without proper follow-up and overzealously self-medicate with over-the-counter (OTC) drugs. In this patient population, the danger of drug toxicity and unchecked drug interaction is a very real one. Levels of compliance with their prescribed treatment regimes may also be low.
- **Obese patients:** Adult patients are considered to be obese when they have a **body mass index (BMI)** of 30 $kg/m^2$ or more, whilst obese children will have a body mass index above the $95^{th}$ BMI-percentile for age and sex. The BMI is calculated using the following formula:

$$BMI\ (kg/m^2) = [body\ weight\ (kg)] \div [height\ (m)]^2$$

Obesity is caused by the excessive accumulation of body fat. The BMI provides a measure of body fat based on weight and height, and is applicable to both males and females. In terms of the impact that obesity may have on drug dosages, consideration needs to be given to factors such as the degree of lipid-solubility of the drug in question, as well as the possible significance of **lean body mass** (LBM) in relation to **total body weight** (TBW). Always consult the relevant prescribing information with regard to possible dose alterations when working with obese and morbidly obese (i.e. when the BMI is 40 $kg/m^2$ or more) patients.

- **Athletes:** Certain drugs are prohibited in sport since they may enhance the performance of athletes, giving them an unfair advantage over their competitors. These performance-enhancing agents are not necessarily taken on purpose. Therefore, special care needs to be exercised when prescribing drugs to athletes, especially because some of the banned substances are prohibited at all times, some only during competition, and others only in certain sports. Expert references need to be consulted for up-to-date information on banned substances in sport.

## 1.6 How do drugs work?

Drugs need to influence body functions to have a therapeutic effect. This type of influencing may be quantitative, but can never be qualitative.

As already mentioned, drugs will influence physiological processes in the body in some or other way. Drugs cannot, however, create new cell or tissue functions (meaning that **qualitative** influencing of body physiology is not possible), but rather, they have the ability to influence body physiology in a **quantitative** way (therefore positively influencing whatever the disease process has altered in a negative way). Drugs may increase or decrease body functions, depending on their mechanisms of action, in other words they may **increase** or stimulate physiological processes, or **decrease**, inhibit or block such processes.

For drugs to actually exert their effects on body physiology, they need to interact with specific target areas, generally referred to as drug **receptors** (i.e. the targets of drug action). The interaction between drugs and their receptors is **chemical** in nature, making organic chemistry and biochemistry important foundation sciences in drug studies.

These drug receptors, or drug targets, are three-dimensional molecular complexes, capable of interacting with drug molecules to form **chemical bonds** between them. Compared to the complex structure of proteins and protein-containing biological macromolecules (such as glycoproteins and lipoproteins) in the body, drugs are relatively simple and small micromolecules. It is the complex structure of these protein-containing macromolecules (large molecules) that makes them ideal drug targets. There are different types of drug target or drug receptor types:

- **Specific ligand receptors:** Drugs that bind to these receptors actually target the binding sites of the normal, physiological, signal-transmitting substances that directly influence cell and tissue functioning. These receptors are found throughout the body and occur in all glandular tissue (endocrine and exocrine), muscle tissue (cardiac, skeletal and smooth muscle) and nervous tissue. Protein-containing macromolecules provide these receptor sites. The signal-transmitting substances are also referred to as **ligands**. These ligands may be:
  - Neurotransmitters (e.g. dopamine, noradrenaline and acetylcholine);
  - Hormones (e.g. adrenaline, oxytocin and insulin); or
  - Autacoids (e.g. histamine, serotonin and the prostaglandins).

  Most of our therapeutically useful drugs exert their effects on body physiology by influencing specific sets of ligand receptors. Receptors of a similar type may be grouped together to form **receptor systems** that reflect their ligand-binding capabilities (e.g. the adrenergic and cholinergic receptor systems).

These receptors may be broadly defined as being cellular molecules that interact with ligands and drugs to establish chemical bonds with them. Once bonded, the **ligand-receptor complex** (or **drug-receptor complex**) that has now formed brings about biochemical changes in the target cells and tissues, which then produce the desired biological effects.

Ligand receptors may be classified as being either membrane receptors or intracellular receptors:

- **Membrane receptors:** These receptors are ligand-binding molecular structures that are found on the outer surface of the cell's plasma membrane. In addition, they have effector sites on the internal surface of the membrane as well, and are therefore also referred to as transmembrane receptors.
- **Intracellular receptors:** Intracellular receptors act as primary target areas for steroids (e.g. steroid hormones, such as androgens, oestrogens and corticosteroids) and the metabolites of vitamin D (a secosteroid). These receptors may be **cytoplasmic** or **nuclear** (i.e. situated inside the nucleus of the cell) receptors. Refer to paragraph 3.7.

- **Enzyme receptors:** Some drugs interact with enzyme receptors as their targets and consequently **inhibit** the normal physiological functions of the enzymes in question. These drugs act as either **competitive inhibitors** (meaning that they compete with the actual enzyme substrates), or **non-competitive inhibitors** (meaning that they change the conformation of these enzymes). Refer to paragraph 3.8.
- **Transport carrier receptors:** Transport proteins (carriers) are involved in the facilitated diffusion and active transport of ions and neurotransmitters (amongst other things) across plasma membranes. Drugs that bind to these carrier proteins will inhibit the proteins' normal functioning by competing with the endogenous **substrates** that are supposed to be transported by the carriers in question. Refer to paragraph 2.2.1.

Some drugs may bind to plasma and tissue proteins, making them pharmacologically inactive in their bonded state. From a pharmacological viewpoint these proteins do not constitute actual drug targets, but rather influence the **distribution** of the drugs in question. Refer to chapter 2.

## 1.7 Structurally specific and non-specific drugs

A drug's chemical structure determines its site of action and the way in which it will influence body physiology.

The ligand receptors that constitute a specific receptor system are three-dimensionally structured in such a way as to allow only specific signal-transmitting

substances (or drugs) to bind to them. The adrenergic receptor system, for example, allows the binding of adrenaline (A) and noradrenaline (NA), whereas the cholinergic receptor system binds acetylcholine (ACh) and nicotine (N).

Therefore, it is generally accepted that drugs that bind to receptors also have specific three-dimensional structures that afford them binding sites on the three-dimensional structures of certain receptors (within specific receptor systems) only. These drugs constitute the class of **structurally specific drugs**, which means that:

- They are therapeutically effective (i.e. are of therapeutic value in the treatment of disease) at relatively small dosages.
- Drugs that act on the same receptor system will exhibit structural similarities.
- Changing their chemical structure will have a major influence on their biological activity at the specific receptor sites.
- Their primary sites of action (target areas) are the specific receptors that are three-dimensionally structured and suitably orientated to bind to (i.e. to form chemical bonds with). Less potent drugs belonging to this class, however, are likely to have more unwanted effects than the more potent ones, since they usually require larger dosages, and therefore also interact with sites other than the primary ones.

The alternative class of drugs is that of the **structurally non-specific ones**. These drugs do not share similarities in their chemical structure, but do have similar therapeutic (or biological) effects, which means that:

- Changes in their chemical structure tend to have very little effect on their pharmacological action.
- They require relatively large dosages to produce their clinical effects.
- Traditionally they were characterised as agents that chemically alter cell membranes, which were believed to be their primary targets. This mechanism is attributable to their high **lipid-solubility**, which enables them to dissolve in the lipid phase of the plasma membrane, accumulating within it, and therefore effectively altering its normal functioning.

  *Ethanol* and the volatile general anaesthetic agents, such as *sevoflurane*, and anaesthetic gases, like ***nitrous oxide*** for example, belong to this class of drugs. By altering the plasma membranes of neurones, they can achieve central nervous system depression and even anaesthesia. However, more recent evidence suggests that drug-receptor interactions at ligand-gated ion channels are at least partly responsible for their therapeutic effects (refer to paragraph 5.1.7).

It should also be mentioned that there are a few exceptions of drugs or drug groups that do not act through drug-receptor interaction, or through any other

form of drug-protein receptor binding and that these drugs bring about their therapeutic effects in other, diverse ways. Some commonly encountered examples include the antacids used to neutralise stomach acid, **chelating agents** used to treat heavy metal poisoning (e.g. *dimercaprol* that forms chelating complexes with mercury, gold and arsenic), the osmotic diuretic, *mannitol*, and *mesna*, which binds to the reactive urotoxic metabolites (that cause haemorrhagic cystitis) of two antineoplastic (anticancer) agents, namely *cyclophosphamide* and *ifosfamide*.

## 1.8 Drug interactions and contraindications

Contraindications make it inadvisable to use certain drugs under specified circumstances where their use may be detrimental or counteract the treatment goals in a given situation.

Sometimes when specific drugs are used concomitantly or during the same treatment period, one drug may influence another's pharmacodynamic or pharmacokinetic profile. Drugs may also interact with other substances such as foodstuffs or liquor. Parenteral drug preparations are also best not mixed in the same syringe or infusion bag or bottle. Where a drug is to be diluted for intravenous injection, the recommendations of the manufacturer need to be followed. Normal saline solution, however, is generally considered to be safe and effective, though this is **not** always the case.

In pharmacology, **contraindications** are special circumstances, symptoms or diseases that make it inadvisable to use a specific drug in a given situation. Contraindications may be **absolute** or **relative**.

## 1.9 Accessing drug information

It is essential that health professionals know how and where to access information on specific drugs or medicines, and how to interpret and utilise the information to ensure safe, responsible and accountable healthcare practice, as well as maximal pharmacotherapeutic benefit to the patients in their care.

Upon successful completion of a new drug's clinical development programme (refer to paragraph 1.10) an application to register or license the new product or medicine (also referred to as a **marketing authorisation**) is made with the regulatory authorities in the countries and territories where the new medicine will be promoted and sold. Data, derived from the development programme, need to be submitted on every aspect relating to the new drug's mechanism of action, pharmacokinetic profile, safety, efficacy and tolerability, manufacturing process, pharmaceutical profile, quality standards and product specifications, stability data, packaging and labelling. Phase III clinical development plays a pivotal role in the finalisation of the product label

(i.e. the full prescribing information) for a new drug or medicine. Therefore, Phase III studies that are submitted as part of the licensing application are referred to a 'pivotal trials'.

The applicant (i.e. the company applying for the licence, which usually, but not necessarily, implies the company who discovered and developed the new drug, and who will be manufacturing, marketing and selling it) has to satisfy all of the regulatory requirements for the registration of a **marketing authorisation**. Therefore, once the new drug or product receives its required registration certificate, licence or marketing authorisation, its full prescribing information, contained in the approved **package insert** and supplemented by a **patient information leaflet**, will be available to healthcare professionals and consumers for their perusal. Certain specifications also apply to the actual packaging used to contain the approved product.

Package inserts and patient information leaflets have to contain all of the information regarded as essential and applicable to the registration status of a specific drug or medicinal product by the relevant regulatory authority. Information that may be found in an approved package insert and its accompanying patient information leaflet can be used to answer the following questions relating to the medicine's use in clinical practice:

- **What type of product is it and how does it work?**
  - Consider the **pharmacological classification** and description of the drug's **mechanism of action** and relevant pharmacodynamic properties.
  - Information on the **composition** of the product or medicine will include all of the active pharmaceutical ingredients (i.e. the drug, or drugs that make up the product in the case of a fixed-dose combination), as well as all of the excipients (i.e. the inactive ingredients used in the pharmaceutical formulation) required by the regulatory authority. The active ingredients (i.e. the actual drugs) are identified by their generic or non-proprietary names for ease of reference.
- **What is or can this product be used for?**
  - It is of vital importance that the **approved indications** are carefully considered.
  - For each of the listed indications scientific evidence of the drug, medicine or product's efficacy and safety would have been provided to the regulatory authority. Products may only be marketed and sold in accordance with their approved label, i.e. those indications that emerged from a comprehensive development plan and subsequently passed the scrutiny of the regulatory authorities.
  - It does, however, happen that drugs are sometimes used for other reasons or indications than those that have already been approved. In these situations the drug or product concerned is being used **off-label**,

which needs to be in the patient's best interest at all times, and should preferably be evidence-based (i.e. backed by scientific evidence or proof).

- **What will the body do to the drug(s)?**
  - Consider all of the relevant biopharmaceutical and pharmacokinetic properties of the drug or drug-combination that are described in relation to the kinetic processes, as well as important pharmacokinetic parameters, where applicable. These may include aspects such as the bioavailability, elimination half-life, hepatic or renal clearance, information on active drug metabolites, etc.
- **How safe and effective is the product?**
  - At the recommended dosage a drug's efficacy or therapeutic benefit should outweigh its possible risks or detrimental effects. However, certain adverse drug reactions (or side-effects) may be life-threatening and even fatal, albeit rare. Many factors contribute towards a drug's risk-to-benefit ratio, including aspects such as age, gender, pregnancy and lactation, concomitant medication and other treatments, as well as co-morbid (i.e. coexisting) and intercurrent (occurring during the course of the illness already being treated) illnesses.
  - In the light of the abovementioned statement, careful consideration needs to be given to the following important aspects of the package insert:

    **Boxed warnings** are of significant importance and will be found as bold-type text enclosed in a text box, if and when required by the regulatory authorities. Read these warnings very carefully since they could have a significant impact on the risk-to-benefit ratio for specific patients in given situations.

    **Contraindications** may be absolute or relative and need to be considered against the background of the patient's health status and risk assessment, since **relative contraindications** only apply in certain patient populations or in the presence of specific risk factors. Relative contraindications are listed or described under warnings. **Absolute contraindications**, however, will prohibit the use of a specific drug, medicine or product, if and when they are present. This includes known hypersensitivity to any of the ingredients contained in the product. Certain drugs may also be contraindicated for use together with the specific product due to the likelihood of serious, dangerous or life-threatening drug interactions that could occur. Furthermore, the product or medicine may be contraindicated during pregnancy and lactation if appropriate.

    **Warnings** (including relative contraindications), **adverse reactions** (side-effects), **special precautions**, **drug interactions** and the use of the specific product in **special patient** populations, which could

include pregnant or breastfeeding mothers, infants and children, the elderly, patients with hepatic or renal impairment, gender and race (if applicable), the smoking habit, implications for fertility and women of childbearing potential, and porphyria. Clinically significant interactions may also be listed for certain foodstuffs and beverages (e.g. grapefruit juice), as well as certain herbal remedies (e.g. St John's wort). A description of the effects of the product or medicine on the patient's ability to drive a motor vehicle or to operate machinery may be required by the regulatory authority. Also consider any statements on specific circumstances or instances for which safety and efficacy of the product have not been established.

- **How should the drug be administered to the patient, what dosage should the patient receive and how often?**
  - The package insert will provide clear instructions on any special preparations that need to be made before administering the product to a patient, such as reconstitution, as well as the route of administration for each individual dosage form, the recommended dosage for each of the approved indications, dosing intervals and the recommended duration of treatment.
  - Aspects such as dosing adjustments for specific patients or clinical conditions, as well as dosing adjustments for specific age groups may be included. Information on maximum recommended dosages, correct usage, taking of the product or medicine in relation to meals, dose **titration**, dose tapering, and monitoring of the patient's reaction to the treatment may be included as needed, or as required by the regulatory authority.
- **Other useful information:**
  - Regulatory authorities have different ways of limiting consumer access to medicinal products, which may be based on their potential to be abused or the perceived dangers involved in using them without the guidance and supervision of a qualified healthcare professional who is authorised to prescribe such medication. A clear distinction is made between over-the-counter (OTC) medicines and prescription-only medicines. The package insert will, therefore, reflect the status of the product in relation to the abovementioned explanation. In South Africa, for example, the package insert will reflect the product's **scheduling status** in accordance with the applicable legislation.
  - The information on a **drug overdose**, whether accidental or intentional, contained in the package insert is aimed at describing the clinical manifestations and possible complications of an overdose, as well as recommendations on how such an overdose should be managed.

Management may include the administration of a known antidote if applicable, interventions aimed at limiting the patient's exposure to the active ingredient(s), careful monitoring of the patient's condition and the use of standard symptomatic and supportive treatment.

- The package insert will also contain information on how the product may be identified, its packaging and presentation, the relevant storage instructions and guidance on how the product should be handled.
- Information aimed directly at the consumer is contained in the patient information leaflet.

Other sources of drug information include pharmacopoeias, medicine formularies, essential drugs lists and treatment guidelines, pharmacology textbooks, peer-reviewed research papers, investigator drug brochures and the Internet. When utilising the latter it is vital that websites are carefully selected and scrutinised for content and credibility. A few suggestions are listed in note 1.3.

**Note 1.3 Where to find drug information on the Internet**

The following sites are recommended, but this list is by no means exhaustive. Reputable search engines may also be employed to access some more of the vast resources available on the Internet today.

- Medicines and Healthcare products Regulatory Agency (MHRA): http://www.mhra.gov.uk
- United States Food and Drug Administration (FDA): http://www.fda.gov
- Drug Information Online: http://www.drugs.com
- RxList: The Internet Drug Index: http://www.rxlist.com

The official websites of the world's leading pharmaceutical and biotechnology companies also contain information on the products that they develop, manufacture, promote and sell.

## 1.10 The development of new drugs

Stringent regulations, international guidelines and ethical codes govern the way in which new drugs are being developed and brought to market. The drug development process ensures that new drugs are safe and effective, manufactured according to the highest standards and marketed in a responsible and scientifically sound manner.

The new drug development process is a complex and highly regulated one with many role-players, significant resources, scientific research processes, complex and interlinked stages of development and enormous financial investment that

need to be carefully managed to discover, design, test, develop and register a new drug for the global market.

Strictly speaking there is a clear distinction between drug discovery and drug development, although many authors use the concept of 'new drug development' to include both of these major stages. The **drug discovery stage** encompasses the highly evolved chemistry and biotechnological techniques used in the pharmaceutical industry today. These complex techniques, related processes and procedures, however, do not fall within the scope of this text. On the other hand many aspects of the **drug development stage** have a direct impact on clinical practice and warrant a more detailed explanation.

During the testing and development of new drugs, the safety, tolerability, efficacy (effectiveness) and usefulness of the drug in question must be determined in the following way:

- **Pre-clinical testing** (laboratory and animal testing) is used to determine the basic pharmacodynamic and pharmacokinetic properties of the drug and to detect acute, sub-acute and chronic toxicity. The aim is to detect any **toxic effects** that the drug may have on cells, tissues and organs, and also any **carcinogenic** (cancer-inducing), **mutagenic** (causing mutant genes) and **teratogenic** (leading to recognisable birth defects) effects. Pre-clinical testing also assists scientists in establishing the drug's therapeutic **index** (i.e. the difference between the minimum plasma concentration at which the drug is effective and the minimum plasma concentration at which the drug becomes toxic).
- Subsequently, **clinical trials** (tests on human subjects) must establish whether cumbersome side-effects (which animals are incapable of complaining about) occur, what the ideal dosing schedule should be and how effective the new drug is, compared to existing drug treatments, or in some instances to a **placebo** ('dummy' treatment). Clinical **trials** entail the testing of drugs on human subjects, where medical supervision is essential to conducting safe and ethical research.

Drug metabolism differs significantly between animals and humans. Therefore, kinetic and dynamic principles, and the toxicity profile of a drug are also investigated further during clinical trials. These trials are conducted in four phases:

- During **Phase I** the drug is tested on a small number of healthy individuals, usually fewer than 100 healthy volunteers. These are so-called first-in-human studies. In the case of antiretroviral agents and the antineoplastic drugs used to treat cancer, for example, the healthy volunteers are substituted with patients suffering from the specific condition. Human pharmacological profiling, safety and tolerability, with the possible inclusion of early efficacy

measurements, form the basis of Phase I development, which is carried out under highly controlled circumstances in specialised clinical research units.

A more recent development was the introduction of the so-called **Phase 0** study as a bridging strategy between the drug discovery stage and the drug development stage. It is aimed at limiting human exposure to drugs that may not be effective and therefore may not warrant further development (which then also carries a huge cost-saving benefit). During a Phase 0 study a very limited number of patients are exposed to a really small, sub-therapeutic dosage of the drug, for a limited period of time. This is referred to as **micro-dosing** and awards researchers the benefit of beginning with human pharmacological profiling of the drug early on (before Phase I commences), but with very limited exposure of the study participants to possible risks involved, as well as to make more informed decisions about future development strategies for the new compound at an exceedingly early stage in the development process.

- **Phase II** introduces the drug to a selected number of diseased patients, suffering from the actual condition that the drug is meant to treat (i.e. exploring the therapeutic benefits in targeted patients), usually a few hundred subjects. Efficacy now starts to form an important part of the study focus, together with safety, as well as the establishment of an optimal dosing regimen. For a number of practical reasons this phase may be subdivided into Phase IIa and Phase IIb.
- Extensive trials, on a much larger scale and usually involving several hundred to several thousand subjects, are conducted during **Phase III**. The major focus during this phase of the drug's clinical development is to establish and confirm its efficacy and therapeutic benefit. These trials are conducted over longer periods of time, utilising a broader range of defined patient populations and may include combination therapy with one or more existing drug treatments. It may also be necessary for the development programme to be continued once an application has been made for marketing authorisation, or for so-called peri-approval studies to be conducted. For this purpose **Phase IIIb** studies are utilised and are considered to be an extension of the Phase III development programme.
- Once marketing of the drug has begun, **Phase IV**, or post-marketing surveillance, commences, and side-effects, additional indications, efficacy and tolerability may be investigated to the full. Data derived from these studies are gathered from the so-called real-world utilisation of the drug in day-to-day clinical practice.

Clinical trials must be carefully planned, well designed and properly controlled. Therefore, the **randomised controlled trial** (RCT) is most often used, especially during the later stages of the drug's clinical development. A single RCT is,

however, usually inadequate for determining the new drug's performance in comparison with standard treatments or placebo. This is because of limited resources and the small number of patients that are usually available for inclusion in a single trial. By combining the results of different randomised trails, which comply with set criteria as to the control, validity and reliability of each one, into one single overview of all available data (i.e. employing a **meta-analysis** of the research findings), this problem may be overcome.

Another recent advance in the drug development process, which challenges the traditional way of conducting RCTs, is the introduction of the concept of **adaptive clinical trials** that will help to shape the way in which clinical trials are designed, conducted and analysed into the future. One example that is already being used entails combining a Phase II and a Phase III trial into one 'seamless' adaptive clinical trial.

The various role-players within the pharmaceutical industry, who are responsible for or involved in new drug development include:

- The pharmaceutical, biotechnology and biopharmaceutical companies who research and develop new drugs and medicines, pioneer groundbreaking new therapies and endeavour to address unmet medical needs. It is currently being estimated that the development of a single new drug could take as long as 10 to 15 years to complete and cost as much as US$ 1.0 billion or more. These drug companies usually have dedicated research and development staff and facilities, but may also collaborate with government organisations, academic institutions, other companies and various service providers to discover, develop, manufacture and promote new medicines.
- Clinical research organisations that provide expert drug development services to the pharmaceutical industry and often participate in drug development programmes to varying degrees.
- Clinical investigators and their investigative site staff, which may include sub-investigators, study coordinators, research nurses, pharmacists and other health professionals, who recruit, screen, enrol, treat, monitor and follow up carefully selected subjects (i.e. study participants or study patients) when **approved** clinical trials are conducted.
- Regulatory authorities have legislative oversight on all matters relating to the approval, conduct and inspection of clinical trials, as well as the investigational product (i.e. the study drug or study medication under investigation). Examples of such regulatory authorities include the United States Food and Drug Administration (FDA), the 'competent authorities' of the Member States of the European Union (e.g. the MHRA in the United Kingdom and the BfArM in Germany), ANVISA (Agência Nacional de Vigilância Sanitária) in Brazil, and the South African **Medicines Control Council (MCC)**. These authorities are usually also responsible for the

subsequent registration of new medicines in their respective countries; however, a single application could also be made to the European Medicines Agency (EMEA) for a marketing authorisation in the European Union (EU).

- Central and local research ethics committees and institutional review boards who ensure that properly approved clinical trials are conducted according to local and international ethical standards and guidelines to protect the rights, safety and wellbeing of all subjects participating in such trials. The World Medical Association's Declaration of Helsinki, the **International Conference on Harmonisation (ICH)**, applicable EU Directives and the relevant parts of the FDA Code of Federal Regulations provide such ethical guidance, as well as rules and regulations where applicable.

## 1.11 Applying the principles of toxicology

Drug toxicity is a vital consideration during the clinical development programme and subsequent registration process of any new medicine or medicinal product. The relative margin of safety that exists between a drug's therapeutic and toxic concentrations may act as a determining factor in its eventual success as a pharmacotherapeutic agent in clinical practice. New drugs undergo rigorous toxicology testing to establish and optimise acceptable levels of safety and tolerability.

As defined in paragraph 1.4, toxicology, within the realm of clinical pharmacology and new drug development, is concerned with the toxic (or poisonous) effects of drugs in overdose, as well as the treatment of poisoning and overdose. The science of toxicology, however, studies all aspects that pertain to toxic substances and poisons (also referred to as toxicants), the detection of such poisons, their mechanisms of toxicity, how the body absorbs, distributes, metabolises and excretes poisonous substances, poison antidotes, the treatment of poisoning and all forensic and medico-legal aspects related thereto.

Therefore, drugs may also be viewed from a toxicological perspective as having **toxicodynamics** and **toxicokinetics**, as compared to pharmacodynamics and pharmacokinetics. The same determining factors and principles will, however, apply. Toxicology is also very concerned with the dose–response relationship in terms of toxic effects in the same way that the pharmacologist is concerned about dose–response relationships in terms of therapeutic effects. An explanation of possible toxic effects associated with drug therapy, as well as the significance of the dose–response relationship, or dosage-dependent toxicity is given in paragraph 1.5.2 and figure 2.5.

CHAPTER TWO

# Pharmacokinetic principles

The concept of pharmacokinetics was introduced in chapter 1.

Pharmacokinetics studies the way in which the processes of absorption, distribution, metabolism (or biotransformation) and excretion determine the movement and fate of drug molecules inside the living body.

Absorption is the first of the kinetic processes. For the absorption of drug molecules to take place, the drug first needs to be delivered or introduced to the body (i.e. administered to the patient).

## 2.1 The routes of drug administration

Drugs are usually either administered **systemically** or applied **topically**. Various routes may be used for the systemic administration or delivery of drugs to the body, the most convenient and acceptable of these being the **oral route**.

The **topical** delivery of drugs is their application to specific body surface areas, where they exert **localised** effects. A cream or lotion may, for instance, be applied to the skin, or an ophthalmic preparation instilled into the eye. These drugs **do not** require absorption into the systemic blood circulation to be effective.

**Systemic** drugs, however, need to be administered in such a way as to allow them to be absorbed into the **systemic blood circulation**. This will provide them with an effective 'carrier' that will transport their molecules to target areas around the body. Some drugs, however, do not require such transport, since they may be administered directly into their target areas. The bronchodilator ***salbutamol***, for example, may be inhaled directly into the lower respiratory tract. The mucous membranes of the airway will also allow for the absorption of the drug into the pulmonary circulation, but its primary site of action is the bronchial smooth muscle itself.

Many different routes of drug administration are used in clinical practice. The various routes all have their indications, advantages and disadvantages. Special circumstances and unique situations determine which route is the most suitable for a certain patient at a given time. Drugs themselves may also determine the route to be used. *Warfarin*, for example, can only be administered orally, while *heparin* can only be injected parenterally. Note 2.1 lists the routes of drug administration most often encountered in clinical practice. Also refer to chapter 13 for information on drug administration in clinical nursing practice.

**Note 2.1 Routes of drug administration**

Aural (into the ear)
Buccal (applied to the inside of the cheek, between cheek and gums)
Intra-arterial (into an artery)
Intra-articular (into a joint space)
Intracutaneous (intradermal, into the skin)
Inhalation (into the lower airway)
Intramuscular (injection into skeletal muscle tissue)
Intrathecal (into the spinal canal)
Intravenous (into a vein)
Nasal (into the nose/nasal passages)
Ocular (into the eye)
Oral (per mouth)
Per rectum (into the rectum)
Per vagina (into the vagina)
Subcutaneous (hypodermic, just beneath the skin)
Sublingual (placed under the tongue)
Topical (applied to surface areas, e.g. the skin or the surface of a wound)
Transdermal (applied to the skin for systemic absorption through it)

Other areas into which drugs may be injected include the vitreous humour of the eye (i.e. intravitreal injection), cutaneous and subcutaneous lesions, nerve tissue and the left ventricle of the heart (**intracardiac** injection). The last-named, previously reserved for the emergency cardiac resuscitation drug ***adrenaline***, is no longer considered to be an acceptable, safe and effective route for drug delivery into the systemic circulation.

During **epidural anaesthesia** the local anaesthetic agent is injected into the epidural space (a potential space that allows for injection of the drug **onto** the dura mater).

**Absorption** refers to the passage of drug molecules from various mucous membranes, skin or subcutaneous tissue into the bloodstream. **Distribution** refers to the transport of these molecules, via the systemic circulation, to the various fluid compartments, tissues and organ systems of the body that constitute their sites of action. Finally, drug action has to be terminated through the **biotransformation** (metabolism) of the drug and the eventual **excretion** of its metabolites from the body.

For these kinetic processes to take place, drug molecules must be able to cross biological barriers (i.e. the plasma membranes of cells, the endothelia of capillary walls, the mucous membranes, etc.). In paragraph 2.2 the ability of drug molecules to actually cross these membranes is discussed in more detail.

### 2.1.1 Oral route (per mouth, *per os*, PO)

The kinetic process of absorption is best introduced by using the oral route of administration as an example. The oral route is generally considered to be the most convenient and acceptable way of administering medication, since swallowing is the natural way of ingesting food and drink. Most laypersons also do not require the assistance of a healthcare professional when taking medicines per mouth (whereas they may need assistance with injections, for example).

Once the drug has been ingested, a number of processes and events determine the actual absorption of the drug molecules into the bloodstream:

- Oral drug formulations (oral dosage forms) are designed to allow the active drug to **dissolve** in the lumen of the gastrointestinal tract (GIT). Most of these dosage forms will dissolve inside the stomach, unless they have been specifically formulated to disintegrate and dissolve further down in the alimentary canal. Enteric-coated tablets, for example, are designed to dissolve in the alkaline environment of the small intestine instead of the acidic environment of the stomach itself. Liquid dosage forms are the best-absorbed oral formulations.
- The stomach cannot be regarded as an absorption organ but may allow some of the dissolved drug molecules to **enter into the bloodstream**. The small intestine, however, with its vast absorptive surface, is the primary site of the absorption of drugs that have been orally administered.
- From the stomach and small intestine, drug molecules therefore have to cross a series of biological membranes and barriers to reach the **hepatic portal circulation**.
- Blood entering the portal circulation then moves through the portal vein, liver, inferior vena cava, right side of the heart, pulmonary circulation and left side of the heart before finally entering the **systemic circulation**, from where the absorbed drug molecules will be distributed to other parts of the body.

Movement of drug molecules from their absorption site in the GIT through the hepatic portal circulation is referred to as their '**first pass**' through the liver. This first pass produces the so-called **first-pass effect**, or pre-systemic elimination of certain drugs (refer to paragraph 2.2.3 and figure 2.2). Figure 2.1 gives a diagrammatic representation of the relationship between the hepatic portal circulation and drug absorption.

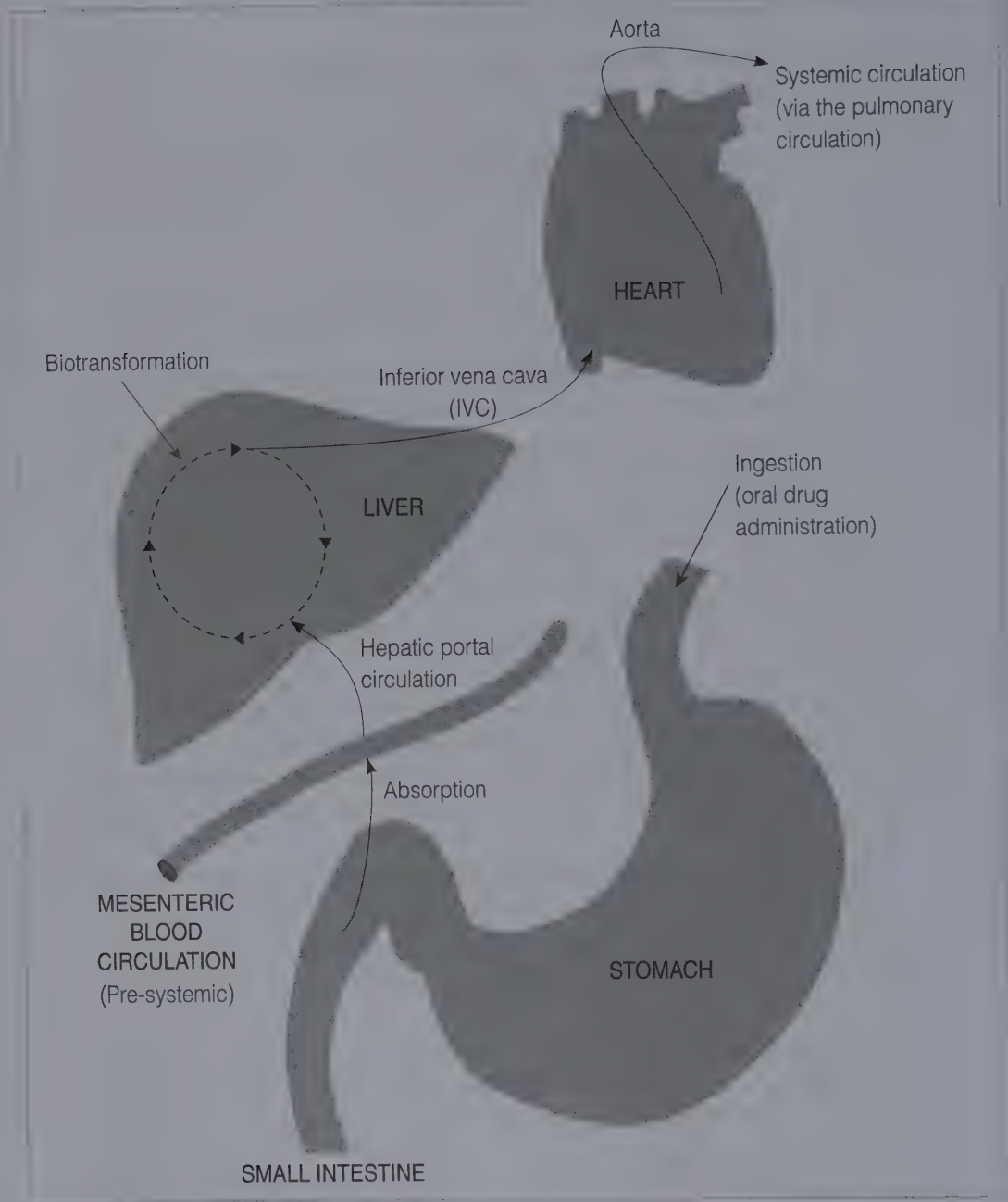



**Figure 2.1 The pathway of drug absorption from the gastrointestinal tract to the systemic blood circulation**

Under normal circumstances gastric emptying will take up to four hours, and transit time through the small intestine will take another six hours to complete. Absorption is explained in more detail in paragraph 2.2.

### 2.1.2 Rectal route (*per rectum*, PR)

Indications for using this relatively unpopular and uncomfortable route of administration include unconsciousness, nausea and vomiting, febrile (feverish) and convulsive states and other situations where the danger of aspiration exists, or where oral administration is undesirable due to gastric irritation, dysphagia and other clinical problems. The active drug is formulated into a rectal suppository, or may be available as a rectal enema.

The absorptive surface of the rectum is small, due to the absence of intestinal villi, which explains the slowed rate of rectal absorption. Anatomically, venous blood from the distal portion of the rectum is drained by the inferior and middle rectal veins, while blood from the proximal rectum drains into the hepatic portal system via the superior rectal vein. The inferior and middle rectal veins, however, directly enter the inferior vena cava via the hypogastric vein, effectively bypassing the hepatic portal system. The existence of a rich anastomosis between the three rectal veins, producing an important area of **portacaval anastomosis** (since the hepatic portal circulation may be significantly bypassed), is of clinical significance. Refer to figure 2.2.

***Diazepam*** and ***metronidazole*** are particularly well absorbed from the rectal mucosa. Many antipyretics, anti-inflammatory drugs, anti-emetics and anti-convulsive drugs, and also the non-selective bronchodilator *aminophylline*, are available as rectal suppository formulations. Suppositories should be carefully inserted into the distal rectum, just above the internal anal sphincter and the anorectal ring.

### 2.1.3 Buccal and sublingual (SL) routes

The mucous membranes of the oral cavity have a very rich blood supply, therefore providing a highly vascular absorptive surface. Lipid-soluble drugs may be rapidly absorbed directly into the systemic circulation, since venous return to the heart is provided via the superior vena cava, thus **bypassing** the hepatic portal circulation (see figure 2.2).

Buccal administration implies spraying or placing the drug formulation between the cheek and gums. For sublingual drug administration, the formulation is placed under the tongue. Drugs administered via these routes need to be soluble in saliva and should be active in very small concentrations.

The sublingual route is popularly used for the administration of *glyceryl trinitrate* during attacks of angina pectoris or in the event of acute myocardial infarction. Certain tablets may also be allowed to dissolve sublingually after they have been chewed.

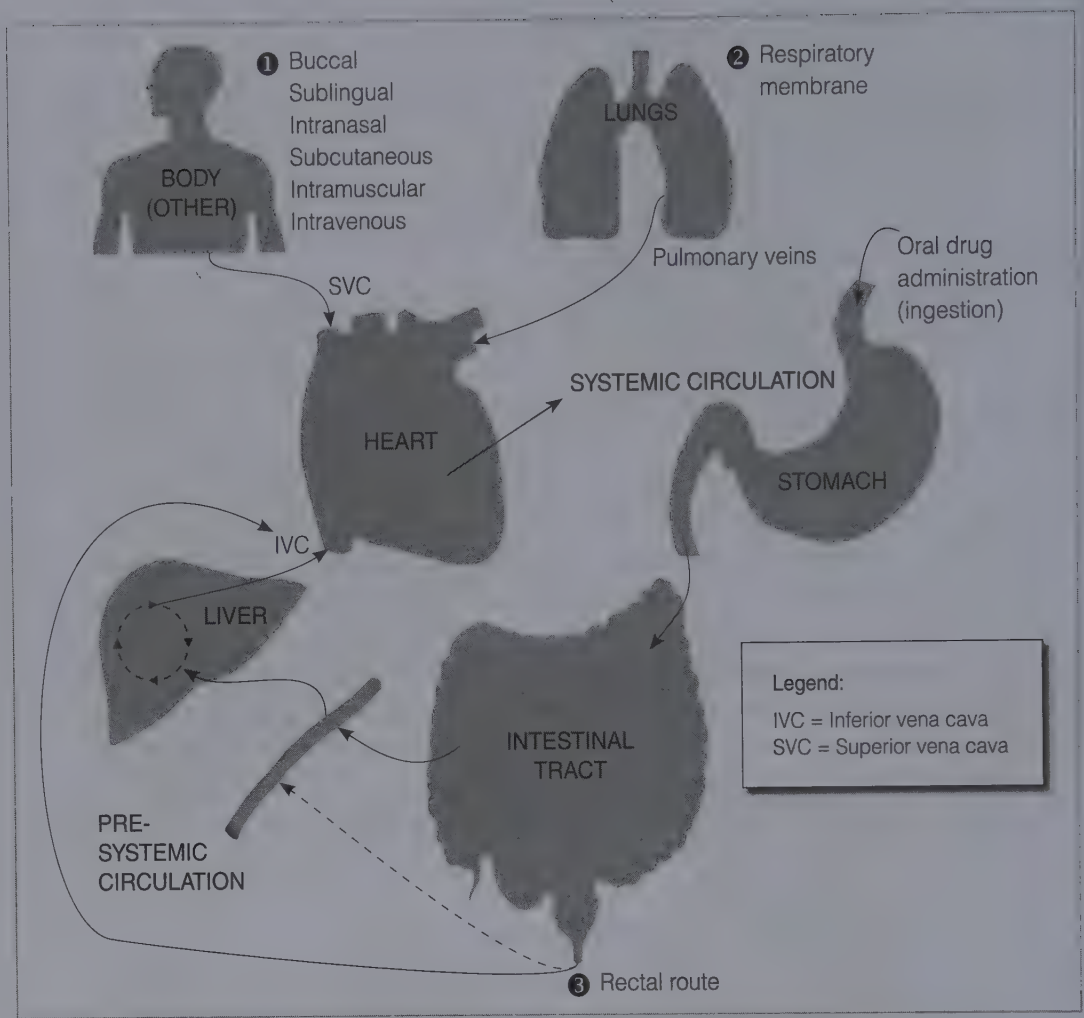



**Figure 2.2 Routes of drug administration that bypass the 'first-pass' effect (i.e. hepatic first-pass metabolism)**

### 2.1.4 Other mucous membranes used to absorb drugs

The other mucous membranes that may be used to absorb drug molecules are those of the lungs and nasal cavity:

- **The nasal mucosa:** Nasal mucous membranes are relatively inefficient as absorptive surfaces for drug molecules, since large percentages of the applied dosages often go to waste. The nasal mucous membrane, however, provides an effective and convenient route of administration for small **peptide** molecules such as *desmopressin* (a synthetic analogue of *vasopressin* (i.e. antidiuretic hormone) used in the treatment of diabetes insipidus). Nasal preparations, used for their localised effects in allergic rhinitis and

sinusitis, are also sprayed into the nasal passages via the nostrils (also refer to figure 2.2).

- **Pulmonary mucosa:** The respiratory membrane (the combined alveolar and capillary membranes) measures approximately 0.5 µm in thickness, making it almost 100 times thinner than the skin. Per minute, the pulmonary circulation receives cardiac output equivalent to the entire output received by the rest of the body. In total surface area, the alveolar surface of the lungs – in the region of 160 to 200 $m^2$ – is comparable to that of the small intestine. The respiratory membrane forms the functional **air-blood barrier** between the pulmonary circulation and the atmospheric air that enters and exits the respiratory units of the lungs. The respiratory gases ($O_2$ and $CO_2$) diffuse through this barrier.

  The combination of the thin respiratory membrane, the vast alveolar surface area and the good pulmonary blood supply makes the pulmonary mucous membranes exceptionally good absorptive surfaces. The emergency cardiac resuscitation drugs ***adrenaline***, ***atropine*** and ***lignocaine*** may therefore be administered via endotracheal tubes, utilising the massive alveolar surface area for absorption into the systemic circulation. Drugs that act on the lung tissue itself may also be administered directly into their site of action. In premature infants *surfactant* is administered via the same route. For optimum utilisation of this route of administration the drug particles need to be small enough to remain suspended as they pass through the lower airway (also refer to figure 2.2).

### 2.1.5 Injectable drugs

There are various routes for injecting drugs into the body:

- **Intravenous injection (IV):** Injecting drugs into the peripheral veins of the upper extremities, or through central venous catheters that provide direct entry into the pulmonary and systemic circulation via the superior vena cava, obviates the need for drug absorption altogether. It is very useful for drugs that have short elimination half-lives (refer to paragraph 2.7.1) and those that require very careful **titration** of their dosages, therefore necessitating continuous intravenous infusions. This route also provides the best possible control over the dosage being administered to the patient. When tissue absorption is compromised in any way (e.g. in burn trauma victims, hypovolaemic patients and patients in severe cardiac failure), or when a patient's condition necessitates an immediate response, this route of administration is extremely useful. It takes less than a minute (as little as 20 seconds when cardiac functioning is optimal) for the administered dosage to mix sufficiently with the circulating blood volume (also refer to figure 2.2).

- **Intramuscular (IM)** and **subcutaneous injection (SC):** These routes utilise blood supply to subcutaneous adipose and skeletal muscle tissue for the absorption of drug molecules. Because skeletal muscle tissue receives more blood supply than subcutaneous fat does, absorption via the intramuscular route is more rapid than absorption after subcutaneous injection. Depot formulations may be injected into muscle to extend the **duration** of the active drug's action over hours, days or weeks. Severe vasoconstriction or hypoperfusion will delay the absorption of drug molecules from these tissues.
- **Intradermal (intracutaneous) injection:** The injected volume must be very small (less that 0.2 ml) and is administered **into** the skin.
- **Intra-articular injection:** Joint spaces may be injected with drugs for a localised effect in arthritic conditions.
- **Intra-arterial injection:** When the localised effect of a drug is wanted in a specific organ only, injecting the drug into the arterial blood supply may be opted for. Carcinomas are sometimes treated in this manner by injecting the oncostatic drug into the appropriate arterial blood supply.
- **Intrathecal injection:** Drugs may be injected directly into the subarachnoid space to bypass the **blood-brain barrier** (the specialised barrier that separates the brain's extracellular fluid and cerebrospinal fluid compartments from the intra-vascular compartment).

### 2.1.6 Transdermal route

This route entails the drug being applied to the skin for absorption into the circulation. A transdermal patch is usually applied behind the pinna of the ear or in a comfortable position on the trunk. Note that the postauricular (behind the ear) skin is much more permeable (up to ten times as much) than that of the thigh or trunk.

### 2.1.7 Topical administration of drugs

Drugs may be applied to body surfaces to exert **localised effects** on the areas of application only. Aural preparations may be administered into the external auditory canal of the ear, or ocular preparations instilled into the eye. Other examples include preparations for application to the skin (e.g. creams and lotions for sunburn), or for the nose (e.g. vasoconstrictors for rhinitis), the mouth (e.g. an antiseptic mouthwash for stomatitis), the throat (e.g. lozenges that contain local anaesthetic agents to alleviate a sore throat) or the vagina (e.g. antifungal preparations for vaginal thrush); or for anorectal application (e.g. haemorrhoid preparations).

## 2.2 Absorption

Drug molecules move into the bloodstream from their site of administration through the kinetic process of absorption. However, the intravenous route of administration obviates the need for drug absorption.

Drug absorption is the movement of drug molecules from their site of administration into the bloodstream. These sites, or routes, of administration are the ones that allow actual systemic administration of the active drug, i.e. the transdermal, enteric, intramuscular and subcutaneous routes, and also the pulmonary mucosa. (The intravenous route is not included here, since it does not require the process of absorption to take place, because drugs are injected directly into the bloodstream.) Also refer to figure 2.2.

Absorption entails entry of the drug molecules into the vascular compartment, meaning that a number of biological barriers or membranes need to be crossed, i.e. mucosal layers, capillary endothelia, or more specialised physiological barriers. Thus, the more readily the drug molecules cross these membranes or barriers, the better the drug is absorbed.

### 2.2.1 The plasma membranes of cells and how drugs cross them

Dynamic, flexible and thin membranes that separate their internal and external environments envelop cells and their intracellular organelles. Plasma membranes provide barriers between the intracellular and extracellular fluid compartments of tissue cells. The **selective permeability** of the membrane allows for the differences in composition of the intracellular and extracellular fluid. Sodium ions ($Na^+$), for example, are found in much higher concentrations in the extracellular fluid (ECF) than in the intracellular fluid (ICF). The opposite is true of potassium ions ($K^+$).

The plasma membrane is composed of two layers of phospholipid molecules, interspersed with cholesterol molecules and globular membrane proteins. Carbohydrate molecules protrude outward from the membrane surface. This bimolecular layer (i.e. two layers of molecules) is a mere 10 nm thick.

Phospholipid molecules have a characteristic 'head' and 'double tail' configuration. A **polar**, hydrophilic (water-soluble) phosphate group forms part of the head, while the double tail is made up of two non-polar, hydrophobic (lipid-soluble) fatty acid chains. The two layers of phospholipid molecules, due to their specific **physicochemical characteristics**, are orientated in such a way as to allow for heads to border the two **water phases** (i.e. the ICF and ECF).

This means that the hydrophobic tails are orientated towards one another and constitute the **lipid phase** of the membrane (see figure 2.3).

Membrane proteins fall into one of two groups, namely **integral proteins** or **peripheral proteins**. **Transmembrane proteins** are integral proteins that

span the entire thickness of the membrane. They may be further divided into **carrier proteins** and **channel proteins**. **Peripheral proteins** are found either on the inner or on the outer surface of the membrane. On the inner surface, these proteins are usually attached to integral proteins and are involved in signal transduction and the regulation and control of intracellular functions (see chapter 3).

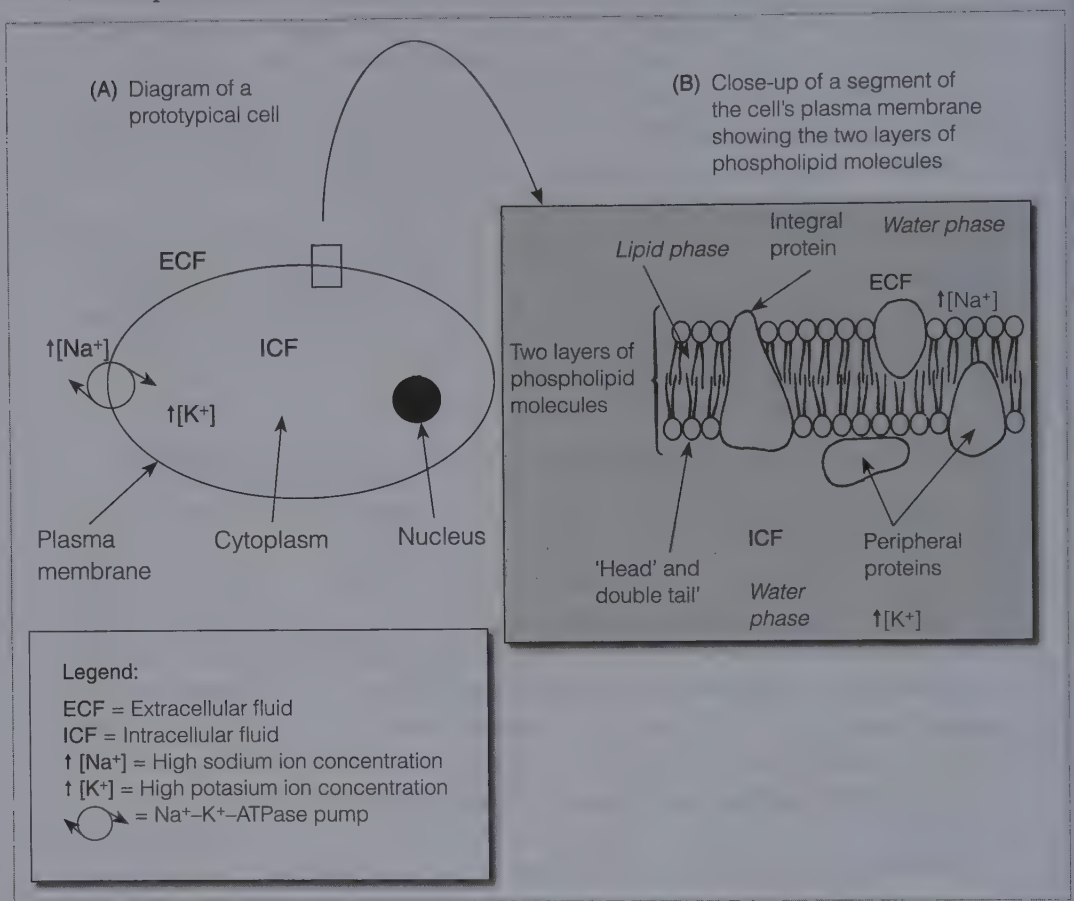



**Figure 2.3 A segment of the plasma membrane of a prototypical cell, showing the arrangement of phospholipid and protein molecules**

Some membrane proteins also act as **catalytic enzymes**. Catalysts increase the rate of chemical reactions without taking part in the actual reaction or being present in any of its products. These enzymes catalyse various cellular reactions.

**Channel proteins** form small aqueous pores or channels in the membrane. These channels serve as passageways for selected polar molecules and ions to cross the membrane. These molecules, however, need to be extremely small (i.e. to have a molecular mass of 100 daltons or less). Channels that allow specific

cations and anions passage across the membrane are called ion channels. These channels may be **gated** (either voltage-gated or ligand-gated) to regulate the ion movement through them. Water molecules also cross the membrane through these channels or pores. **Carrier proteins**, on the other hand, are involved in the active transport of molecules or ions, or in facilitated and exchange diffusion of such particles (also refer to chapter 3).

Carbohydrate molecules on the cell surface may be bound to lipids, to form glycolipids, or to proteins, to form glycoproteins and proteoglycans. Proteins, with their carbohydrate constituents, give the membrane an outwardly negative charge and also provide the unique, three-dimensional receptor sites to which hormones, neurotransmitters and autacoids are able to bind.

The unique characteristics of the plasma membrane explain its selective permeability. Drug molecules, which are foreign to the human body, need to utilise available transport processes to enable them to actually cross these membranes. Ways in which drug molecules may cross the plasma membrane, therefore, include diffusion (which may be passive or facilitated) and active transport:

- **Simple passive diffusion:** This transport process does not require cellular energy since molecules possess inherent kinetic energy that moves them along their concentration gradients from an area of higher concentration to an area of lower concentration. Small, non-polar, lipid-soluble molecules, such as the respiratory gases $O_2$ and $CO_2$, cross the lipid phase with ease by utilising simple, passive, **lipid diffusion**. Gated ion channels allow selected cations and anions to diffuse through them, along their electrochemical gradients. Polar, water-soluble molecules, which are small enough, can therefore readily move through the channels or pores in the membrane by passive diffusion as well, though this is referred to as **aqueous diffusion**. A $CO_2$ molecule has a relative molecular mass of 44 Da, while $H_2O$ has a molecular mass of only 18 Da. For comparison, a glucose molecule has a molecular mass of 180 Da, haemoglobin 68 000 Da and the plasma protein albumin has a molecular mass of 69 000 daltons, or 69 kDa.
- **Facilitated diffusion:** Carriers are involved in moving larger molecules that are incapable of simply diffusing through the lipid phase across the membrane. This process does not require cellular energy.
- **Active transport:** Some molecules require transport across the plasma membrane against their concentration gradients. Energy and carrier proteins are required to achieve this. The $Na^+$-$K^+$-ATPase pump is an excellent example of an active transport process. It utilises adenosine triphosphate (ATP) directly. Adenosine triphosphatase (ATPase) is a membrane-bound enzyme that acts as the carrier. This pump helps to maintain the high intracellular potassium ion concentration and the high extracellular sodium

ion concentration by sequentially moving three sodium ions ($Na^+$) into the ECF for every two potassium ions ($K^+$) that is pumped into the cell.

Carrier proteins exhibit specificity for their particular substrates (the substances that they usually carry) and may actually become saturated. Drugs that utilise transport carriers need to resemble the substrates in question and will compete with the natural substances that they are actually intended to carry. The number of drugs that meet the structural requirements for carrier transport is very limited.

From the abovementioned explanation it is clear that certain physicochemical properties of drug molecules will also determine their ability to cross plasma membranes (or other more specialised biological barriers).

These characteristics are:

- **Lipid-solubility:** Drugs that are more lipid-soluble tend to penetrate plasma membranes more readily. The physicochemical property in question is that of the **lipid-water partition coefficient** of the drug. This expresses the drug's relative solubility in lipids as opposed to water. Drugs with high partition coefficients are referred to as lipid-soluble. Those with a coefficient that is markedly lower than 0.1 are said to be water-soluble. Most lipid-soluble drugs can, however, still readily dissolve in water. Only **un-ionised** molecules are lipid-soluble. Water-soluble drug molecules that are small enough can cross plasma membranes through aqueous diffusion via channels or pores in the membrane. *Ethanol*, for example, has a molecular mass of less than 50 Da.
- **Size of the drug molecules:** Most drugs have very low relative molecular masses (less than 1 500 daltons, with the majority actually having molecular masses of less than 500 Da). Even in the case of lipid-soluble drugs, the higher the molecular mass, the more difficult it will be for the molecules to cross the plasma membrane. Thus, the smaller the size of their molecules, the more readily drugs cross plasma membranes.
- **Ionisation of the drug molecules:** Charged molecules, or highly polar ones, may carry charges that are complementary to the glycoprotein surface of the plasma membrane, making it difficult for them to cross from the extracellular to the intracellular fluid compartment. Molecules that carry similar charges to the ones on the cell's surface may be repelled from it. Molecules that do not carry electrical charges or exhibit polarity are said to be **un-ionised** or **non-polar** molecules. These molecules are able to cross membranes much more readily than the charged ones. *Liquid paraffin*, for example, has large organic molecules that carry hydrophobic groups. Even though it is a highly lipid-soluble substance, it is not absorbed from the

gastrointestinal tract because the hydrophilic groups found on the surfaces of the plasma membranes repel its large hydrophobic molecules.

Intracellular pH (7.0) is lower than the pH of the extracellular fluid (7.35). More hydrogen ions ($H^+$-ions, or protons) are therefore found inside cells. The pH of the surrounding medium determines the extent to which drug molecules within the medium are ionised. Most drugs are weak acids or bases. Acids are proton donors and ionise by giving off hydrogen ions, that is, acids ionise through **dissociation**; $HA = A^- + H^+$. Bases ionise through **association** because they are proton acceptors ($BH^+ = B + H^+$). Drugs will accumulate where they ionise (a phenomenon known as '**ion trapping**'). Acidic drugs, therefore, tend to stay in the extracellular fluid, whereas basic drugs tend to accumulate in the intracellular compartment. The degree of ionisation of a drug's molecules is determined by the pH of the surrounding medium and the $\mathbf{pK_a}$ of the drug (the pH at which half of the drug's molecules are ionised).

Note 2.2 summarises the physicochemical properties necessary for crossing plasma membranes and other biological barriers via the various transport processes that are available to drug molecules.

**Note 2.2 Physicochemical properties that facilitate and promote transport across plasma membranes and other biological barriers**

**In the case of simple, passive diffusion:**
Drugs should preferably have

- small molecules (especially in the case of aqueous diffusion)
- a high degree of lipid-solubility
- molecules that do not carry charges (i.e. un-ionised molecules).

**In the case of facilitated and exchange diffusion and active transport:**
Drugs must

- resemble the original substrates that are usually transported by the carriers involved in these processes
- bind to the actual carrier proteins.

## 2.2.2 Drug absorption

As already mentioned, drug molecules should possess certain physicochemical properties to allow them to **penetrate** or cross biological membranes. However, there are a number of other factors that also determine the rate and extent of drug absorption from various sites of administration:

- **Dissolvability:** Oral administration requires that the drug molecules, whether they are water-soluble or lipid-soluble, first dissolve in water. Drugs that are highly lipid-soluble and are therefore not able to dissolve in water

will not be absorbed from the GIT (e.g. *liquid paraffin*). Drugs that are too water-soluble (like the aminoglycosides) cannot diffuse across the lipid phase of the plasma membrane and will therefore also not be significantly absorbed by the GIT. When drug molecules are transferred from a solid dosage form (e.g. tablets or granules) into solution the process is referred to as **dissolution**. Also note that solid dosage forms need to **disintegrate** before dissolution can take place.

- **Absorptive surface:** The stomach cannot even begin to compare to the small intestine and respiratory membranes in surface area. The larger the surface area available for drug absorption, the better the actual absorption will be (sometimes irrespective of some of the other physicochemical properties). When gastric emptying is slowed due to the presence of food in the stomach, absorption of orally administered drugs will also be delayed. An increase in the transit time through the gut, as is the case with diarrhoea for example, may decrease the absorption of drug molecules due to their more rapid movement past the absorptive surface of the small intestine.
- **Perfusion:** Absorption from any site of administration may be limited whenever the perfusion of the site in question is inadequate. When skin and adipose tissue perfusion is poor due to the presence of circulatory shock, a transdermal skin patch or subcutaneous injection may be found to be very ineffective in delivering a drug systemically. Similarly, the intramuscular administration of drugs in patients who have suffered severe burn trauma is contraindicated because peripheral tissue sites are being poorly perfused. This may cause the injected drugs to accumulate in the skeletal muscle tissue.
- **Special biological barriers:** Drug molecules may find some highly specialised biological barriers very difficult to penetrate. Only drugs with a relatively high degree of lipid-solubility are capable of penetrating the blood–brain barrier (BBB) for example. The thyroid and prostate glands are also notoriously difficult to penetrate with drugs. The placental barrier, on the other hand, is quite ineffective as a barrier in pharmacological terms. So too are the endothelia of capillary and glomerular vessels. Only drugs that are plasma-protein bound (see paragraph 2.3) will have difficulty crossing these membranes.

### 2.2.3 Systemic bioavailability

Only a fraction of a drug's dosage actually reaches the systemic circulation after oral administration. One reason is that not all of the drug molecules are in fact absorbed from the GIT (due to the pharmaceutical characteristics of their dosage form, their molecular size, degree of ionisation and lipid-solubility, the quality of mesenteric blood flow, etc.). Another very important factor is the

biotransformation of the drug molecules on their first pass through the liver. All of the absorbed drug molecules pass through the liver the first time. The liver may actually eliminate a significant percentage of these drug molecules on their way to the inferior vena cava. On subsequent passes through the liver, smaller fractions of the absorbed drug will be biotransformed.

The **systemic bioavailability** of a drug is the fraction *(F)* or percentage of the orally administered dosage that actually reaches the systemic blood circulation. For intravenous injection, where absorption does not need to take place at all and the entire dosage is delivered into the circulation, the bioavailability is 100% (i.e. $F = 1.0$). Other routes of drug administration are associated with fractions of less than 1.0.

## 2.3 Distribution

Distribution may be regarded as the second of the four kinetic processes. Once drug molecules reach the systemic blood circulation they are transported to other parts of the body. At capillary level these molecules then leave the bloodstream to enter the other fluid compartments of the body.

The bloodstream transports drug molecules, not only to their **sites of action** (or target areas), but also to their **sites of elimination**. Drug distribution is the movement of drug molecules **from** the circulation. Drug molecules are transported either in their free form or bound to plasma proteins. Molecules in their free form are pharmacologically active and able to cross membranes.

Molecules that are plasma-protein bound are pharmacologically inactive and cannot exit the circulation without being 'released' from their bonds first. Almost all drugs are partially bound to plasma proteins, some to a lesser and some to a greater extent, while being transported by the bloodstream. Certain drugs may even compete for binding sites on the plasma proteins. *Warfarin* is a good example of a drug that is almost entirely plasma-protein bound (up to 98%).

Drug molecules are not distributed in equal quantities to all tissues and organs around the body. Rather, those organs that receive larger percentages of the total cardiac output will initially receive larger percentages of the absorbed drug dosages as well:

- The lungs receive 100% of the right ventricle output.
- At rest, 80% of the left ventricle output is distributed among organs that are particularly vascular (blood-vessel rich). These are the brain, myocardium, adrenal glands, thyroid gland, liver and kidneys. The kidneys receive 25% of the entire left ventricle output.

- During the later stages of pregnancy the uterus and placenta may be included in the list above.
- Distribution to other tissues occurs in the following order: skeletal muscle tissue, then skin and adipose tissue and finally the avascular (not containing any blood vessels) structures such as ligaments, tendons and cartilage.

The extent of a drug's distribution in the body may be expressed as the drug's **apparent volume of distribution ($V_d$)**. This is the volume into which the specific drug dosage will need to be dissolved for it to reach the same concentration as it does in the plasma. Drugs that penetrate the intracellular fluid compartment therefore have larger apparent volumes of distribution, whereas drugs that are largely plasma-protein bound exhibit much smaller volumes of distribution.

## 2.4 The termination of drug action

Drug action may be terminated through elimination. This comprises the kinetic processes of metabolism, or biotransformation, and excretion. A few other processes, however, may also terminate the actions of certain drugs.

The action of absorbed drugs may be ended (or terminated) in a number of ways:

- **Drug action may be terminated through biotransformation:** The microsomal enzymes of the liver and the non-microsomal enzymes of other tissues may detoxify and inactivate circulating drugs.
- **Drugs may be excreted by the kidneys, lungs and liver (biliary excretion) and in body secretions:** The excretion of drugs in breast milk was described in paragraph 1.5.3. Drugs with a volatile nature are excreted in part by the lungs. Nasal secretions, saliva and sweat may contain the secreted molecules of certain drugs. Excretion is discussed in more detail in paragraph 2.6.
- **Drug action may be decreased or terminated by miscellaneous mechanisms:** Other mechanisms for the termination of drug action include:
  - **Redistribution:** Drugs with large volumes of distribution (see paragraph 2.3) may be redistributed to other tissue areas. For example, the highly lipid-soluble anaesthetic agent, *sodium thiopentone* (refer to chapter 5) is rapidly distributed to highly perfused organs (it reaches the central nervous system (CNS) fast enough to induce general anaesthesia). From there, it diffuses to the skeletal muscle and adipose tissue more slowly. The drug then needs to diffuse back into the central circulation in order to be eliminated. Although the patient may recover from the anaesthesia rather quickly, total recovery to a state of full wakefulness and mental ability may take several hours.

- **Tolerance:** The development of drug tolerance was discussed in paragraph 1.5.2.
- **Drug antagonism:** The actions of certain drugs may be terminated through the use of **antagonists**. The actions of an agonist, for example, may be terminated through the use of its corresponding competitive antagonist. Refer to chapter 3.

**Elimination** is the process whereby drug action is terminated via biotransformation or excretion. The elimination processes of certain drugs may become **saturated** (i.e. reaching their maximum capacity). These drugs will accumulate in the bloodstream, should their rates of absorption exceed their rates of elimination, and may reach toxic plasma levels. Drugs such as these are said to follow **zero-order elimination kinetics**. Most drugs, however, follow **first-order elimination kinetics** (refer to paragraph 2.7.2).

## 2.5 Metabolism

Metabolism may be seen as the third of the four kinetic processes. Except for the first-pass effect, drugs are metabolised after having been absorbed and distributed.

The liver is the primary organ responsible for drug metabolism (or **biotransformation**) in the body. However, other tissues may also participate in the metabolism of drugs. These include the lungs, kidneys, skin, adrenal cortex, brain and intestines. Drug molecules need to actually enter liver cells to access the **liver microsomal enzymes** responsible for their biotransformation. This requires their molecules to be non-polar and rather lipid-soluble.

Almost all endogenous substances that require biotransformation are water-soluble. The steroid hormones are an important exception. These hormones, together with drug molecules that mostly exhibit lipid-solubility, undergo liver biotransformation, since they are capable of entering liver cells. Drugs that have chemical structures similar to the water-soluble endogenous substances are biotransformed by **non-microsomal enzymes**, or they may be excreted in their unchanged (original) form. These latter enzymes are the **plasma esterases, such as cholinesterase,** or the **mitochondrial enzymes** such as monoamine oxidase (MAO).

### 2.5.1 Biotransformation phases and reactions

Liver metabolism basically entails the **biotransformation** of drug molecules into more polar, water-soluble metabolic products (metabolites). The kidneys can then excrete these metabolites since tubular reabsorption can no longer take place (refer to paragraph 2.6.2). Generally drugs are metabolised in two phases:

- **Phase I:** The reactions that take place during phase I metabolism are aimed at unmasking or inserting functional groups that produce **more** polar and water-soluble metabolites, which are less active. **Oxidation** is the most common phase I reaction. **Reduction** and **hydrolysis** are other phase I reactions.
- **Phase II:** This phase is characterised by **conjugation reactions**. During these reactions an endogenous conjugate (a substrate such as glucuronic acid) is joined to the polar group that was added during phase I. The resultant metabolic products (conjugated products) are **wholly inactive** and **highly ionised**. The kidneys can therefore readily excrete these metabolic products. Acetylation may be an exception to the rule, since acetylated metabolites may actually be less water-soluble than their parent drugs (e.g. the sulphonamides), necessitating adequate hydration to prevent the possibility of **crystalluria** (i.e. when crystals are excreted in the urine).

Drug molecules that already contain the functional groups which are usually added during phase I reactions immediately enter phase II biotransformation. Drugs may even be taken in their inactive form (as so-called pro-drugs) and be biotransformed into active metabolites by phase I reactions. A good example of a drug that requires biotransformation into its active metabolite to be effective is *tilidine*, the opioid analgesic. *Tilidine* should therefore always be administered **orally** so as to facilitate first-pass metabolism and optimise its biotransformation into its active metabolite, nortilidine. Figure 2.4 summarises the three different phase I biotransformation events that are of clinical significance in pharmacotherapy.

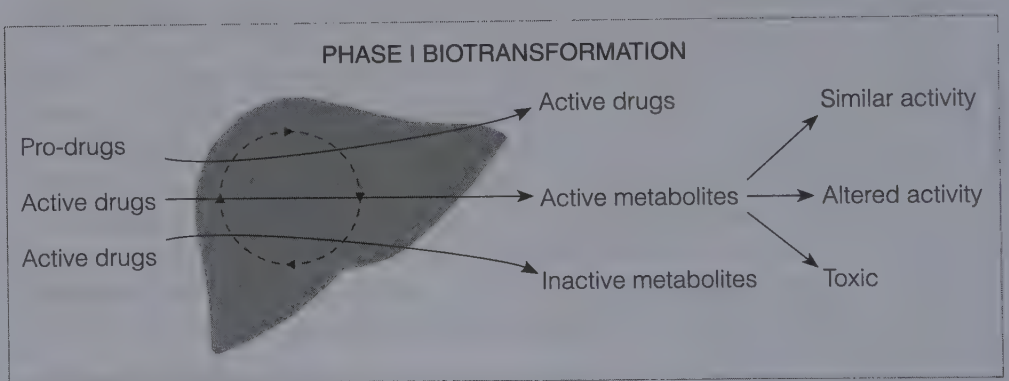



**Figure 2.4 The possible outcomes of phase I liver biotransformation**

## 2.5.2 The rate of liver biotransformation

The rate of liver metabolism, or **hepatic clearance**, of a drug is determined by hepatic blood flow and the **extraction ratio** of the drug. The extraction ratio is expressed as a fraction (i.e. from 0 to 1) and gives an indication of how much of

the drug will be removed on a single pass through the liver (0 indicates that none of the drug is removed and 1 implies that the drug is completely removed). The extraction ratio multiplied by hepatic blood flow equals what may be termed the 'hepatic clearance' of the drug in question. ***Lignocaine*** is an example of a drug with a very high extraction ratio. Therefore, it cannot be administered orally because the first-pass effect will eliminate virtually the entire drug from the bloodstream. Another example is *glyceryl trinitrate*, which must be administered via the buccal or sublingual route. The bioavailability of these drugs is extremely poor.

Drugs that exhibit a very low extraction ratio, including *warfarin* and ***phenytoin***, are biotransformed at a much slower rate since the liver has got a smaller capacity for biotransforming these drugs, compared to its capacity for biotransforming those with higher extraction ratios. Very little of the drug is removed on a single pass through the liver.

Certain drugs may act as **inducers**, others as **inhibitors**, of liver microsomal enzymes, especially the **cytochrome P450 enzymes**, implying that they can increase or decrease the rate at which substances, such as other drugs, are biotransformed (and, therefore, extruded) by the liver. Some interactions between such enzyme inducers or inhibitors and other drugs are of real clinical significance. Table 2.1 lists some important examples of such enzyme inducers and inhibitors.

**Table 2.1 Examples of drugs that induce or inhibit liver microsomal enzymes**

| Inducers | Inhibitors |
|---|---|
| Barbiturates<br>Carbamazepine<br>Dexamethasone<br>Phenytoin<br>Rifampicin | Chloramphenicol<br>Cimetidine<br>Ciprofloxacin<br>Clarithromycin<br>Erythromycin<br>Fluconazole<br>Fluoxetine<br>Isoniazid (INH)<br>Itraconazole<br>Ketoconazole<br>Ritonavir |
| Also note:<br>Chronic alcohol use<br>Cigarette smoke<br>St John's wort | Also note:<br>Grapefruit juice |

Note that enzyme induction will lead to increased levels of the relevant drug metabolite(s), which may be active or inactivated, while enzyme inhibition will cause an accumulation of the relevant parent drug or compound, albeit a pharmacologically active substance or a pro-drug.

## 2.6 Excretion

The kidneys are not the only excretory organs in the body. Organs such as the lungs and exocrine glands may also participate in the excretion of drugs. Excretion is the last of the four kinetic processes.

Drugs may be excreted in a variety of ways: via the lungs, the gastrointestinal tract, or the kidneys, and also in body secretions such as saliva, tears and sweat. An important kinetic feature of excretion is the fact that a drug's concentration is higher in the organ(s) that excrete it than in the rest of the body. This explains why drug toxicity is usually detected in these organs first.

### 2.6.1 Biliary excretion

Drugs and their metabolites may be actively transported from the bloodstream to the bile. The liver acts as the excretory organ for highly polar substances (i.e. substances that are water-soluble), with molecular masses in excess of 300 to 350 Da. Certain drug molecules that have undergone conjugation with glucuronic acid (i.e. glucuronide conjugates), such as the metabolites of ***erythromycin*** and ***chloramphenicol*** in particular, may be excreted in this manner. In some instances **bacteria** in the small intestine may again hydrolyse the conjugated metabolites, following their biliary excretion into the gut. Hydrolysis will make these metabolites more lipid-soluble again. This facilitates their reabsorption into the bloodstream, a process known as **enterohepatic cycling**.

**Clinical application**

A very important aspect of the phenomenon of **enterohepatic cycling** is the potential **failure of oral contraceptives** (orally administered oestrogens) when used concomitantly with certain antibiotics. Antibiotics that kill intestinal bacteria will cause a decrease in the enterohepatic cycling of the oestrogens that they facilitate. This will decrease the concentration of the contraceptives in the plasma, and will consequently also lessen their effectiveness. Patients should be warned about the possible failure of their oral contraceptives, and the use of alternative contraceptive methods, whilst on antibiotic treatment. Also refer to table 2.1 for other drugs that may increase the rate of oestrogen biotransformation (i.e. the enzyme inducers).

### 2.6.2 Renal excretion

Whenever drugs are excreted in the urine it is either in their original, unchanged, polar, water-soluble form (called the parent drug or compound), or in the form of their polar, water-soluble drug metabolites (produced during drug biotransformation). Renal excretion involves three important physiological

processes, namely glomerular filtration, active tubular secretion and passive tubular reabsorption:

- **Glomerular filtration:** The pores of the glomeruli are big enough to allow all drug molecules which are not plasma-protein bound passage into the renal tubuli. As the unbound drug molecules are filtrated by the glomerulus, so more and more of the plasma-protein bound fraction will also become unbound.
- **Active tubular secretion:** Carrier proteins, referred to as secretion carriers, are found in the proximal convoluted tubules of the nephron. Certain drugs may **competitively inhibit** these carriers. Drugs that compete for binding sites on the organic acid carriers are of much greater clinical significance than those that compete for the organic base carriers. Also, for drugs that are actively secreted, glomerular filtration is of lesser importance. Table 2.2 contains some examples of clinically significant competitors for binding sites on the acid and base carriers (also referred to as the anionic and cationic pumps).

**Table 2.2 Examples of clinically significant competitors for the organic acid and base carriers**

| Competitors for the organic acid carriers | Competitors for the organic base carriers |
|---|---|
| Furosemide | Amiloride |
| Penicillin | Morphine |
| Probenecid | Neostigmine |
| Salicylates | Procaine |
| Thiazide diuretics | |

- **Passive tubular reabsorption:** A drug's degree of ionisation and lipid-solubility will determine the extent to which it may be **reabsorbed** from the nephron and back into the bloodstream. Biotransformation is aimed at rendering drugs more polar and water-soluble so as to prevent their reabsorption from the renal tubules (also see paragraph 2.5.1). Ionised molecules are therefore not reabsorbed, but un-ionised ones undergo passive reabsorption. Since a drug's p$K_a$ and the environmental pH of its molecules determine its degree of ionisation (refer to paragraph 2.2.1), the tubular pH will influence the extent to which certain drugs (those that are weak acids or bases) are excreted in the urine. **Alkalinising** the urine will increase the rate of excretion of a weak acid, whilst **acidifying** the urine will increase the rate of excretion of a weak base. These facts are utilised during the treatment of certain forms of drug overdose. An ***aspirin*** overdose, for example, is treated with *sodium bicarbonate* to alkalinise the urine, and also to treat the metabolic acidosis that the overdose causes. The proximal convoluted tubule also has reabsorption

carriers for organic acids and bases. These carriers are of particular importance in the treatment of **gout** (refer to chapter 10).

## 2.7 Applied pharmacokinetics

The value of the various pharmacokinetic principles lies in their applicability to clinical practice situations.

Pharmacokinetic processes determine how the human body deals with foreign substances, such as drugs, once they are introduced to the body. These processes are determinants of many important aspects of pharmacotherapy and the intricacies and complexities of drug treatment. The pharmacokinetic principles that are discussed in this section may be directly applied to clinical nursing practice.

### 2.7.1 Elimination half-life ($t_{½}$)

The elimination half-life, or $t_{½}$, of a drug may be defined as the amount of time that it will take for the drug's **plasma concentration to be reduced by 50%** (i.e. the time required for the drug's plasma concentration to be halved). Various factors may prolong a drug's $t_{½}$, including liver and kidney failure, old age and many others.

### 2.7.2 Zero-order and first-order kinetics

A few drugs follow what is referred to as **zero-order (or non-linear) elimination kinetics**. Most of the drugs that are of therapeutic value, however, exhibit **first-order (or linear) elimination kinetics**. The distinction between these two kinetic principles may be described as follows:

- **Zero-order kinetics:** Drugs that exhibit or follow zero-order kinetics have elimination processes in the body that may become **saturated** (i.e. reaching their maximum capacity). A **constant amount** of the drug is eliminated per time unit. This phenomenon is also referred to as dosage-dependent kinetics. The implications are that increasing dosages of these drugs will prolong their plasma half-lives and cause their plasma concentrations to reach excessively high levels. Examples of drugs that follow zero-order elimination kinetics are:
  - *Heparin*
  - The salicylates (large dosages of ***aspirin***)
  - ***Phenytoin***
  - *Ethanol*
  - In overdose, the tricyclic antidepressants, the barbiturates and the benzodiazepines

- **First-order kinetics:** The biotransformation and excretion processes of these drugs **will not become saturated**. This phenomenon is therefore also referred to as dosage-independent kinetics and implies that a **constant fraction** of the drug is eliminated per time unit.

### 2.7.3 Bioavailability and apparent volume of distribution ($V_d$)

The systemic bioavailability of a drug is the fraction *(F)* of the orally administered dosage that actually reaches the systemic blood circulation. The apparent volume of distribution expresses the extent of a drug's distribution throughout the various fluid compartments of the body. These principles have been dealt with in paragraphs 2.2.3 and 2.3.

### 2.7.4 The kinetic principles of a single drug dosage

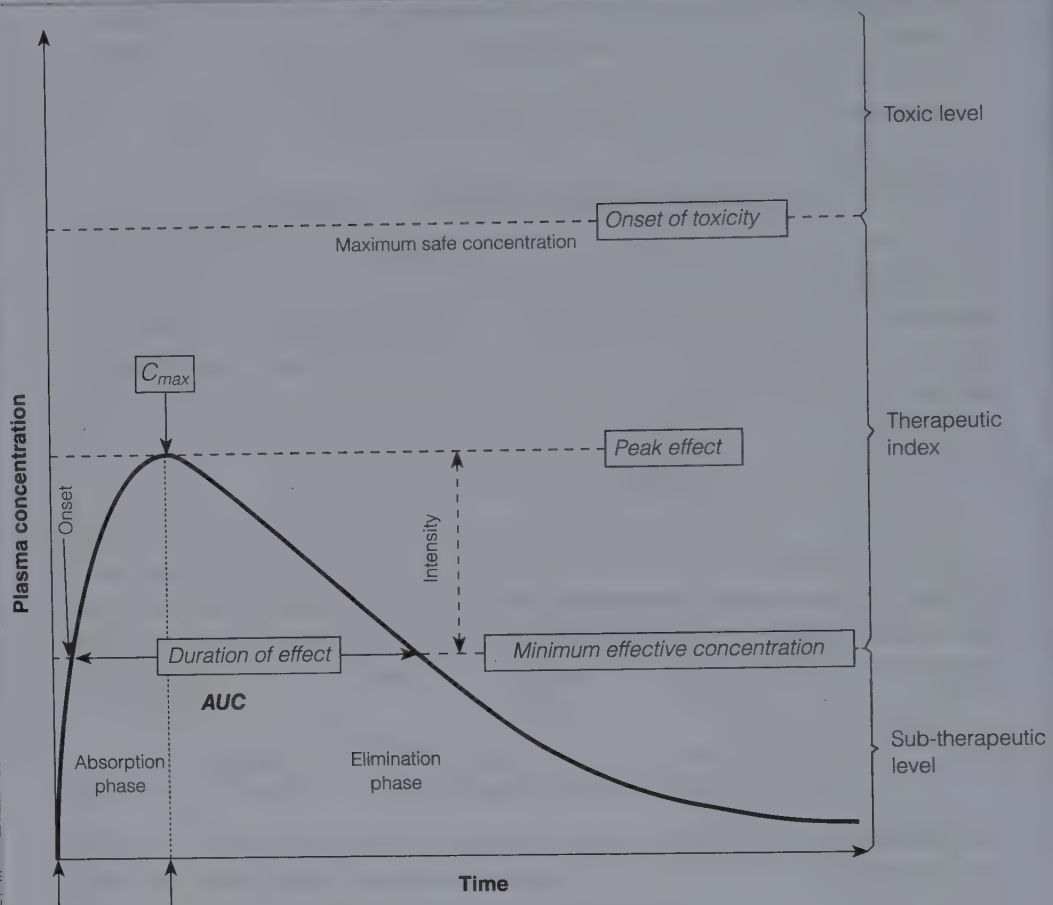
When a drug is administered as a single (or once-off) dosage the plasma concentration will increase as the drug is absorbed. The plasma concentration peaks when absorption is complete, then it gradually declines again as the drug is eliminated from the body. These principles, as they apply to a **single oral drug dosage**, are illustrated and elucidated in figure 2.5.

### 2.7.5 Kinetic principles of multiple and continuous dosages: The steady-state concentration ($C_{ss}$)

Drugs that exhibit first-order elimination kinetics (see paragraph 2.7.2), which are administered as multiple or continuous therapeutic dosages, will gradually accumulate in the body until a **plateau concentration** is reached. This plateau concentration is a state during which the rate of a drug's absorption is equal to the rate of its elimination. A more or less constant plasma concentration may therefore be maintained. This concentration is referred to as the drug's steady-state concentration, or $C_{ss}$.

The following points relate to $C_{ss}$ and are of importance:

- Drug accumulation to a point where $C_{ss}$ is reached is a first-order kinetic process because the steady-state concentration is reached when the rate of absorption equals the rate of elimination and the processes involved in first-order kinetics cannot be saturated.
- The time required for $C_{ss}$ to be reached is a function of the $t_{½}$ of the drug in question, because it relates the rate of the drug's absorption to the rate of its elimination (with the latter being determined by its elimination half-life). For all practical purposes, first-order processes require about four to five times the drug's $t_{½}$ to complete. Therefore, four to five half-lives are required to reach $C_{ss}$ as well.




**Explanation:**

- $T_{max}$ is the time required to reach $C_{max}$ (i.e. the peak plasma concentration).
- The **duration of the therapeutic effect** is seen from the time that the absorption phase reaches the **minimum effective plasma concentration**, until the time that the elimination phase again decreases the plasma concentration to a level below the minimum effective plasma concentration.
- The **absorption phase** commences with the administration of the dosage, and lasts until $C_{max}$ is reached. Thereafter the elimination phase begins and lasts until such time as the drug has been completely eliminated from the body. During the absorption phase the rate of drug absorption is greater than the rate of the drug's elimination from the body, and *vice versa* for the **elimination phase.** $C_{max}$ is reached when the rate of absorption is equal to the rate of elimination.
- The **therapeutic index** (or therapeutic range) is the difference between the minimum plasma concentration at which the drug is effective and the level demarcating the **onset of toxicity** (i.e. the minimum plasma level at which the drug becomes toxic).
- The AUC or 'area under the [plasma concentration-time] curve' refers to the entire area underneath the actual curved line.

**Figure 2.5 A plasma concentration-time curve illustrating the pharmacokinetic principles and parameters associated with a single oral drug dosage**

- In general the time required to reach the steady-state concentration is independent of the dosage, rate or frequency of drug administration. One important prerequisite, however, is that intermittent dosages of the drug must be given at dosage intervals of less that 1.4 times its $t_{½}$ if $C_{ss}$ is to be reached. Increasing the dosage will increase the steady-state concentration, but will not facilitate reaching $C_{ss}$ sooner.
- Drugs with shorter half-lives reach $C_{ss}$ more rapidly and their plasma concentrations tend to fluctuate more significantly between dosages.

**Clinical application**

To illustrate the principle of administering intermittent drug dosages with the purpose of reaching and maintaining a steady-state concentration, the following example may be considered:

The plasma elimination half-life of a drug is 10 hours and it is administered every eight hours. The following points apply to $C_{ss}$:

- $C_{ss}$ will be reached after four to five half-lives, i.e. after four to five times 10 hours (or 40 to 50 hours), irrespective of the dosage.
- For $C_{ss}$ to be reached after 40 to 50 hours the dosage intervals should be less than 1.4 times 10 hours (i.e. less than 14 hours) apart. Therefore, eight-hourly intervals would be adequate.
- It is also important to note that the effectiveness of a change in the patient's dosage regimen (i.e. an increased or decreased dosage) can only be fully evaluated after another four to five half-lives have lapsed, because a new steady-state concentration must first be reached.
- The same principles apply to missing or skipping a dosage, especially when the drug in question has a rather short half-life and the dosage that has been missed causes such a significant decrease in the plasma concentration that $C_{ss}$ is lost. This implies that another four to five half-lives may be required to regain $C_{ss}$.

## 2.7.6 Loading and maintenance dosages

Situations arise in clinical practice where a more rapid therapeutic effect is desired with a drug that has a relatively long $t_{½}$. In a situation like this, a single (first dosage) or divided (first and second dosages) **loading dosage**, or bolus dosage in the case of intravenous administration, is administered to establish the desired **therapeutic effect** (at a therapeutic drug concentration) more rapidly. **Maintenance dosages** (i.e. dosages that are given at regular dosage intervals to maintain the desired therapeutic effects of the drug over time) are then used to reach and maintain the desired **steady-state concentration**. Therefore, the loading dosage does **not** facilitate the reaching of $C_{ss}$ any sooner, but does facilitate a more rapid onset of the drug's action and therapeutic effects.

### 2.7.7 Therapeutic index

The therapeutic index of a drug is the difference between the minimum plasma concentration at which the drug is effective and the minimum plasma concentration at which it becomes toxic. The therapeutic index gives a general indication of a specific drug's **margin of safety**. Drugs with small therapeutic indices may reach toxic levels very easily. *Warfarin*, ***theophylline***, the aminoglycosides and ***digoxin*** are examples of drugs that exhibit very small therapeutic indices. A small therapeutic index may also be referred to as a **narrow therapeutic margin**, or a **small therapeutic window**, when referring to the range of plasma levels between the minimum effective level and the level demarcating the onset of toxicity. Also refer to figure 2.5.

CHAPTER THREE

# Pharmacodynamic principles

In chapter 1 the basis of drug action, namely the interaction between drug molecules and receptors (also known as drug targets), was introduced. Receptors fall into one of three important categories, namely:

- Specific ligand receptors (subdivided into membrane receptors and intracellular receptors)
- Enzyme receptors
- Transport carrier receptors

Sometimes the specific ligand receptors are referred to as 'true' drug receptors, while enzyme and transport carrier receptors are grouped together with plasma and tissue proteins to form a 'silent' receptor category. Therefore, in practice it has become the custom for the term 'receptor' to be used when referring to ligand receptors only.

Proteins and protein-containing macromolecules provide the actual receptor binding sites used by drug molecules, and also a variety of endogenous signal transmitters (i.e. neurotransmitters, hormones, cytokines and autacoids). Pharmacodynamics studies the way in which drugs influence body processes through their interaction with specific receptors, and therefore their mechanisms of action and their resultant effects. A number of pharmacodynamic principles are of importance in gaining insight into the mechanisms of drug action. These principles are elucidated in this chapter.

## 3.1 Receptor binding and affinity

Drugs need to bind to their receptors to produce their effects. Drug molecules form chemical bonds with their receptors, the strength of which is determined by the receptor affinity of the drug (the sum total of the attractive forces between a drug and its receptors).

Before a drug can exert any cellular response or clinical effect, its molecules must first bind to its specific target receptors. Chemical bonds form between the drug molecules and their receptor binding sites. These bonds are almost always of a weak, reversible, but dynamic nature.

A few substances, however, are capable of forming strong, covalent (i.e. irreversible) bonds with their receptors. The receptors are usually destroyed because of these bonds. The effects of these substances or drugs can only be

terminated once suitable protein structures that contain new receptor binding sites have been synthesised. This explains their prolonged duration of action. Examples of drugs or substances that form covalent bonds with their receptors are the organophosphate pesticides and the antihypertensive drug *phenoxybenzamine*, which is used to stabilise the blood pressure of a patient suffering from phaeochromocytoma prior to surgical intervention.

**Affinity** may be defined as the tendency or degree to which drug molecules are drawn to their receptors. It therefore provides us with an indication of the strength of the chemical bonds that form between the molecules and receptors. Drugs with a high affinity for their receptors will exhibit a higher tendency to combine with those receptors than drugs with low affinities. The higher a drug's affinity for its receptors, the more **potent** the drug will be.

To simplify the actual process of drug action, the following events may be described, as they relate to the binding of a drug to its target receptors:

- Generally speaking, drug molecules may be seen as chemical messengers wanting to convey their messages (chemical signals) to biological targets so as to effect biochemical or electrical changes in **effector organs** (the organs on which chemical substances or nerve impulses exert their effects).
- Drug molecules form chemical bonds with their receptors. This produces drug-receptor complexes (i.e. drug molecules bound to receptors).
- Once the drug-receptor complex has formed, a series of bio-chemical or electrical events is set in motion. The **initial** events serve to amplify and transmit the original message to the functional parts of target cells. This is known as **signal transduction** (see paragraph 3.3).
- The process of signal transduction may take place, either through direct influencing of membrane permeability (i.e. the opening of ion channels), or through a G-protein-coupled transduction process (see paragraph 3.3).
- The **subsequent** events allow for the biological effects seen in target tissues and body fluids. Well-known G-protein-coupled receptors are the muscarinic acetylcholine receptors, the dopamine receptors, the serotonin (or 5-HT) receptors and the β-adrenergic receptors (see chapter 4).

Once a drug has been introduced to the body and has reached its target tissues, drug-receptor **association** begins. This is the process by which drug-receptor complexes are formed. The time that a drug molecule actually spends on its receptor, however, is measured in milliseconds. This implies that drug-receptor dissociation also takes place. In pharmacology, it is said that a state of **equilibrium** has been reached when the rate of drug–receptor association equals the rate of drug–receptor dissociation.

On the molecular level, drug action leads to direct or immediate consequences such as changes in cellular and tissue functions. Organ function may be

affected, either directly, or indirectly. Other indirect or delayed consequences are changes in organ system functioning and eventual changes in the functioning of the entire body. Some of these changes are beneficial (those that the initial drug treatment was aiming for), while others may be **unwanted** (refer to paragraph 1.5.2).

## 3.2 The biophase

The area directly surrounding the receptor binding site is called the **biophase**. Drug molecules need to actually reach the biophase in high enough concentrations to allow them to bind to enough of their receptors to produce a significant clinical effect. Some drugs may be administered directly into their biophase (inhaling a bronchodilator, for example), which means that smaller dosages are required and less systemic side-effects are elicited.

## 3.3 The transduction of chemical signals

Once a drug has formed a functional bond with its receptor (i.e. a drug-receptor complex has formed), a chain, or cascade, of cellular events is set in motion, which will culminate in the biochemical and physiological effects of the drug. Such a cascade of cellular events, set in motion by receptor binding and then amplified, is referred to as **signal transduction**. In paragraph 1.6 the different types of receptors were described. Membrane receptors may influence membrane permeability for certain ions directly, or they may be **G-protein coupled**. When membrane permeability is influenced, a response may be expected within milliseconds, while G-protein-coupled responses manifest themselves within seconds to minutes.

Receptors that are G-protein coupled make use of **intracellular second messengers** for their signal transduction. Some drugs, through receptor binding, activate these second messengers, while others may inhibit them. Cyclic AMP (cAMP), inositol triphosphate ($IP_3$) and diacylglycerol (DAG) are examples of such second messengers. Intracellular calcium ions ($Ca^{2+}$) may also act as second messengers. Several agonists are capable of producing an increase in the cytoplasmic calcium ion concentration. These calcium ions are subsequently involved in various cellular processes that result in their effector reactions.

## 3.4 Regulating flow through ion channels

Specific transmembrane proteins, called channel proteins, form ion channels (see paragraph 2.2.1) in the plasma membrane. Specific ion channels exhibit **selectivity** for their specific ions only. For example, separate ion channels for $Na^+$, $Ca^{2+}$ and $Cl^-$ may be present on a single plasma membrane. Such ion channels are usually **gated,** either through the actions of ligands (i.e. ligand-

gated ion channels), or through their sensitivity to electrical impulses (i.e. voltage-gated ion channels).

Some drugs may bind to target areas on the channel proteins directly. Once the drug–receptor complex has formed, the conformation of the channel is changed. Subsequently the permeability of the channel for its specific ions is **increased** (i.e. the channel is 'opened'). Ions are then allowed to move along their electrochemical gradients rapidly and rush into the cell, where they initiate biological responses. A well-known example of such a membrane receptor is that of the nicotinic receptor that interacts with acetylcholine (see chapter 4).

Ion channel permeability may also be **decreased** with certain drugs. In such cases the permeability of the ion channel is prevented from being increased by endogenous substances, or voltage-sensitive ion channels may be prevented from opening in response to nerve impulses. A good example of the latter is that of the local anaesthetic agents that prevent voltage-sensitive $Na^+$-channels from opening in response to depolarisation (refer to chapter 5).

Some G-protein-coupled receptor mechanisms also regulate the flow of ions through specific ion channels. In these instances the G-protein coupling does not activate intracellular second messengers (see paragraph 3.3), but rather decreases the permeability of the ion channels directly.

## 3.5 Agonists, antagonists and intrinsic activity (IA)

Drugs may be classified as being **agonists, dualists** or **antagonists**, depending on the ability of their drug-receptor complexes to elicit or initiate **active** cellular responses or cellular effects. **Intrinsic activity**, or IA, describes the **biological effectiveness** of the drug-receptor complex (in other words, the ability of the drug to elicit a cellular response). IA, also referred to as intrinsic efficacy, is expressed as a fraction (i.e. a value ranging from zero to one). Zero indicates that no effect whatsoever will be elicited by the drug, and one indicates that the maximal cellular response will be initiated. All of the endogenous signal transmitters have intrinsic activities that are equal to one. The active cellular responses, however, may be either **excitatory** or **inhibitory** in nature. Dopamine and serotonin (or 5-HT), for example, elicit excitatory responses, while the endogenous neurotransmitter gamma-aminobutyric acid (GABA) elicits an inhibitory response.

In terms of intrinsic activity, drugs may be categorised as full agonists, competitive antagonists or dualists:

- **Full agonists:** These are drugs that have intrinsic activities equal to one. Therefore, they are capable of eliciting maximal cellular responses. An agonist also displays strong affinity for its receptors.

- **Competitive antagonists:** Drugs that exhibit intrinsic activities of zero are called competitive antagonists. They usually display higher affinities for their receptors than their corresponding agonists. Competitive antagonists are also referred to as receptor **blockers**. As the term implies, these drugs merely block receptors so as to prevent agonists, such as endogenous signal transmitters, from forming functional agonist-receptor complexes and therefore exerting their effects on their target organs. They cannot actively reverse the effects of their corresponding agonists. Two other important characteristics of this type of antagonist are the following:
  - The competitive antagonist can displace its corresponding agonist from its receptor-binding site because of its greater receptor affinity.
  - Once it is bound to its receptor, an increase in the concentration of the agonist in the biophase will again displace the antagonist from its binding site. The effects of a competitive antagonist are therefore said to be **surmountable**.

  Refer to note 3.1 for a practical example of the relationship between an agonist and its corresponding competitive antagonist. The drug-receptor complexes that are formed between competitive antagonists and their receptors, which do not elicit active cellular responses are said to be **passive** in nature. As already mentioned, such drugs merely **prevent** endogenous (chemical or nerve) or agonistic drug stimulation of the receptor system in question.
- **Dualists:** Some drugs are neither full agonists, nor competitive antagonists. Rather, they may be categorised as being **partial agonists**, also referred to as **agonist-antagonists**. They have intrinsic activities ranging between zero and one (i.e. less than one). A dualist with an IA > 0.5 will more likely display agonistic activity, while one with an IA < 0.5 will more likely display antagonistic (receptor-blocking) activity. Also, administering a dualist on its own will usually elicit its agonistic activities. It will, however, display its competitive antagonistic properties, should an agonist already be present.

Drugs that are capable of acting as receptor blockers in more than one receptor system are called **multipotent blockers**. Their chemical structures allow them some degree of non-selective, antagonistic effects of an **antimuscarinic**, **antihistamine**, **$\alpha_1$-adrenergic blocking** and **local anaesthetic** nature. Examples of these multi-potent blockers are the 'older' type of antihistamines, the tricyclic antidepressants and the phenothiazines.

Except for competitive antagonists, there are also four types of **non-competitive antagonists** (described by Sommers 2000: 14–17). These antagonistic drugs are used to actively counteract the effects of agonistic drugs, or other chemical substances in the body. They are:

- **Functional or physiological antagonists:** A functional antagonist is actually an agonist that acts on a different receptor system, where it elicits the opposite physiological effects to those elicited by the initial agonist. ***Adrenaline***, for example, is the functional antagonist of histamine (refer to note 3.2).

**Note 3.1 The relationship between an agonist and its corresponding competitive antagonist**

During **anaphylactic reactions** the massive release of **histamine**, an endogenous neurotransmitter, and therefore a full agonist at histamine receptors, causes a series of life-threatening pathophysiological events. These include widespread vasodilatation, with increased capillary permeability, fluid shifts and circulatory shock, bronchospasm and glottis oedema.

The use of **antihistamines** in the management of anaphylaxis, however, will not be life-saving. Since antihistamines are **competitive antagonists** of histamine, especially at its $H_1$-receptors, the massive amounts of circulating histamine (the agonist) will continue to displace (or surmount) the antihistamines from their receptor-binding sites.

Rather, as a life-saving emergency intervention, the **functional antagonist** of histamine (see note 3.2) is administered first. Thereafter, the unpleasant symptoms of the severe allergic reaction, including pruritus, nausea and vomiting, may be managed with an antihistamine. The drug treatment of anaphylaxis is discussed in more detail in chapter 12.

**Note 3.2 Adrenaline, the functional antagonist of histamine**

***Adrenaline*** may be used to effectively manage the life-threatening clinical problems that are brought about by anaphylactic reactions (see note 3.1). ***Adrenaline*** is a full agonist in the adrenergic receptor system (refer to chapter 4). Some of its effects include vasoconstriction and bronchodilatation. Therefore, it counteracts the life-threatening effects of histamine through agonistic stimulation of another receptor system. The drug treatment of anaphylaxis is discussed in more detail in chapter 12.

In the healthy body the chief physiological agonists of the sympathetic and parasympathetic nervous system subdivisions, namely adrenaline and acetylcholine respectively, also act as functional or physiological antagonists in target areas such as the bronchial smooth muscle and the pacemaker cells of the heart.

- **Chemical antagonists:** A chemical antagonist forms a chemical bond with the agonist, thereby decreasing its affinity for its receptor-binding sites. The concentration and effectiveness of the agonist is therefore reduced. Two examples of chemical antagonists are:

- *Protamine sulphate*, which is used to terminate the effect that *heparin* has on blood coagulation (clotting) through ionic bonding.
- The **chelating agent** *dimercaprol*, which is used to treat arsenic and mercury poisoning by rendering the agonist more water-soluble and therefore making it more suitable for renal excretion. Iron poisoning may be treated in the same way with *desferrioxamine* as the chelating agent. Chelates that form in the lumen of the digestive tract will not be absorbed.

➲ **Metaffinoid antagonists:** These antagonists change the conformation of the receptor-binding sites utilised by agonists. This implies that the agonist will no longer be capable of fitting optimally onto its receptor-binding sites. The metaffinoid antagonist, therefore, influences receptor occupation by the agonist. In the case of enzymes this type of antagonism is called **allosteric antagonism**.

➲ **Biochemical or pharmacokinetic antagonists:** A biochemical antagonist directly decreases the concentration of the agonist in the biophase. This may be achieved by either accelerating the agonist's biotransformation or excretion, or by competing with the agonist for transport to its receptors.

## 3.6 Receptor density and receptor reserve

Most of the receptors used by drug molecules are located on the outer surfaces of plasma membranes. Receptor density for specific drugs, however, is rather low. In spite of the low receptor density, full agonists can still elicit a maximal cellular response without even occupying all of their available receptors, i.e. they leave some receptors unoccupied and therefore in reserve. This is known as their **receptor reserve**. In the case of partial agonists (i.e. dualists), there is no receptor reserve, i.e. they could not elicit a maximal cellular response even if it were possible for them to occupy **all** of their receptors. The maximal effect elicited by a dualist is therefore quantitatively less 'potent' than the effect that could have been obtained with a full agonist.

## 3.7 Intracellular receptors

The steroid hormones have **intracellular receptors** (also refer to paragraph 1.6). For receptor binding to take place, these hormones, or their **analogues**, need to reach their intracellular binding sites first. The receptors for the corticosteroids are situated in the cytoplasm, and once steroid-receptor binding takes place the steroid-receptor complexes become activated and translocate (i.e. move from one location to another) to the cell nucleus. There they bind to **steroid-response elements** in the DNA and subsequently influence the transcription of certain genes. Transcribing RNA-polymerase activity and messenger-RNA (mRNA) production in the nucleus

may therefore be **increased**, or **inhibited**. The former culminates in the synthesis of new **polypeptides** (arbitrarily, these are chains of 20 to 50 amino acids linked together by peptide bonds) or proteins. The receptors for the other steroid hormones and the active form of vitamin $D_3$ are found inside the cell nucleus (i.e. they have nuclear receptors as opposed to the cytoplasmic receptors of the corticosteroids). The exact nature and functions of such newly-formed polypeptides or proteins depend on the specific hormone that initially bound to the intracellular (steroid) receptor. Because of the complexity of this process, the cellular response may take several hours or even days to occur. Also refer to figure 7.2.

## 3.8 Enzyme receptors

Most drugs that have enzymes as their targets will act to **inhibit** the normal functioning of such enzymes. Enzymes are proteins that act as catalysts of biochemical reactions in the body. A catalyst increases the rate at which such chemical reactions take place, without participating in the reactions themselves. Enzymes act on **substrates**. They cannot control the direction of the reactions that take place, but will rather cause a proportionate increase in the rates of both the forward and reverse reactions. To illustrate this, the well-known example of the carbonic acid/bicarbonate buffer reaction may be used. Consider the chemical equation in figure 3.1:

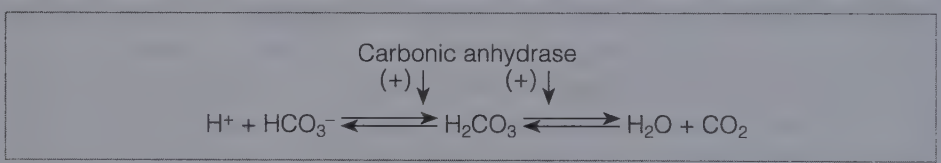



**Figure 3.1 The carbonic acid/bicarbonate buffer system**

The enzyme that catalyses the above reaction is called **carbonic anhydrase**, and controls both the forward reaction on one side of the equation and the reverse reaction on the other.

Also consider the example illustrated in figure 3.2. Xanthine oxidase (XO) is responsible for catalysing the reaction by which hypoxanthine is converted to xanthine and subsequently to uric acid. Hypoxanthine and xanthine are the **substrates** and xanthine oxidase the **enzyme**.

The names of enzymes are easily recognisable by the occurrence of the suffix '-ase' in their names, for example cyclooxygenase, carbonic anhydrase and xanthine oxidase (digestive enzymes such as pepsin and rennin are noteworthy exceptions).

Inhibiting enzyme function implies the following:

- There will be an increase in the substrate concentration, since the action of the catalyst is removed.

➲ There will be a decrease in the concentration of the products of enzyme activity.

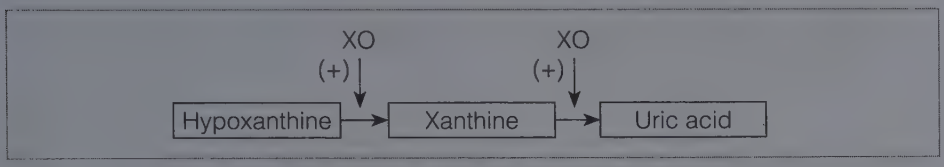



**Figure 3.2 The action of xanthine oxidase (XO)**

Drugs may be used for the primary purpose of attaining either one of the abovementioned outcomes. Also refer to paragraph 1.6 for more information on enzyme receptors.

*Glyceryl trinitrate* and *sodium nitroprusside* are examples of drugs that actually **activate** enzymes. These drugs are discussed in more detail in chapter 6.

## 3.9 Transport carrier receptors

These receptors are described in paragraphs 1.6 and 2.2.1.

CHAPTER FOUR

# Neurotransmitters and their receptor systems

**Suggested revision**

***Anatomy and physiology:***

- Central and peripheral nervous system
- Somatic nervous system
- Cranial and spinal nerves
- Ganglia, preganglionic and postganglionic neurons
- Autonomic nervous system (sympathetic and parasympathetic divisions and their effector organs)
- Action potential, nerve impulses, neurotransmitters and synapses

This chapter deals with the specific ligand receptors utilised by the neurotransmitters that are of pharmacological significance. These are:

- Noradrenaline (NA) and the adrenergic receptor system
- Acetylcholine (ACh) and the cholinergic receptor system
- Dopamine (DA) and the dopaminergic receptor system
- Serotonin, or 5-hydroxytryptamine (5-HT), and its receptors
- Histamine (H) and its receptors (the histaminergic receptors)
- The endorphins, dynorphins, enkephalins and other endogenous opioid peptides, and their receptors
- Gamma (γ-) aminobutyric acid (GABA) and its receptors
- Glycine, glutamate and aspartate, and their receptors

## 4.1 Aspects of the transmission of efferent nerve impulses

Synaptic clefts exist between the end-bulbs of neuronal axons and the dendrites of adjacent neurons within the nervous system, whether central or peripheral, or between these end-bulbs and the neuronal effector cells outside of the nervous system. For neurons to convey their 'messages' across these synaptic clefts they require chemical messengers called **neurotransmitters**.

Efferent neurons (i.e. nerve cells that carry impulses *away* from the CNS) synapse, either with one another (inside the nervous system), or with their effector cells (outside the nervous system). Neurons generate and transmit

electrical impulses to convey their 'messages' to their target areas. However, since the end-bulbs of axons are not in *direct* contact with the dendrites of adjacent neurons, or with effector cells (such as muscle fibres and glandular tissue cells), chemical messengers are used to convey the 'messages' that these electrical impulses contain across these **synaptic clefts**, which are the gaps that exist between the axonal end-bulbs of neurons and their effector surfaces. (These junctions are also simply referred to as synapses. Neurons are also said to *synapse* with one another or with their effector areas.) In the case of the motor neurons of the somatic nervous system, the synapses between the axonal end-bulbs and the plasma membranes of striated muscle fibres are called **neuromuscular** junctions (or **motor endplates**). Furthermore, it should be noted that the synapses between the efferent neurons of the autonomic nervous system and their effector cells are also referred to by some authors as **neuroeffector junctions** to differentiate them from neuromuscular junctions and from the 'true' synapses that exist between adjacent neurons within the nervous system.

The chemical messengers used to convey messages across the synaptic clefts are called **neurotransmitters** (ligands that are of immense pharmacological importance). Therefore impulse transmission is said to be chemically mediated. Transmission always takes place in one direction only, from a presynaptic (before the synapse) neuron to a postsynaptic (after the synapse) effector area (an adjacent neuron or effector cell). Neurotransmitter molecules, upon release, interact with receptor-binding sites. This allows for signal transduction and the subsequent cellular responses to take place (refer to paragraph 3.3).

Neurotransmitter substances are stored in synaptic vesicles that are contained within the terminal ends of neurons. These vesicles release their chemical messengers into the synaptic cleft through the process of exocytosis (fusion of the storage vesicle with the plasma membrane of the end-bulb, with subsequent rupture and discharge of its contents). The neurotransmitters are synthesised, either in the neuronal cell body, or (mostly) within the end-bulb itself.

Neurotransmitter release (through the process of exocytosis) is initiated by the rapid influx, into the neuronal end-bulb, of calcium ions via voltage-gated calcium channels in the plasma membrane. This occurs in response to depolarisation by the action potential, which has been propagated along the axon.

Once the neurotransmitter has been released and its message has been conveyed, its action is terminated through its **enzymatic breakdown** in the synaptic cleft, terminal axon, or other tissues and organs throughout the body. The enzymes in question are specific to certain neurotransmitters or groups of neurotransmitters that are structurally alike. **Acetylcholinesterase** and

**pseudocholinesterase** are the enzymes that inactivate acetylcholine (ACh), for example. On the other hand, the enzymes that inactivate noradrenaline (NA) are **monoamine oxidase** (MAO) and **catechol-O-methyltransferase** (COMT). The metabolic products of the enzymatic breakdown (a form of biotransformation) are returned to the axonal end-bulbs, through active transport by membrane pumps, to be used in the synthesis of more of the neurotransmitter substance in question. **Re-uptake** of unused, unchanged neurotransmitter molecules into the end-bulb also takes place (and some of the metabolic by-products are excreted in the urine).

Upon activation, many of the so-called **presynaptic receptors** which are present on presynaptic neuronal membranes act as **negative-feedback mechanisms** for further neurotransmitter release. This serves to halt the excessive release of neurotransmitter substances from their storage vesicles. Consider the example of noradrenaline release from its storage vesicles, which is discussed in paragraph 4.6.3.

## 4.2 Organisation of the peripheral nervous system

It is of value to use the following organisational plan of the **efferent peripheral nervous system** when attempting to elucidate the pharmacodynamics of the various drugs acting upon it:

- Somatic nervous system
- Autonomic nervous system:
  - Sympathetic division
  - Parasympathetic division

When studying pharmacology it is useful to have an organisational plan of the peripheral nervous system as a point of departure. Pharmacologically speaking, the following basic organisational plan of the nervous system elucidates many aspects of the action of drugs on the peripheral nervous system and its subdivisions:

- Functionally, the nervous system may be divided into a central and a peripheral subdivision.
- The peripheral nervous system may then be further divided into **afferent** (carrying impulses **to** the CNS) and **efferent** (carrying impulses **from** the CNS) pathways.
- The efferent pathways may be either **somatic** (skeletal muscle innervation to facilitate body movement), or **autonomic** (comprising sympathetic and parasympathetic efferents).

Figure 4.1 illustrates the abovementioned subdivisions.

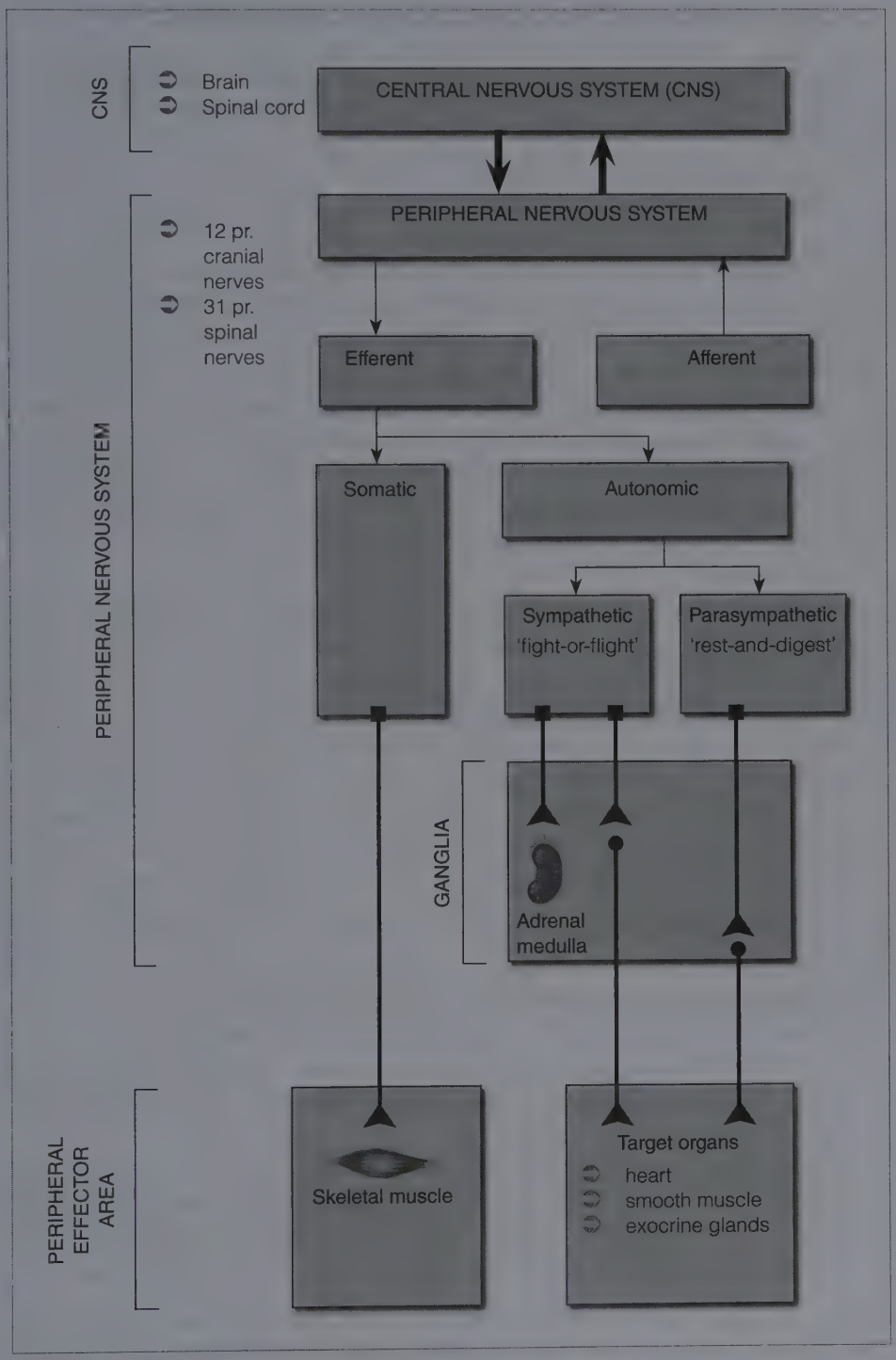



**Figure 4.1 Organisation of the peripheral nervous system**

## 4.3 Subdivisions of the autonomic nervous system

Differences between the two subdivisions of the autonomic nervous system, namely the sympathetic and parasympathetic nervous systems, provide for two very important receptor systems:

- The adrenergic receptor system
- The cholinergic receptor system

Two opposing subdivisions of the autonomic nervous system regulate those body functions that are not under wilful control. These are the **sympathetic** and **parasympathetic** nervous systems. The extraordinary relationship between the sympathetic and parasympathetic divisions is dynamic, and is characterised by a careful homeostatic balance. Most of the sympathetic division's functions are derived from noradrenaline interacting with adrenergic receptors, while acetylcholine interacts with cholinergic receptors to produce parasympathetic effects. The effects of noradrenaline may, under stressful conditions, be augmented (strengthened) by adrenaline, a neurohormone released by the adrenal medulla.

The well-known characterisation of the sympathetic division as providing '*fight-or-flight*' responses only, while the parasympathetic division is responsible for the '*rest-and-digest*' functions, tends to leave us with the misconception that sympathetic functions only occur during 'homeostatic emergencies' (such as dehydration, hypoglycaemia and circulatory shock) or at times of high physiological demand (such as demanding exercises, physical exertion, or having to maintain a normal core body temperature when the environmental temperature suddenly and sharply decreases). However, these two divisions actually complement each other through selective innervation and carefully positioned receptors that constitute the **adrenergic** and **cholinergic** receptor systems:

- **Adrenergic receptor system:** Noradrenaline is the physiological ligand responsible for most of the sympathetic division's normal functions. In peripheral effector areas (those areas where target receptors actually elicit their effects) this receptor system constitutes the α- and β-adrenergic receptors and their subtypes.
- **Cholinergic receptor systems:** Acetylcholine is the physiological transmitter substance. The acetylcholine receptors are found as muscarinic receptors in peripheral effector areas and as nicotinic receptors in the autonomic ganglia. Both of these receptor types have subtypes as well.

Figure 4.2 illustrates the relationship between the sympathetic and parasympathetic divisions of the autonomic nervous system and the organs that they innervate.

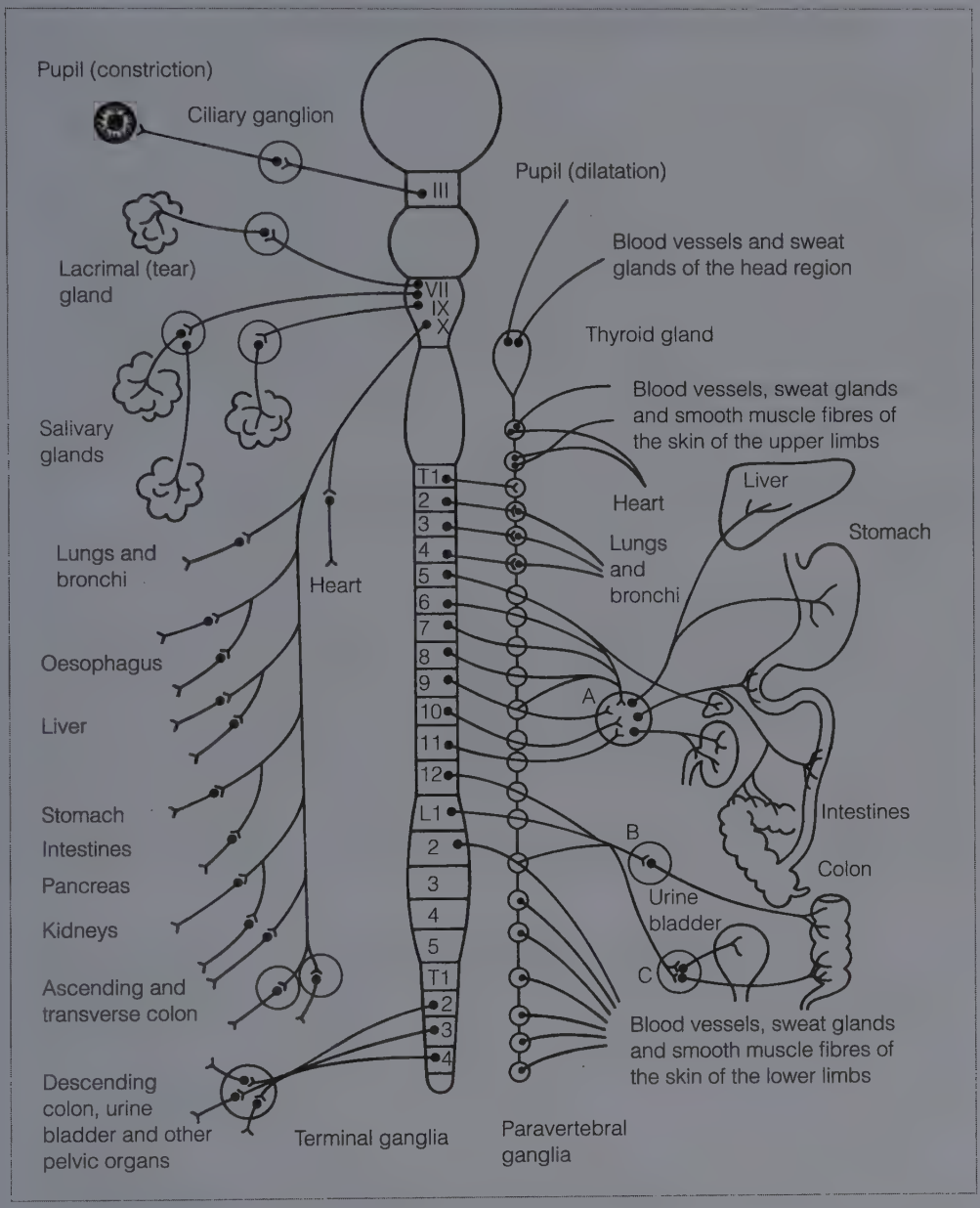



**Figure 4.2 Diagram of the parasympathetic (left) and sympathetic (right) outflow of the autonomic nervous system: A, B and C represent collateral ganglia**

## 4.4 Receptors of the somatic nervous system

The somatic nervous system uses acetylcholine as its transmitter at the neuromuscular junction (or motor endplate). The receptors are of the $N_m$-subtype, as explained in paragraph 4.7.2.

A very important functional aspect of the coordination and control of wilful skeletal muscle movements, and the initiation and completion of intricate and complex motor tasks, is the control over them that is provided by the **central nervous system** (CNS) (also refer to paragraph 4.5). Three major areas are involved. They are the motor cortex, the cerebellum and the **basal nuclei** (the latter form part of the extrapyramidal system). Dopamine and acetylcholine play a vital role in regulating muscle tone and coordinative movement (see paragraphs 4.7 and 4.8).

## 4.5 Receptors of the central nervous system (CNS)

The CNS, comprising the brain and spinal cord, has to fulfil intricate and very important integrative and coordinative functions within the nervous system. These functions are the complex processes of receiving afferent nerve impulses from the periphery, interpreting them, and converting them into suitable and appropriate efferent impulses that may be relayed back to the periphery. Important functional areas, systems and centres within the CNS are particularly necessary to achieving the goals of coordinative and integrative functioning. These include the limbic system, the reticular activating system (RAS) and basal nuclei, the medullary centres of the brain stem (including the emetic centre, cough centre, respiratory centre and vasomotor control centre) and the thalamus and hypothalamus.

A variety of receptors and receptor systems are involved in impulse transmission within the CNS. Not all of these are necessarily of pharmacological significance. However, the major CNS neurotransmitters that are of interest here, are acetylcholine, noradrenaline, dopamine, serotonin (or 5-HT), the opioid peptides and GABA, as well as histamine, glycine, glutamate and aspartate.

Generally speaking, a neurotransmitter is synthesised within the neuron that releases it, and stored inside vesicles that are found within the terminal axonal end. To qualify as a neurotransmitter, the substance has to be released into the synapse upon receiving nerve cell stimulation (in the form of an electrical impulse) and must have suitable processes in place to inactivate it within the synaptic cleft.

The receptors either make use of G-protein coupling with second messengers (such as cAMP, $IP_3$ and DAG), or they are directly associated with ion channels where they alter the influx of sodium, potassium, calcium or chloride. Receptors of the former kind are known as **metabotropic** receptors,

while those of the latter kind are known as **ionotropic** receptors when the receptors of the amino acid transmitters (i.e. glycine, glutamate, aspartate and GABA) are referred to.

Neurotransmitters may act in one or more of three different ways:

- They may elicit either inhibitory or excitatory responses in postsynaptic membranes. **Excitation** implies the **depolarisation** of the postsynaptic membrane, while **inhibition** is the **hyperpolarisation** of the membrane.
- They may act as **neuromodulators**, meaning that they have the ability to modulate (modify or adjust) the capacity of the postsynaptic membrane to respond to other neurotransmitters.
- They may act as **co-transmitters**, meaning that they may be released from a neuronal end-bulb together with another neurotransmitter substance, so that the one transmitter may enhance the effects of the other.

These neurotransmitters and their receptor systems are described in more detail in the sections that follow.

## 4.6 Adrenergic receptors

***Important adrenergic receptors and their subtypes:***
- α-adrenergic receptors, with $\alpha_1$- and $\alpha_2$-subtypes
- β-adrenergic receptors, with $\beta_1$-, $\beta_2$- and $\beta_3$-subtypes

***Neurotransmitters:***
- Noradrenaline (NA) facilitates normal sympathetic nervous system functioning.
- Adrenaline (A), the neurohormone, augments the 'fight-or-flight' response.

***Inside the central nervous system (CNS):***
- $\alpha_1$- and $\beta_1$-receptors are involved in **excitatory** CNS functioning.
- $\alpha_2$- and $\beta_2$-receptors are involved in **inhibitory** CNS functioning.
- Some notable CNS functions which are influenced by these adrenergic receptors are mood processing, anxiety processing and sensory processing, facilitating alertness and wakefulness. The catecholamines may produce fear, anxiety, aggression, irritability and emotional outbursts.

Noradrenaline, together with dopamine and adrenaline, are called the **catecholamines**. They constitute three different products, derived from three different stages of the same enzymatic conversion process, which utilises the amino acid **tyrosine** as its base sub-strate. Figure 4.3A illustrates this process and elucidates the relationship between dopamine, noradrenaline and adrenaline.

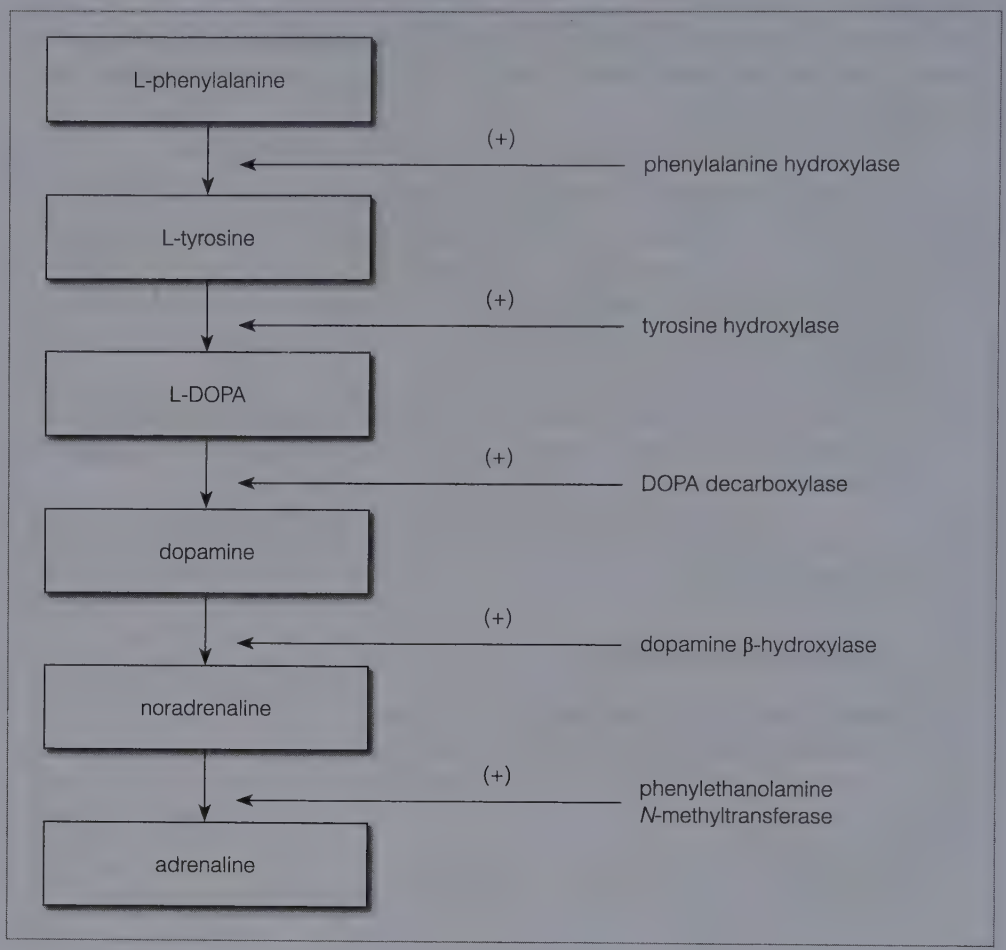



**Figure 4.3A Catecholamine synthesis**

Tyrosine may be derived from dietary intake or may be synthesised from the essential amino acid **phenylalanine**, which is found in the liver. **Phenylalanine hydroxylase** is the enzyme that converts phenylalanine into tyrosine. Persons suffering from **phenylketonuria** have an insufficiency of phenylalanine hydroxylase.

Adrenaline, the neurohormone of the sympathetic nervous system, is released into the bloodstream by the secretory cells of the adrenal medulla. The latter should be viewed as an enlarged and specialised sympathetic ganglion. About 10% of the medullary cells produce and secrete noradrenaline. Roughly 80 to 90% of these cells contain the additional enzyme **phenylethanolamine *N*-methyltransferase**, which converts noradrenaline to adrenaline and therefore releases adrenaline during stressful conditions such as anxiety, fear, pain, physical trauma and exertion or a sharp decrease in environmental temperature. Refer to figure 4.3B.

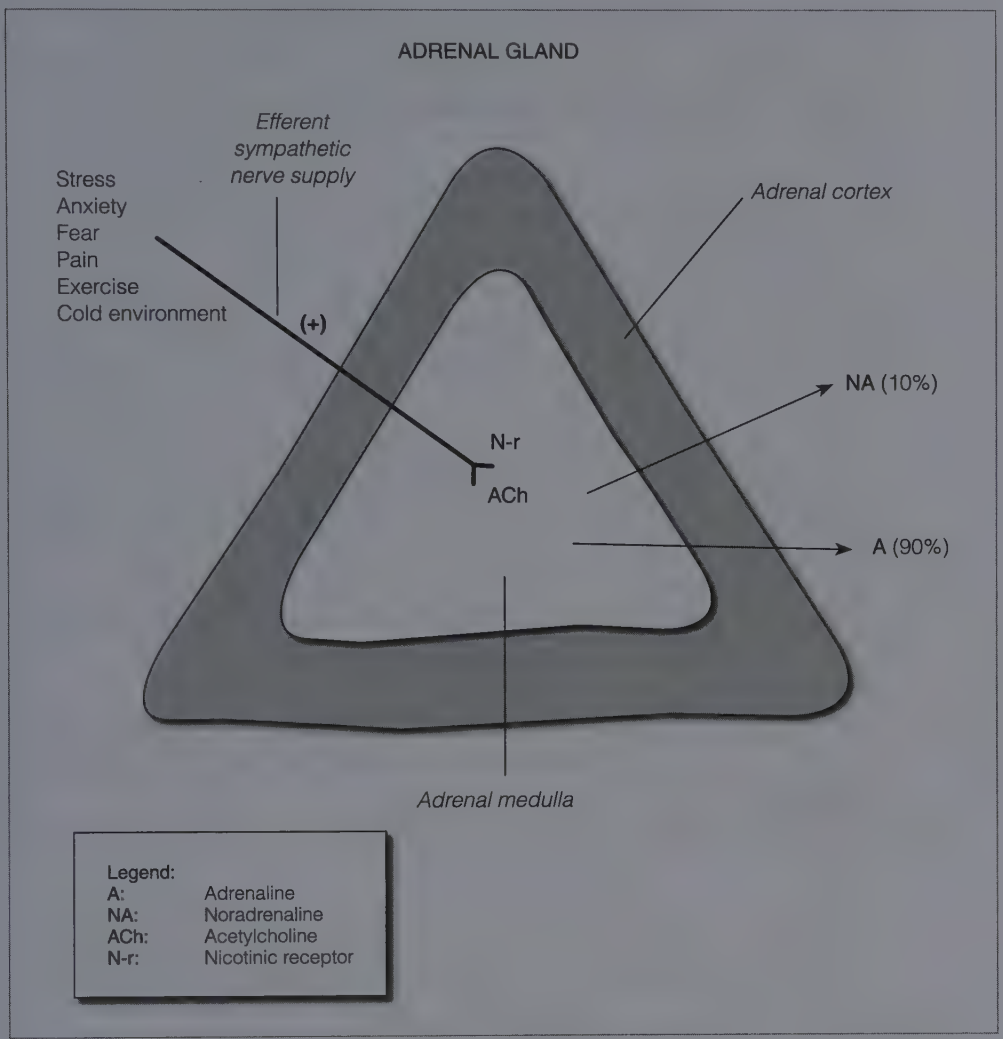



**Figure 4.3B Noradrenaline and adrenaline release from the adrenal medulla**

When the catecholamines are present in normal physiological concentrations, noradrenaline may be expected to stimulate α-receptors, adrenaline will stimulate β-receptors and dopamine will stimulate dopamine-receptors. Their selectivity, however, decreases when **supraphysiological** dosages are administered.

## 4.6.1 The α-adrenergic receptors

- The $\alpha_1$-receptors:
  - These are **postsynaptic** receptors.
  - Their **second messengers** are $IP_3$ and DAG, as well as intracellular calcium ions (see paragraph 3.3).
  - Stimulation of these receptors produces **smooth muscle contraction**.

- The $\alpha_1$-receptors are present on:
  - The vascular smooth muscle of most arterioles and veins in the body: stimulation produces **vasoconstriction** and a subsequent rise in arterial blood pressure.
  - The radial muscle (or dilator pupillae muscle) of the eye: stimulation produces **mydriasis** (dilatation of the pupil). Refer to paragraph 12.2.
  - The trigone (the triangular area between the openings of the two ureters and the opening of the urethra on the inside of the urinary bladder) and the bladder neck: in males, stimulation causes the trigone and bladder neck to contract during ejaculation. This effectively prevents retrograde ejaculation into the bladder. The seminal vesicles and vas deferens also contain $\alpha_1$-receptors that facilitate their contraction during ejaculation. This propels semen into the prostatic urethra, from where emission (ejection) then takes place. It is of interest to note that parasympathetic nerve fibres innervate the blood vessels of the external genitalia, including the penis and clitoris. Also refer to paragraph 10.3.
  - The smooth muscle sphincters of the bladder and gastrointestinal tract: stimulation produces smooth muscle contraction.
- The $\alpha_2$-receptors:
  - For all practical purposes these are **presynaptic** receptors that are found on sympathetic neurons, although blood platelets, and also some **postsynaptic** tissues, possess $\alpha_2$-receptors.
  - Stimulation of these receptors decreases cAMP (see paragraphs 3.3 and 4.6.4).
  - Presynaptic receptor stimulation provides for the inhibition of further NA release through a 'negative' feedback mechanism. This provides these neurons with an **auto-regulatory mechanism**. The resultant effect is a decrease in **sympathetic out-flow**.
  - Stimulation in peripheral tissues produces, among other effects, decreased insulin secretion, decreased formation of aqueous humour in the eye and mediation of platelet aggregation.
  - In the central nervous system (CNS) the $\alpha_2$-receptors mediate certain effects, which include the regulation of arterial blood pressure.

### 4.6.2 The β-adrenergic receptors

- The $\beta_1$-receptors:
  - These are **postsynaptic** receptors.
  - Their **second messenger** is cAMP (see paragraphs 3.3 and 4.6.4).
- The $\beta_1$-receptors are present in/on:
  - The heart, both in the supraventricular (SA-node and AV-node), and the ventricular chambers: stimulation produces **positive cardiac effects**

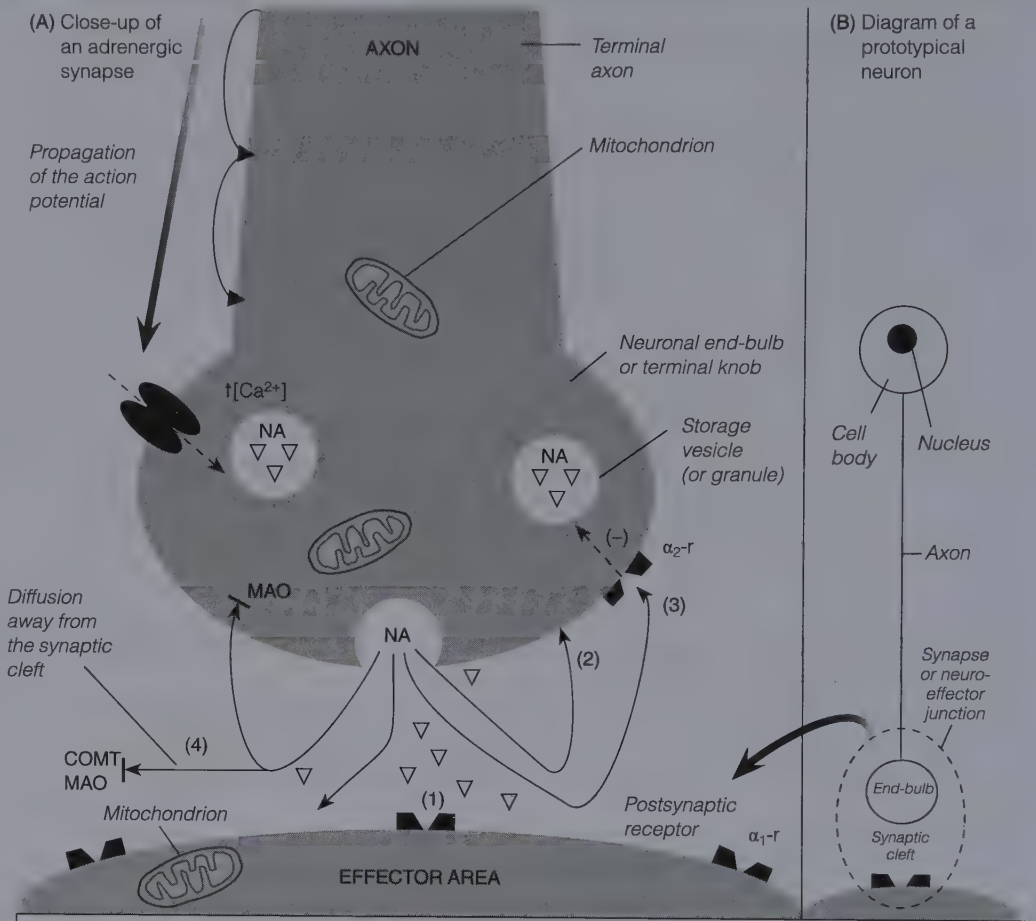
(i.e. stimulation of the heart). These effects are positively **chronotropic** (heart rate increases), positively **inotropic** (they increase the force of myocardial contraction, atrial and ventricular contractility and excitability), positively **dromotropic** (they increase depolarisation and discharge of the SA-node and increase the velocity, or rate, of AV-conduction) and positively **lusitropic** (they improve the relaxation functions of the myocardium and cardiac chambers).

- The juxtaglomerular cells of the vas afferens (in the kidney): stimulation increases **renin secretion**, with subsequent activation of the **RAAS** (the renin-angiotensin-aldosterone system). Also refer to paragraph 12.3.

- The $\beta_2$-receptors:
  - These are **postsynaptic** receptors.
  - Their **second messenger** is cAMP (see paragraphs 3.3 and 4.6.4).
  - Stimulation of these receptors produces **smooth muscle relaxation**, glycogenolysis, gluconeogenesis and some degree of skeletal muscle fibre contraction that produces muscle tremors in the presence of increased sympathetic outflow.
- Important $\beta_2$-receptors are present on:
  - The vascular smooth muscle of skeletal muscle blood vessels: stimulation produces **vasodilatation** of these vessels.
  - Bronchial smooth muscle: stimulation produces **bronchodilatation**.
  - The fundus of the uterus: stimulation causes **relaxation of the pregnant uterus** and may be utilised in the prevention of premature labour.
- The $\beta_3$-receptors:
  - These are **postsynaptic** receptors.
  - Their **second messenger** is cAMP (see paragraphs 3.3 and 4.6.4).
  - $\beta_3$-receptors are present in adipose tissue, where stimulation leads to **lipolysis** (hydrolysis of triglycerides in adipose tissue, which releases fatty acids into the bloodstream during stressful situations).

Both noradrenaline and adrenaline exhibit so-called calorigenic effects on the body, meaning that they will increase the body's metabolic rate, oxygen requirements and heat production. The catecholamines have plasma half-lives of less than a minute. They are degraded, and their actions terminated, by the enzymes monoamine oxidase (MAO) in adrenergic nerve endings and elsewhere, and by catechol-O-methyltransferase (COMT) in various tissues, including the liver, lungs, kidneys and intestines. Refer to paragraph 4.6.3 and figure 4.4.

## 4.6.3 Noradrenaline as an example of neurotransmission




Legend:

Voltage-gated calcium-channel, opened in response to depolarisation resulting from the propagation of the action potential (the influx of calcium-ions [$Ca^{2+}$] facilitates the release of NA from its storage vesicles through the process of exocytosis, i.e. calcium-induced exocytosis)

Adrenergic receptors, both pre-synaptic and post-synaptic

▽ Molecules of noradrenaline (NA) that are released into the synaptic cleft

COMT: Catechol-O-methyltransferase

MAO: Monoamine oxidase

NA: Noradrenaline

(–): Negative feedback

Events:

(1) Postsynaptic receptor binding and stimulation (using postsynaptic $\alpha_1$-receptors as an example)

(2) Re-uptake of NA into the neuronal end-bulb, or terminal knob

(3) Stimulation of the presynaptic $\alpha_2$-receptor with subsequent negative feedback

(4) Degradation by the MAO and COMT enzymes. MAO is present in the presynaptic neuronal end-bulb and plays a particularly significant role in the biotransformation of NA within the nerve ending. COMT and MAO are also widely distributed throughout the body and are particularly abundant in the kidneys and liver. (Also note that these two enzymes can metabolise all of the catecholamines, i.e. dopamine, noradrenaline and adrenaline.)

**Figure 4.4 Noradrenaline release into the synaptic cleft**

Neurotransmission across a synaptic cleft usually involves **four key events**, namely neurotransmitter release, receptor binding, inactivation and re-uptake.

Figure 4.4 illustrates the various events involved in neurotransmitter release, receptor binding, inactivation and re-uptake, using noradrenaline and an autonomic nervous system efferent as an example. The principles illustrated in this diagram apply to neurotransmission within the CNS as well as throughout the human body.

### 4.6.4 G-protein coupling and the role of adenylyl cyclase

Receptors that are G-protein coupled, such as the $\alpha_2$-receptor and the β-receptors, exert their intracellular effects through intracellular second messengers, as explained before. The second messenger cAMP is of particular importance in the functioning of β-adrenergic receptors, and warrants further explanation. Refer to figure 4.5.

The enzyme **adenylyl cyclase** converts intracellular ATP to cAMP. Adenylyl cyclase, therefore, must be induced by G-protein coupling of a 'stimulatory' (or $G_s$) nature. Stimulation of $\alpha_2$-receptors, on the other hand, produces a $G_i$ (or 'inhibitory') coupling. **Phosphodiesterase** (PDE) rapidly terminates the action of cAMP by converting it to the inactive 5'-AMP.

As part of the abovementioned process, cAMP becomes the key to the actions that take place inside cells. Cyclic AMP influences other intracellular enzymes (namely tissue-specific protein kinases) to produce unique cellular effects. Therefore the specific enzymes that are present within the cells in question determine these effects.

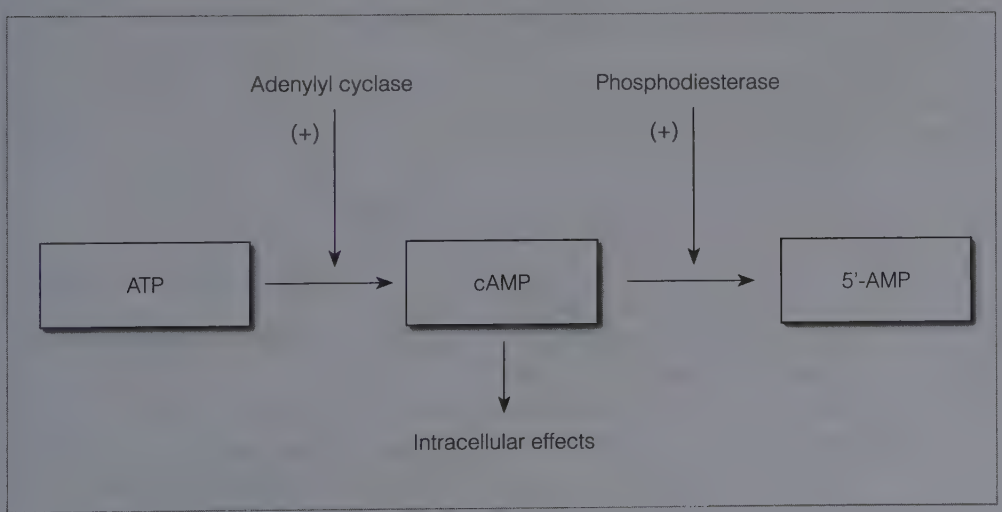



**Figure 4.5 Adenylyl cyclase, cAMP and phosphodiesterase**

## 4.7 Cholinergic (acetylcholine) receptors

***Important receptors and their subtypes:***

- Muscarinic (M) acetylcholine receptors, with $M_1$-, $M_2$- and $M_3$-subtypes (as well as $M_4$- and $M_5$-receptors)
- Nicotinic (N) acetylcholine receptors, with $N_m$- and $N_n$-subtypes, as well as the '$N_{CNS}$'-subtype in the brain and spinal cord

***Neurotransmitter:***

- Acetylcholine (ACh)

***Inside the central nervous system (CNS):***

- $M_1$- and $M_3$-receptors (as well as $M_5$-receptors, which appear to be similar to the $M_1$- and $M_3$-receptors) are involved in **excitatory** CNS functioning.
- $M_2$-receptors (and the similar $M_4$-receptors), are involved in **inhibitory** CNS functioning.
- The nicotinic receptors in the CNS (i.e. the '$N_{CNS}$'-receptors) are involved in **excitatory** CNS functioning.
- Some notable CNS functions which are influenced by these cholinergic receptors are: motor coordination, memory and sensory processing, learning, sleep, arousal and awareness. Acetylcholine is present in high concentrations within the cerebral cortex, basal nuclei, hippocampus and thalamus. It opposes dopamine in the basal nuclei (more specifically, in the corpus striatum) that form part of the extrapyramidal system. Acetylcholine achieves neuromodulation and increases cortical activity.

Acetylcholine is synthesised from choline and active acetate (acetyl-CoA) in nerve endings. The catalytic enzyme responsible for its formation is known as **choline acetyltransferase**. Its degradation, on the other hand, is achieved by rapid hydrolisation (within milliseconds). Acetylcholinesterase, in synaptic clefts and motor endplates, and pseudocholinesterase (also known as butyrylcholinesterase), in the liver and blood plasma, are two of the enzymes that break down acetylcholine. Choline is obtained from dietary intake, and acetyl-CoA is derived from mitochondrial action.

### 4.7.1 The muscarinic acetylcholine receptors

- The $M_1$-receptors:
  - These are referred to as '**neural**' receptors.
  - Their **second messengers** are $IP_3$ and DAG, as well as intracellular calcium ions (see paragraph 3.3).
  - Their receptors are found in the CNS, in autonomic ganglia and on presynaptic nerve terminals. The presynaptic receptors have a similar function to presynaptic $\alpha_2$-receptors, but work in terms of ACh release.
- The $M_2$-receptors:
  - These are referred to as **'cardiac'** receptors.

- Stimulation of these receptors **decreases** cAMP (see paragraph 3.3).
- These receptors are found in **supraventricular cardiac tissue,** on the SA-node and AV-node in particular. Stimulation of these receptors causes a slowed rate of AV-conduction and subsequently also a slowed heart rate. These receptors are, however, also present inside the central nervous system.

➲ The $M_3$-receptors:
- These are referred to as **'smooth muscle/glandular'** receptors.
- Their **second messengers** are $IP_3$ and DAG, as well as intracellular calcium ions (see paragraph 3.3).
- These receptors are found on **smooth muscle** and **exocrine glands**. Stimulation of these receptors causes smooth muscle contraction and stimulation of exocrine gland secretions (e.g. saliva, bronchial secretions and perspiration).

➲ The $M_4$- and $M_5$-receptors are both present in the CNS.

### 4.7.2 The nicotinic acetylcholine receptors

➲ The $N_m$-receptors:
- These are the **'neuromuscular'** receptors, and therefore actually 'belong' to the somatic nervous system.
- Stimulation of these receptors on the motor endplate produces skeletal muscle contraction.

➲ The $N_n$-receptors:
- These are referred to as **'neuronal'** receptors.
- They are found in all autonomic ganglia. Their stimulation therefore causes excitation of postganglionic neurons.

➲ The '$N_{CNS}$'-receptors:
- These are excitatory receptors, found on both presynaptic and postsynaptic neuronal membranes in the brain and spinal cord.
- The CNS effects of nicotine are attributable to the stimulation of at least one of their subtypes.

## 4.8 Dopamine (DA) and its receptors

### 4.8.1 The $D_1$-type receptors ($D_1$ and $D_5$)

➲ Peripherally (in terms of neurotransmission) these receptors are present on vascular smooth muscle cells, particularly those of the coronary, renal, mesenteric and intracerebral vessels. They are also present in the CNS.

➲ Their **second messenger** is cAMP (see paragraph 3.3).

➲ Peripheral receptor stimulation relaxes vascular smooth muscle with subsequent vasodilatation and **increased blood supply** to organs such as

the kidneys, brain and myocardium, as well as those that are supplied by the mesenteric circulation.

***Important dopamine receptors and their subtypes:***

- Dopamine receptors of the $D_1$-type ($D_1$- and $D_5$-subtypes)
- Dopamine receptors of the $D_2$-type ($D_2$-, $D_3$- and $D_4$-subtypes)

***Neurotransmitter:***

- Dopamine (DA)

***Inside the central nervous system (CNS):***

- $D_1$-receptors occur together with $D_5$-receptors, which are similar to them.
- $D_2$-receptors occur together with $D_3$- and $D_4$-receptors, which are similar to them.

The dopamine receptors in the CNS are involved in **inhibitory** CNS functioning.

- The following areas within the CNS, which are of particular pharmacological importance, contain various dopamine-receptors:
  - ***The chemo-emetic trigger zone*:** Refer to paragraph 12.1.
  - ***The nigrostriatal pathway of the extrapyramidal system*:** This dopaminergic pathway links the substantia nigra to the corpus striatum (i.e. two of the basal nuclei that form part of the extrapyramidal system) and has an important inhibitory function. It is opposed by the excitatory function of ACh in the corpus striatum. The extrapyramidal system facilitates motor coordination and helps to maintain normal gait and posture. Competitive antagonists of these receptors may therefore elicit **akathisia** (motor restlessness and an inability to maintain seated posturing), skeletal muscle **dystonia** (abnormal muscle tone, usually rigidity) and **dyskinesia** (difficulty in performing voluntary movements). Therefore, dopamine and acetylcholine oppose one another to produce a balance between muscle tone and muscle relaxation.
  - ***The mesocortical and mesolimbic pathways*:** These pathways connect areas of the midbrain (mesencephalon) to the prefrontal cortex and the limbic system respectively and are involved in mood states and motivation (including reaction to environmental stimuli), as well as the ability to judge behaviour, reasoning, conscience and other functions. Increased activity in the mesolimbic pathway could result in hallucinations and delusions, while decreased activity in the mesocortical pathway that projects to the prefrontal cortex could result in a state of withdrawal, apathy and a loss of motivation (refer to chapter 5).
  - ***The tubero-infundibular pathway of the hypothalamus*:** This pathway transports dopamine to the anterior hypophysis, where it inhibits the release of prolactin, thereby decreasing breast milk production. For this reason dopamine is sometimes referred to as a 'prolactostatin' (a hypothalamic substance that inhibits the synthesis and release of prolactin from the anterior hypophysis).

### 4.8.2 The $D_2$-type receptors ($D_2$, $D_3$ and $D_4$)

- These receptors are present in the sympathetic and central nervous systems, and modulate neurotransmission in these systems.

- Stimulation of these receptors **decreases** cAMP (see paragraph 3.3).

## 4.9 Serotonin (5-hydroxytryptamine, 5-HT) and its receptors

***Important receptors and their subtypes:***

- 5-hydroxytryptamine (5-HT) receptors, with their subtypes:
  - 5-$HT_1$, with a significant distinction between 5-$HT_{1A}$- and 5-$HT_{1D}$-receptors (other subtypes also exist)
  - 5-$HT_2$-receptors (further subtypes also exist, e.g. 5-$HT_{2A}$ and 5-$HT_{2C}$)
  - 5-$HT_3$-receptors
  - 5-$HT_4$-receptors
  - 5-$HT_5$-, 5-$HT_6$- and 5-$HT_7$-receptors (these receptors are less well known)

***Neurotransmitter:***

- 5-hydroxytryptamine (5-HT)

***Inside the central nervous system (CNS):***

- 5-$HT_{1A}$- and 5-$HT_{1D}$-receptors are involved in **inhibitory** CNS functioning.
- 5-$HT_2$-, 5-$HT_3$- and 5-$HT_4$-receptors are involved in **excitatory** CNS functioning.
- Some notable CNS functions which are influenced by these 5-HT-receptors are: appetite, vomiting, the processing of emotions, pain and emotional responses, mood, wakefulness, sleep and hallucinations. 5-HT-receptors are particularly abundant in the neuronal tracts that project from the raphe nuclei in the pons and central brain stem. Serotonin is converted to melatonin in the pineal gland.

Serotonin is synthesised from the essential amino acid tryptophan. The highest concentrations of serotonin in the body are found in the enterochromaffin cells of the gastrointestinal tract. It is also present in platelets and specific neurons of the central nervous system. It acts as a vasoconstrictor (however, this depends on the specific blood vessels in question, as well as the prevailing sympathetic nervous system activity) and exhibits pro-aggregatory effects on blood platelets. Serotonin is partly degraded by MAO; otherwise there is re-uptake of the unchanged serotonin. It also acts as an **autacoid** (i.e. a so-called local hormone) in peripheral tissues.

### 4.9.1 The 5-$HT_1$-receptors

- Stimulation of these receptors **decreases** cAMP (see paragraph 3.3).
- The 5-$HT_{1A}$-receptors may be influenced in the management of **anxiety** (see chapter 5).
- The 5-$HT_{1D}$-receptors may be influenced in the management of **migraine headaches** (see paragraph 12.5.2).
- Serotonin (or 5-HT) is a vasoactive substance, implying that 5-$HT_{1D}$-receptor stimulation will result in **vasoconstriction**. These vascular 5-HT-receptors are widespread throughout the body.

### 4.9.2 The 5-$HT_2$-receptors

- Their **second messengers** are $IP_3$ and DAG, as well as intracellular calcium ions (see paragraph 3.3).
- These receptors (more specifically the 5-$HT_{2A}$-receptor subtype) may be influenced in the management of **psychotic disorders** (e.g. schizophrenia). Refer to chapter 5.

### 4.9.3 The 5-$HT_3$-receptors

- These receptors are involved in the ligand-gating of cation ($Na^+$ and $K^+$) channels.
- Centrally, these receptors are found in the solitary tract nucleus and chemoemetic trigger zone, while peripherally they are found at the origins of vagal afferents. They are therefore involved in **nausea and vomiting** (refer to paragraph 12.1).

### 4.9.4 The 5-$HT_4$-receptors

- Their **second messenger** is cAMP (see paragraph 3.3).
- Peripherally, 5-$HT_4$-receptors are involved in the regulation of gastrointestinal muscle tone and **motility** (spontaneous movement).

## 4.10 Histamine (H) and its receptors

***Important receptors and their subtypes:***

- Histamine (H) receptors, with their subtypes:
  - $H_1$-receptors
  - $H_2$-receptors
  - $H_3$-receptors

***Neurotransmitter:***

- Histamine (H)

***Inside the central nervous system (CNS):***

- Histamine acts as an **excitatory** neurotransmitter within the CNS, via $H_1$-receptor activation. Antagonists at these central $H_1$-receptors cause sedation.
- Some notable CNS functions which are influenced by the histamine receptors are: vasomotor control, sleep, arousal and wakefulness, and temperature regulation.
- All three receptor subtypes are present within the CNS.
- However, $H_3$-receptors mostly occupy presynaptic positions. Together with the postsynaptic $H_2$-receptors they play an inhibitory role within the CNS.

Histamine is an interesting and important signal transmitter substance, since it acts both as a neurotransmitter within the CNS and as an important **autacoid**

within peripheral tissues, a characteristic that it shares with serotonin. Histamine is synthesised from the amino acid **histidine**.

Peripherally, histamine is stored in a bound and inactive form within the storage vesicles (or granules) of **mast cells** (in tissues) and **basophils** (in the bloodstream). Mast cells have a highly predictable distribution pattern inside the human body since they serve to 'protect' open-ended organ systems. These organ systems, being 'open' to the external environment, contain an abundance of these cells. These are the open-ended tracts of the respiratory and gastrointestinal systems.

The obvious exposure of the skin to the external environment also explains the abundance of mast cells found within it, especially in those areas that readily 'blush'. Histamine is also secreted in the fundus of the stomach, where its function is to interact with $H_2$-receptors and thereby stimulate the secretion of gastric acid by the stomach's parietal cells (see chapter 9).

Histamine is a particularly important mediator of the **inflammatory process**. This process, as a pathophysiological entity, is activated within peripheral tissue areas when **mast cell degranulation** occurs. This degranulation may be triggered in the following ways:

- Physical trauma of the tissue cells in question
- An interaction between IgE (immunoglobulin E) antibodies and suitable IgE antigens (i.e. the formation of antigen–antibody complexes) that causes **allergic reactions** (localised histamine release) or **anaphylaxis** (systemic histamine release)
- Exposure to snake and wasp venom
- Large molecules such as those found in the serum of animals (e.g. equine serum), or the rather large molecules of dyes and alkaloid bases such as ***morphine***, and the depolarising skeletal muscle relaxants such as *tubocurarine* and *atracurium*

**Note 4.1**

The fact that certain drug and venom molecules may cause mast cell degranulation therefore does not necessarily imply that there has been an allergic reaction to one of the said molecules.

### 4.10.1 The $H_1$-receptors

- Their **second messengers** are $IP_3$ and DAG, as well as intracellular calcium ions (see paragraph 3.3).
- They are involved in **allergic reactions**. Some of the effects of $H_1$-receptor stimulation include: allergic rhinitis, conjunctivitis, urticaria, pruritus

(histamine stimulates sensory neurons to produce itching) and angioneurotic oedema.

- Stimulation of these receptors is also responsible for the vasodilatation and the increased vascular (capillary) permeability that accompany allergic reactions and inflammation. Erythema and oedema, including potentially fatal glottis oedema, may ensue. Blood pressure may be decreased to such an extent that anaphylactic shock develops.
- Bronchial smooth muscle contraction causes bronchoconstriction (with wheezing and possible bronchospasm). Contraction of gastrointestinal smooth muscle results in colic, and exocrine gland secretions are increased through $H_1$-receptor stimulation.

### 4.10.2 The $H_2$-receptors

- Their **second messenger** is cAMP (see paragraph 3.3).
- These receptors are involved in allergic reactions as well, but to a lesser extent. Their primary function is to facilitate the secretion of gastric acid in the stomach.
- $H_2$-receptors are also present in the heart. When stimulated they increase heart rate and contractibility.

### 4.10.3 The $H_3$-receptors

- $H_3$-receptors mostly occupy presynaptic positions on axonal end-bulbs. Stimulation of these receptors will result in a decreased release of various neurotransmitters.
- Allergic reactions and anaphylaxis are discussed in more detail in paragraph 12.5.1.

## 4.11 The opioid peptides and their receptors (μ, δ, κ and σ)

***Important receptors and their subtypes:***

- Receptors utilised by the endorphins, dynorphins, enkephalins and other endogenous opioid peptides, with their subtypes:
  - mu- (μ) and delta- (δ) receptors
  - kappa- (κ) receptors
  - sigma- (σ) receptors (σ-receptors are not considered to be true opioid peptide receptors, but they do explain many of the unwanted effects of some opioid analgesics such as *pentazocine*)

***Neurotransmitters:***

- Endorphins (especially β-endorphin), dynorphins, enkephalins (e.g. [Leu]- and [Met]-enkephalin) and other endogenous opioid peptides

***Inside the central nervous system (CNS):***

- The opioid peptides are **inhibitory** neurotransmitters within the CNS. Opioid receptors are found throughout the brain, especially in the limbic system, as well as the brain stem and the posterior (dorsal) horn of spinal cord grey matter.
- Some notable CNS functions which are influenced by these receptors are: emotions and the processing of pain stimuli (the emotional aspects of pain perception), mood and consciousness. Stimulation of these peptide receptors may also suppress brain stem functions such as coughing and respiration.
- All of the receptor subtypes are present within the CNS.
- Stimulation of these receptors causes a **decrease** in cAMP (see paragraph 3.3), inhibits the opening of calcium-channels, and facilitates the opening of potassium-channels.

### 4.11.1 mu- (μ) and delta- (δ) receptors

These two receptor subtypes closely resemble one another in their functionality. A huge problem with opioid analgesics, however, is tolerance (especially in chronic pain management and chronic care settings). According to Sommers (2000: 83), patients who develop tolerance to the analgesic effects of mu-receptor agonists could still obtain satisfactory levels of pain relief with delta-receptor stimulation.

There are at least two important mu-receptor subtypes:

- **$\mu_1$-receptors:** These receptors are involved in the analgesic and euphoric effects of the opioids and are found in the CNS.
- **$\mu_2$-receptors:** These receptors are found in the CNS, where they are implicated in the respiratory depression caused by the opioid analgesics, and also peripherally in the GIT, where they cause constipation.

The delta-receptors are also of importance in peripheral tissues. Further subtypes of these receptors, as well as subtypes of the kappa- and sigma-receptors, also exist.

### 4.11.2 Effects of opioid peptide receptor stimulation

Table 4.1 gives an exposition of the most significant effects that stimulation of the opioid receptors has on nervous system functioning. It also highlights the usefulness and some of the expected side-effects of the opioid analgesics.

**Table 4.1 Opioid receptors**

| | Mu (μ) | Delta (δ) | Kappa (κ) | Sigma (σ)* |
|---|---|---|---|---|
| **Pain** | Strong analgesic effects at spinal and supraspinal (brain) level, as well as peripherally | Spinal analgesic effects | Peripheral and spinal analgesic effects | |
| **Mood and consciousness** | Euphoria, sedation | | Sedation, dysphoria | Dysphoria, hallucinations and nightmares |
| **Breathing** | Suppresses the respiratory centre (also suppresses the cough centre) | Some respiratory depression | | Stimulation, tachypnoea |
| **Blood pressure and pulse rate** | May cause bradycardia | | | Increases blood pressure and pulse rate |
| **Gastrointestinal tract** | Smooth muscle contraction with spastic paralysis of the small intestine, leading to constipation; also causes nausea and vomiting | | | |
| **Other** | Miosis | | | Mydriasis, hypertonia |

*Not a true opioid receptor.

## 4.12 γ-aminobutyric acid (GABA) and its receptors

GABA is an amino acid transmitter which is found in very high concentrations within the CNS. Its synthesis from glutamate is catalysed by **glutamic acid decarboxylase (GAD)**, which utilises vitamin $B_6$ as a co-factor. (This explains why a vitamin $B_6$-deficiency results in CNS hyperexcitability and convulsions.) GABA also acts as an important transmitter in the control of movement.

Chorea-like conditions, such as Huntington's disease, are characterised by decreased GABA and glutamate decarboxylase concentrations.

***Important receptors and their subtypes:***

- $GABA_A$-receptors
- $GABA_B$-receptors

***Neurotransmitter:***

- γ-aminobutyric acid (GABA)

***Inside the central nervous system (CNS):***

- GABA is the major **inhibitory** neurotransmitter within the CNS. It is a particularly important transmitter in the cerebellum and basal nuclei.
- Some notable CNS functions which are influenced by these GABA-ergic receptors are: motor coordination (control of movement) and control over the excitability of neurons.

The $GABA_A$-receptors are **ionotropic** (they are in fact macromolecular complexes that act as ligand-gated chloride channels, and are also referred to as $GABA_A$-chloride ionophores), and the $GABA_B$-receptors are **metabotropic** in nature (see paragraph 4.5). Table 4.2 provides a comparison between the GABA-receptors and the main receptor subtypes of the other three amino acid transmitters, namely glycine, glutamate and aspartate (also refer to paragraph 4.13).

**Note**: The benzodiazepines (BZDs) have specific BZD-receptors (or BZD-binding sites). These receptors are in fact found **on** the $GABA_A$-receptor complexes in the central nervous system, but are distinct from the actual GABA-binding sites (refer to paragraph 5.1.2 and note 5.1 for more information on these receptors).

## 4.13 Glycine, glutamate and aspartate, and their receptors

***Important receptors and their subtypes:***

- Glycine-receptors
- EAA-receptor subtypes, namely NMDA-, AMPA- and kainate-receptors

***Neurotransmitters:***

- Glycine
- Excitatory amino acid (EAA) transmitters, namely glutamate and aspartate

***Inside the central nervous system (CNS):***

- Glycine is an **inhibitory** neurotransmitter, similar to GABA and particularly prominent in the brain stem and spinal cord.
- Glutamate and aspartate (i.e. the EAAs) are very powerful excitatory neurotransmitters and both are found in very high concentrations within the CNS.
- Glutamate is the principal excitatory neurotransmitter in the CNS. The opposing excitatory and inhibitory effects of glutamate and GABA respectively, control the overall excitability of the central nervous system.

Amino acids are found throughout the body and fulfil a wide variety of important biochemical functions. However, four amino acids that are of particular interest to pharmacology have also been ascribed neurotransmitter roles within the CNS. These are GABA, glycine, glutamate and aspartate. Glycine is an inhibitory amino acid transmitter, similar to GABA. Glutamate and aspartate are powerful excitatory amino acid (EAA) transmitters. Table 4.2 provides a summary of these amino acid transmitters and their main receptor subtypes.

Glutamate, in high concentrations, can induce neurotoxic cell death. This property of glutamate is referred to as **excitotoxicity**, a characteristic that has been linked to pathological conditions such as brain ischaemia and hypoglycaemia where a massive release of the amino acid transmitter coincides with impaired neuronal re-uptake. There may also be a link between high levels of glutamate and an increase in seizure activity in the brain.

**Table 4.2 Receptors of the amino acid transmitters**

| | **Excitatory amino acid (EAA) transmitters** | | | | **Inhibitory amino acid transmitters** | | |
|---|---|---|---|---|---|---|---|
| **Transmitter** | Glutamate, Aspartate | Glutamate | | | GABA | | Glycine |
| **Receptor name** | NMDA-r | AMPA-r | Kainate-r | mGlu-r | $GABA_A$-r | $GABA_B$-r | Gly-r |
| **Alternative name** | GluN-r | GluA-r | GluK-r | - | - | - | - |
| **Receptor type** | Ionotropic | Ionotropic | Ionotropic | Meta-botropic | Ionotropic | Meta-botropic | Ionotropic |
| **Receptor motif** | Ligand-gated ion channel | Ligand-gated ion channel | Ligand-gated ion channel | G-protein coupled receptor (GPCR) | Ligand-gated ion channel | G-protein coupled receptor (GPCR) | Ligand-gated ion channel |
| **Comments** | The danger exists of NMDA-r and mGlu-r involvement in the excitotoxic effects of high glutamate concentrations in the brain. | | | | The $GABA_A$-r also constitutes the site of action for the benzodiazepines and barbiturates. | | |

## 4.14 Selective and non-selective receptor influencing

Drugs may act as **selective** or **non-selective** agonists or competitive antagonists. The more selective a drug is, the more specific the receptor subtype is with which it interacts.

Drugs may exhibit selectivity for a specific receptor system, one or more of the system's receptor subtypes, or even for a specific function of a receptor subtype. To fully appreciate the concept of selectivity, study the following three examples of drugs acting on the adrenergic receptor system:

- ***Adrenaline*** is a full agonist at both α- and β-receptors. Therefore, it is said to be a **non-selective** adrenergic agonist (also known as a non-selective sympathomimetic drug – i.e. a drug that **mimics** the actions of the sympathetic nervous system).
- *Isoprenaline (isoproterenol),* a synthetic catecholamine, acts as an agonist at β-receptors, but not at α-receptors. Therefore, it is said to a **β-selective adrenergic agonist**, but it is a **non-selective β-agonist**, since it does not distinguish between the $\beta_1$- and $\beta_2$-receptor subtypes (although it is a more potent agonist at the $\beta_2$-receptor than at the $\beta_1$-receptor).
- *Dobutamine* is a highly **selective $\beta_1$-receptor agonist**, and even displays selectivity for the **positive inotropic effects** of the sympathomimetic drugs.
- Similarly, the **β-receptor blockers** (i.e. competitive antagonists at β-receptors) may be divided into **non-selective β-blockers** (i.e. those that act as competitive antagonists at both $\beta_1$- and $\beta_2$-receptors), and **selective $\beta_1$-receptor blockers** (the so-called cardio-selective β-blockers).

The above examples are described in more detail in chapter 6. The **multipotent receptor blockers** were discussed in paragraph 3.5.

# Part 2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CHAPTER FIVE

# Drugs and the nervous system

**Suggested revision**

***Anatomy and physiology:***

- Central and peripheral divisions of the nervous system
- Neurons, nerve impulses and neurotransmitters
- The blood–brain barrier (BBB), choroid plexus, brain ventricles, meninges and cerebrospinal fluid (CSF)
- The diencephalon (thalamus, hypothalamus and epithalamus), limbic system, basal nuclei, reticular formation, reticular activating system (RAS) and autonomic nervous system
- Consciousness, wakefulness, sleep, perception, cognition, learning, memory, mood, behaviour and behavioural motivation
- Somatic nervous system, motor pathways and motor control

***Pathology, pathophysiology and neuropsychology:***

- Pain
- Anxiety, depression and schizophrenia
- Parkinson's disease, Alzheimer's disease and epilepsy

The major neurotransmitters, and aspects of neurotransmission itself, were discussed in chapter 4. The present chapter describes how nervous system functioning is influenced by a variety of drugs that aim to manage problems such as visceral pain, seizures, anxiety and mood disorders, degenerative nervous system disorders and psychoses, or to bring about a state of sedation or general anaesthesia.

## 5.1 Drug action within the central nervous system (CNS)

Drugs may be used to augment or suppress (i.e. modulate) existing central nervous system functioning.

### 5.1.1 Opioid analgesics

The receptors (i.e. μ, δ, κ and σ) of the opioid peptides were discussed in the previous chapter. Two major drug groups are utilised in the pharmacotherapeutic management of pain, namely the opioid analgesics for (moderate to) severe pain (discussed here), and the non-opioid analgesics that are generally used in the management of mild to moderate pain:

- **The opioid analgesics:** These drugs are either related to morphine in structure and action, or they are synthetic **derivatives** with different chemical structures. ***Morphine*** is by far the most important of the opioid analgesics. It is a **plant alkaloid** that is extracted from the wild opium poppy *Papaver somniferum*. A second alkaloid, ***codeine***, is extracted from the same plant. ***Codeine*** and ***morphine*** are classified as **phenanthrenes** (opioid alkaloids that act as narcotic analgesics). The **benzylisoquinolines** are alkaloids that do not display the typical effects of the opioid analgesics. *Papaverine* acts as an antispasmodic and *noscapine* as a cough suppressant. The opioid analgesics suppress the neurotransmission of pain sensations due to their primary action in the spinal cord and brain (i.e. where their *supraspinal* receptors are located). They are the drugs of choice in the management of visceral and severe pain.

  The opioid analgesics may be classified in a variety of ways. In clinical practice, however, the most practical classification is based upon the degree of efficacy that may be expected from each one of the more commonly used drugs. Therefore, a distinction is made between high-potency agents, low-potency agents, and opioid agents of intermediate potency. Some authors choose to refer to high-, low- and intermediate-efficacy agents. Their degree of potency, or efficacy, is dependent on whether they act as **full agonists** at μ-receptors, since most of the currently available opioid analgesics exert their analgesic effects via these receptors, whether they are **high- or low-affinity** μ-agonists, or whether they are μ-receptor **dualists**. Refer to paragraph 4.11. ***Naloxone*** is an opioid-receptor **antagonist**.

  Also note that the opioid analgesics, in contrast to the non-steroidal anti-inflammatory drugs (or NSAIDs), cannot be used in the management of pyrexia (fever) or inflammation.

### Opioid analgesics

- The opioid analgesics act as either full agonists (of high or low affinity) or partial agonists (dualists) at the opioid receptors (refer to paragraph 4.11). ***Morphine*** is more water-soluble than ***codeine***. It is a high-affinity agonist at μ-receptors and a very potent opioid. ***Codeine*** is not nearly as potent as morphine (it is a low-affinity agonist). The μ-agonists also cause smooth muscle contraction, and therefore produce a spastic paralysis of the small intestine, which leads to constipation.
- ***Pethidine***, *dipipanone* and *fentanyl* (as well as *sufentanil, alfentanil* and *remifentanil*) are examples of **full agonists**. Opioid **dualists** with analgesic effects, which act on the κ- and σ-receptors, are *pentazocine* and *tilidine*. *Pentazocine* produces a feeling of dysphoria and increases the blood pressure and pulse rate. *Tilidine* must be administered orally, since it is a pro-drug and only its active metabolite is pharmacologically active. *Buprenorphine* is a high-affinity dualist.
- ***Tramadol*** is a low-affinity μ-agonist which has negligible effects on the other opioid receptors. Unlike other opioid analgesics it also has serotonergic and noradrenergic properties.

- There is a very real danger that the full μ-receptor agonists will cause dependency; the dualists generally do not cause this problem.
- ***Pethidine*** (also known as *meperidine*) has a rapid onset of action, but its analgesic effects are limited to a few hours in duration. It has a toxic metabolite that accumulates with repeated administration, which makes it poorly suited to the management of chronic pain, but it is still suited to the postoperative setting. It is the opioid drug of choice in obstetrics, ureter colic and biliary obstruction.
- Other examples of opioid analgesics include *methadone* (high potency) and *dextropropoxyphene* (low potency).
- ***Morphine***, and the other opioid analgesics to varying degrees, can elicit adverse effects such as respiratory depression, truncal rigidity, sedation, nausea and vomiting, urinary retention, constipation, miosis, tolerance and dependence.
- ***Naloxone*** is a competitive antagonist at the opioid receptors but has a shorter half-life than morphine has, for instance. It may be used in cases of ***morphine*** and other opioid overdosage.

- **The non-opioid analgesics:** These drugs, in contrast to the opioid analgesics, act within peripheral tissues, where they facilitate the inhibition of pain impulse formation. The prostaglandins are important mediators of somatic pain sensations, or so-called dermal, subcutaneous and musculoskeletal pain. These drugs are described in more detail in chapter 7.

### 5.1.2 Anxiety disorders and the anxiolytic drugs

The range of anxiety disorders that are recognised by the DSM-IV-TR® (i.e. the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*) range from acute stress disorder, generalised anxiety disorder (GAD) and social anxiety disorder to phobias, panic disorder, post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD). Anxiety is associated with an *imbalance* in the **serotonergic system** (serotonin, or 5-HT, mainly originates from the raphe nuclei in the pons and central brain stem) and an *excess* of **noradrenaline** (mainly originating from the NA-producing neurons of the locus ceruleus) in the brain. 5-HT has a very diverse array of functions within the CNS and its role in the pathophysiology of the various anxiety disorders is complex and not yet fully elucidated. In the past it has been suggested that, similar to and together with noradrenaline, an *elevated* 5-HT concentration in the brain produces anxiety. However, the GABA-synergists (see below), as well as the serotonin-re-uptake inhibitors (see paragraph 5.1.3) are successfully being used to manage a variety of anxiety disorders, and these two drug classes essentially bring about opposite effects on the 5-HT concentration in the brain. Therefore, in patients suffering from anxiety disorders, a serotonergic system *imbalance* (i.e. an altered serotonergic system) probably constitutes a more descriptive cause. A close interrelationship also exists between the serotonergic system and the noradrenergic system in the brain.

**Sedatives** (also referred to as anxiolytic drugs or anxiolytic sedatives) may be used to alleviate the symptoms of acute anxiety. These drugs cause sedation and,

therefore, they have a calming effect, which reduces the feelings of anxiousness. Often the same drugs, or agents belonging to the same group of drugs, are used as **hypnotics** (i.e. they cause drowsiness and may be used to bring about and maintain a state of sleep). Therefore, the term 'sedative-hypnotic' is often encountered in pharmacology textbooks. For example, the benzodiazepines (BZDs) may be used as anxiolytic sedatives, or as hypnotics. On the other hand, *buspirone* is an example of a 'selective anxiolytic' drug that does not have any sedative-hypnotic effects, and *zolpidem* is used as a hypnotic drug, but lacks significant anxiolytic activity. The long-term management of anxiety disorders such as GAD, PTSD and OCD, however, is often better achieved with one of the selective serotonin re-uptake inhibitors (SSRIs), or with a dual-re-uptake inhibitor (see paragraph 5.1.3).

GABA is the major inhibitory neurotransmitter in the brain (refer to paragraph 4.12) and the $GABA_A$-receptor complex, specifically, makes an excellent drug target in the treatment of anxiety, since $GABA_A$-receptor stimulation effectively suppresses the release of the appropriate transmitter substances (i.e. noradrenaline and 5-HT) involved in the 'chemical pathogenesis' of anxiety.

### Note 5.1 The $GABA_A$-receptor complex (or $GABA_A$-chloride ionophore)

The $GABA_A$-receptor is a macromolecular complex that acts as a ligand-gated chloride channel. The receptor complex is made up of five subunits that form the ion channel. In addition to the naturally-occurring ligand, GABA, these receptor complexes also provide binding sites for the BZDs, the barbiturates, and *ethanol*. When GABA binds to these receptors the ligand-gated chloride channels open, thus facilitating the influx of chlorine ions with a subsequent hyperpolarisation of the neuronal cell membranes. When the benzodiazepines bind to their receptors (or binding sites) on the $GABA_A$-chloride ionophore, they will **enhance** the normal action of GABA on the same receptors (i.e. they strengthen the degree of GABA-ergic transmission in the brain, and are therefore referred to as 'GABA-synergists').

### The GABA-synergists

**Benzodiazepines:**

- The benzodiazepines (BZDs) enhance GABA transmission through their interaction with unique BZD-receptors that are found on the $GABA_A$-receptor complexes in the brain. Refer to paragraph 4.12 and note 5.1.
- These drugs have a variety of uses, including their anxiolytic, sedative and hypnotic actions. They may also be used as anticonvulsants, anaesthetic agents and skeletal muscle relaxants, and they cause anterograde amnesia. These effects, however, are dosage-dependent. The BZDs cause anxiolysis and sedation at much lower dosages, for example, than the ones required to bring about a state of anaesthesia and skeletal muscle relaxation.

- The BZDs are classified as being long-acting, intermediate-acting, short-acting or ultra-short-acting, on the basis of their plasma half-lives (combined with the half-lives of their active metabolites, if any):
  - **Long-acting:** Probably the best-known BZD, which incidentally also has one of the longest half-lives, is ***diazepam***. Other examples of these long-acting BZDs are *chlordiazepoxide, clonazepam, clorazepate, flurazepam, ketazolam* and *nitrazepam*. The long plasma half-lives may produce a so-called hangover effect (referred to as residual sedation).
  - **Intermediate-acting:** These drugs have plasma half-lives of less than 24 hours, as opposed to the long-acting agents that have half-lives of more than 24 hours. Examples include *alprazolam, bromazepam* and ***lorazepam***.
  - **Short-acting:** These BZDs are particularly useful in the management of insomnia. Examples are *temazepam, triazolam, brotizolam, loprazolam, oxazepam* and *lormetazepam*.
  - **Ultra-short-acting:** *Midazolam* has a very short plasma half-life and works particularly well as an intravenous agent for the induction of general anaesthesia or for titrated sedation by means of a continuous intravenous infusion. **Note that authors differ somewhat in their delineation of the various groups**; some also consider *triazolam* to be ultra-short-acting.
- *Flumazenil* is the BZD antidote, but has quite a short half-life, especially when compared to the half-lives of the long-acting BZDs. *Flumazenil* is highly effective in diagnosing BZD overdose and is capable of supporting the patient's vital functions. It is a competitive antagonist at BZD-receptors.
- Tolerance and drug dependency, following continuous use, are very real adverse effects of the benzodiazepines. The BZDs also have an additive effect to alcohol (all sedatives interact with alcohol).

**Other GABA-synergists:**

- These drugs are more appropriately used in the management of insomnia, and not as anxiolytics.
- *Zopiclone* is a cyclopyrrolone and *zolpidem* is an imidazopyridine. These drugs act on the same receptors as the BZDs. As already mentioned *zolpidem* has similar sedative-hypnotic effects to the BZDs, but lack their anticonvulsant, anxiolytic and skeletal muscle relaxant properties. *Zopiclone*, on the other hand, has similar properties to those of the BZDs.

## 5-$HT_{1A}$-receptor dualists

- The azapirones, like *buspirone* for example, are highly selective anxiolytic drugs and do not cause sedation or skeletal muscle relaxation, nor do they have any anticonvulsant effects. *Buspirone* is a dualist (or **partial agonist**) at 5-$HT_{1A}$ receptors.
- *Buspirone* has the advantage of not being additive to alcohol and not causing dependency. However, its onset of action is rather slow.

**Other drugs**

- *Hydroxyzine* is an 'older type' **antihistamine**, with good sedative properties. It is notoriously painful as an intramuscular injection.
- The somatic manifestations of anxiety (caused by increased sympathetic nervous system activity), such as skeletal muscle tremors, erratic breathing and palpitations, may be managed with a suitable β-blocker.

### 5.1.3 Depression and the antidepressants

**Mood disorders** are characterised by **mood episodes**, which range from *depression* to *mania*. The DSM-IV-TR® recognises four distinct mood episodes, namely major depressive episode, manic episode, mixed episode and hypomanic episode. These mood episodes are used to characterise and diagnose a variety of mood disorders, including major depressive disorder (MDD) and the bipolar disorders (formerly known as *manic-depression*).

Depression, in direct contrast to the characterisation of anxiety as being a '*serotonin- and noradrenaline-excess condition*' (although, as explained in paragraph 5.1.2, a serotonergic *imbalance* is probably more descriptive), is associated with a **deficiency** in the **serotonin** (5-HT), and **noradrenaline** concentrations in the brain (and to a lesser extent of dopamine as well). The aim of antidepressant therapy is therefore to **increase** these synaptic neurotransmitter concentrations. There are several mechanisms that may be utilised to achieve this goal. Unfortunately, the major depressive patient's mood will only begin to improve after about 14 days, or more, on drug treatment. In severe cases, associated with a definite threat of self-harm or self-injury, or where pharmacotherapy has failed, or is contraindicated, electroconvulsive therapy (ECT) must be considered.

Also note that, as part of their long-term treatment, anxiety disorders such as GAD, OCD, panic disorder (PD) and PTSD are managed with antidepressants that inhibit the re-uptake of serotonin, which include *clomipramine*, the selective serotonin re-uptake inhibitors (SSRIs), and the serotonin and noradrenaline re-uptake inhibitors (dual-re-uptake inhibitors, or SNRIs). These drugs may help to restore the **serotonergic system imbalance** that exists in these patients.

**Mood-stabilisers** are used in the management of the bipolar disorders. The best-known mood-stabiliser is *lithium*, which requires careful, individualised dosing regimens and therapeutic drug monitoring. Other examples of drugs that may be used as mood-stabilisers include antiepileptic agents such as ***carbamazepine***, ***valproate*** and ***lamotrigine***. Antipsychotic drugs may be used in the management of acute mania.

## The tricyclic antidepressants (TCAs)

- These drugs are **multipotent blockers** (see paragraph 3.5). Their unique 3-ring molecular structure allows them to effectively inhibit the re-uptake of both noradrenaline and serotonin from their synapses back into the terminal axons of their presynaptic neurons. Furthermore, their molecular structure also allows them to act as blockers of muscarinic receptors, which explains their anti-cholinergic side-effects, as well as $\alpha_1$-adrenergic and $H_1$-receptors.
- The anti-cholinergic side-effects limit their use because they are contraindicated in patients who suffer from glaucoma and benign prostatic hyperplasia (BPH). The effects of *imipramine* on the smooth muscle sphincter of the bladder neck make it especially useful in the management of nocturnal enuresis in children. ***Amitriptyline*** and *nortriptyline* may also be used for the latter indication.
- Generally speaking, the TCAs are far better inhibitors of NA-re-uptake than 5-HT-re-uptake. *Clomipramine*, however, exhibits good inhibition of the re-uptake of both neurotransmitters.
- Many of the TCAs are quite sedating and may return sleeping patterns to normal, therefore making it unnecessary to add a sedative to the treatment regime. Examples include ***amitriptyline*** and *trimipramine*, as well as *clomipramine* (one of the more sedating TCAs, as opposed to *imipramine*, which is one of the less sedating TCAs).
- As already mentioned the TCAs also act as antagonists at $\alpha_1$-receptors, which may cause orthostatic hypotension. In overdose this causes a severe decrease in arterial blood pressure. An overdose may also elicit life-threatening and deadly cardiac dysrhythmias, including ventricular fibrillation (i.e. the TCAs are **cardiotoxic** in overdose).
- The anti-cholinergic side-effects of the TCAs also make them unsuitable for use in cardiac patients, such as those suffering from ischaemic heart disease, myocardial infarction and cardiac failure. Their antagonistic effects on cardiac muscarinic receptors will leave sympathetic outflow unopposed, with subsequent tachycardia and an increased cardiac workload and myocardial oxygen demand.
- ***Amitriptyline*** and *nortriptyline* may also be used in the management of neuropathic pain.
- ***Amitriptyline*** is converted to *nortriptyline* (its principal active metabolite) in the liver. *Nortriptyline* is also less sedating than its parent compound.
- Other examples are *dothiepin* (also known as *dosulepin*) and *desipramine*, which is an active metabolite of both *imipramine* and its analogue *lofepramine*.

## The selective serotonin re-uptake inhibitors (SSRIs)

- These drugs selectively inhibit the re-uptake of serotonin (5-HT) and have a much more favourable side-effect profile in terms of anticholinergic (i.e. antimuscarinic) and cardiotoxic effects, when compared to the TCAs.
- The SSRIs are more popular than the TCAs, because they have fewer side-effects, but are generally as effective in managing depression as the latter.

- The SSRIs may cause appetite suppression and weight loss, but are not registered for use in weight-loss programmes. Excessive sweating, sedation, dry mouth, gastrointestinal disturbances and sexual dysfunction are cumbersome side-effects.
- Examples of SSRIs are ***fluoxetine***, *paroxetine* and *citalopram*, *escitalopram*, *sertraline* and *fluvoxamine*.

## The monoamine oxidase inhibitors (MAOIs)

- Inhibition of the enzyme monoamine oxidase (MAO) will effectively inhibit the enzymatic breakdown of noradrenaline (as well as adrenaline and dopamine), and also of serotonin. There are two isoforms of this enzyme, namely MAO-A (which primarily metabolises adrenaline, noradrenaline and serotonin), and MAO-B (which is more specific for dopamine). MAO also metabolises a number of other biogenic amines, including dietary amines (certain foodstuffs contain tyramine for example).
- The 'older' MAOIs, such as *tranylcypromine*, do not differentiate between the two isozymes, MAO-A and MAO-B, and also inhibit the enzyme irreversibly (by forming covalent bonds).
- *Moclobemide* is a **reversible inhibitor of MAO-A** (i.e. a so-called RIMA). It displays a high degree of selectivity and affinity for the MAO-A isozyme.
- The MAOIs are renowned for their interactions with foodstuffs and certain other drugs. *Moclobemide* has a less significant interaction with tyramine-containing foodstuffs than *tranylcypromine* has.

## Other antidepressant drugs

- *Mianserin* is a blocker of pre-synaptic $\alpha_2$-receptors, thus inhibiting the negative feedback mechanism that usually halts NA-release into the synaptic cleft. Together with the closely-related drug, *mirtazapine*, they are referred to as tetracyclic antidepressants.
- *Reboxetine* is a selective noradrenaline-re-uptake inhibitor, or NARI (but is not a multipotent blocker).
- *Venlafaxine* inhibits the re-uptake of both serotonin and NA, without being a multipotent blocker. Together with *duloxetine*, they are referred to as dual-re-uptake inhibitors, or SNRIs.
- Examples of other antidepressants are *bupropion* (this drug is also used as an aid to assist patients with smoking cessation), *maprotiline*, *nefazodone* and *trazodone*.

## Clinical application

- The TCAs are **cardiotoxic** antidepressants. In major depression with a significant suicide risk, the patient should receive only one week's worth of tablets or capsules at the onset of the treatment. These drugs have very narrow therapeutic indices and are extremely dangerous in overdose.

- The combination of anxiety and depression (i.e. an 'anxious depression') is poorly understood or explained in terms of neurotransmitter substances, but does respond to a suitable antidepressant in combination with a BZD.
- Patients who receive MAOIs, especially the older non-selective inhibitors of monoamine oxidase, should be warned about the possibility of hypertensive crisis, which may occur when tyramine-containing food is ingested (because MAO usually breaks down tyramine in the intestinal tract; tyramine is an indirect-acting sympathomimetic substance). Foodstuffs that contain tyramine include yeast extracts, beans, red wine, pickled fish and certain cheeses.

### 5.1.4 Drugs used in the management of Parkinson's disease

Parkinson's disease (also referred to as primary or idiopathic parkinsonism) is characterised by a **decrease** in the dopamine concentration within the basal nuclei that are involved in the coordination of motor function (especially in the case of complex body movements and to maintain normal gait and posture). The basal nuclei form part of the extrapyramidal system, where dopamine is especially found in the nigrostriatal pathway (i.e. the pathway from the substantia nigra to the corpus striatum). Acetylcholine, which opposes dopamine in the basal nuclei (more specifically, in the corpus striatum), then shows a relative **increase**, implying that the normal balance between dopamine and acetylcholine has been disturbed. This imbalance produces the characteristic skeletal muscle rigidity, rhythmical muscle tremors, drooping posture, typical mask-like facies (facial expression) and other signs of this debilitating neurological condition.

Drug treatment may be aimed at managing the dopamine deficit, the relative acetylcholine excess and the skeletal muscle tremors. Dopamine itself is incapable of crossing the BBB. *L-Dopa*, an amino acid and dopamine's precursor, is capable of crossing the blood-brain barrier through an active transport mechanism. This implies satiability of *L-Dopa*'s uptake into the CNS.

*L-Dopa (levodopa)* is converted to dopamine by the enzyme dopa-decarboxylase (see figure 4.3A). Since the enzyme is found both peripherally and centrally, *L-Dopa* is combined with a dopa-decarboxylase inhibitor to prevent peripheral decarboxylation. *Carbidopa* and *benserazide* are examples of such drugs that are used in combination with *levodopa*. These enzyme inhibitors do not cross the BBB. Therefore, they also have the advantage of significantly reducing the peripheral side-effects of *levodopa* (when converted to dopamine in the periphery), including cardiac arrhythmias, nausea and vomiting. Patients taking *levodopa* on its own (i.e. without a peripheral dopa-decarboxylase inhibitor) must also not receive any vitamin $B_6$ (pyridoxine) supplements, since this vitamin acts as a co-enzyme to dopa-decarboxylase.

Dopamine-receptor agonists may be used to stimulate postsynaptic D-receptors in the corpus striatum directly. *Bromocriptine, cabergoline* and *pergolide* are ergot derivatives that do not differentiate between the $D_1$-type and the $D_2$-type

dopaminergic receptors (*bromocriptine*, for example, is an agonist at the $D_2$-type receptors and a dualist at the $D_1$-receptors). The newer drugs belonging to this group, namely *pramipexole* and *ropinirole*, are non-ergot agonists with selective activity at the $D_2$-type receptors. Therefore, the newer, more selective drugs have fewer side-effects and are better tolerated than the older ergot alkaloids.

*Selegiline* selectively and irreversibly inhibits the isozyme MAO-B to effectively prevent the enzymatic breakdown of dopamine in the corpus striatum (where this isozyme is the prevalent form of MAO). This inhibitor of MAO-B does not interact with tyramine-containing foodstuffs at the normal, recommended dosage. *Rasagiline* is a newer, more potent and selective inhibitor of MAO-B. *Tolcapone* and *entacapone* selectively inhibit the enzyme COMT (see paragraph 4.6.3 and figure 4.4), and therefore also conserve dopamine.

An interesting addition to the drug array used in the management of Parkinson's disease is the antiviral drug *amantadine*, which also acts as a rather weak dopaminergic drug, which improves the conformation of the D-receptor, allowing the neurotransmitter to achieve a better fit on its receptor. It may also facilitate the release of dopamine from its nerve endings and could possibly prevent its re-uptake as well. Furthermore, *amantadine* has anti-muscarinic properties and is an NMDA-receptor antagonist.

The anti-muscarinic agents such as ***orphenadrine, biperiden*** and *trihexyphenidyl* may be used to manage the clinical problems caused by the relative increase in acetylcholine. Skeletal muscle tremors may be managed through the use of non-selective β-adrenergic receptor blockers.

Parkinsonism may also be **drug-induced** in cases where competitive antagonists of the D-receptors in the basal nuclei (especially in the corpus striatum) are administered. The abovementioned anti-muscarinic drugs may alleviate some of these so-called extra-pyramidal side-effects (also refer to paragraph 5.1.5).

### 5.1.5 Anti-schizophrenic drugs

Drugs that are used to treat schizophrenia may also be effective in managing other psychotic disorders (e.g. those that are substance-induced or that occur as a direct physiological consequence of a general medical condition, as categorised by the DSM-IV-TR®). These anti-schizophrenic agents are also referrred to as **neuroleptic** or **antipsychotic** drugs. Generally speaking, the anti-schizophrenic agents have diverse receptor-binding profiles with varying degrees of anti-dopaminergic and anti-serotonergic effects that explain their efficacy as antipsychotic agents (see below). In addition they exhibit varying degrees of anti-muscarinic, $H_1$-receptor blocking and $\alpha_1$-adrenoceptor blocking effects that are partially responsible for their cumbersome side-effect profiles. These anti-muscarinic side-effects include blurred vision, urinary retention, constipation and a dry mouth. Central $H_1$-receptor antagonism causes sedation and vascular $\alpha_1$-adrenoceptor antagonism

may result in postural (orthostatic) hypotension. Furthermore, most antipsychotic agents are associated with weight gain, albeit to varying degrees.

Two important dopaminergic pathways are involved in the neuropathology of schizophrenia, namely the **mesocortical** and **mesolimbic** pathways of the 'mesocorticolimbic' system (also refer to paragraph 4.8). One possible explanation for the presence of both **positive** (e.g. hallucinations, delusions and disorganised thought processes) as well as **negative** (e.g. withdrawal, apathy and a lack of motivation) symptoms in schizophrenic patients is that a **dopaminergic imbalance** exists, which is marked by mesolimbic 'hyperactivity' and mesocortical 'hypoactivity'. In particular, antipsychotic effects may be observed, which even more specifically relate to the positive symptoms of schizophrenia, when the $D_2$-receptors in the mesolimbic pathway are blocked with D-receptor antagonists. In addition to the dopaminergic system imbalance, schizophrenia is also characterised by the involvement of the serotonergic system, as illustrated by the effectiveness of drugs that act as antagonists at 5-$HT_2$-receptors (more specifically at the 5-$HT_{2A}$-receptor subtype).

The mesocorticolimbic system has to maintain a normal balance, midway between irrational thought processes and fears, delusions and hallucinations on the one hand, and emotional detachment and a lack of interest in the environment on the other hand. Therefore, in schizophrenia and other psychotic disorders, the aim of an antipsychotic (or neuroleptic) drug treatment regimen would be to restore stability in the mesocorticolimbic system of the brain. Therefore, the two major drug targets in the treatment of schizophrenia are the $D_2$-receptors and the 5-$HT_{2A}$-receptors. However, the dopaminergic $D_4$-receptors may also play an important role.

$D_2$-receptors are found in the mesolimbic pathway, as well as the nigrostriatal pathway of the extrapyramidal system and the tubero-infundibular pathway of the hypothalamus. Therefore, $D_2$-receptor blockers will not only alleviate the positive symptoms of schizophrenia, but will also elicit extrapyramidal side-effects (i.e. drug-induced parkinsonism) and give rise to increased serum prolactin levels.

Two major classes of antipsychotic agents are currently available, and some scientists are of the opinion that *aripiprazole* should be viewed as the first agent in a new 'third' class of antipsychotic agents:

- **First-generation antipsychotics:** These agents are also referred to as the **typical** or **classical** antipsychotics. As a class these agents display a higher affinity for $D_2$-receptors than for 5-$HT_{2A}$-receptors. Extrapyramidal side-effects (EPS) and tardive dyskinesia (TD) feature more prominently when these agents are used. Another side-effect of the first-generation antipsychotics, which is **life-threatening**, is termed neuroleptic malignant syndrome (NMS) and involves skeletal muscle rigidity, hyperthermia, instability of the autonomic nervous system and alterations in the patient's level of consciousness (i.e. NMS resembles malignant hyperthermia). Damage to the skeletal muscles

may result in myoglobinuria and subsequent renal failure. Some of these agents may also cause $QT_c$-interval prolongation on the electrocardiogram (ECG).

***Chlorpromazine***, *trifluoperazine, thioridazine* and ***fluphenazine*** are examples of **phenothiazines**, a diverse drug group with multipotent receptor-blocking properties and a variety of uses, including antihistamine, anti-emetic and anti-schizophrenic action. The phenothiazines are subdivided into three distinct groups, based on their chemical structures, since their 3-ring molecular structure may have one of three different types of side-chains attached to the central ring, namely an aliphatic, piperidine or piperazine side-chain:

- The **aliphatic** group: These drugs are strongly sedative, but are the least potent neuroleptics, with marked anti-muscarinic, antihistamine and anti-adrenergic (i.e. $\alpha_1$-adrenoceptor blocking) effects. Examples include ***chlorpromazine***, *triflupromazine* and ***promethazine***. Of note is the fact that ***promethazine*** is an outstanding antihistamine, but not suitable for use as a neuroleptic agent because it only possesses one-tenth of the anti-dopaminergic activity of ***chlorpromazine*** (it is, however, also employed as an anti-emetic agent, especially for use in the prevention and treatment of motion sickness and postoperative nausea, as a sedative, and as pre-medication for sedation and the relief of fearfulness prior to surgery, or even during labour). ***Promethazine*** should, however, be used with extreme caution in children under the age of two years. In addition to being the prototype neuroleptic agent, ***chlorpromazine*** is also used as an anti-emetic agent and in the management of intractable (i.e. stubborn or refractory) hiccups. *Trimeprazine* (also known as *alimemazine*) is also used as a pre-medication prior to surgery, and should also be used with extreme caution in children under the age of two years.
- The **piperidine** group: Phenothiazines with piperidine side-chains have a lower incidence of EPS because they have a higher tendency towards producing anti-muscarinic effects. *Thioridazine* belongs to the piperidine group, is very sedating, and is a particularly cardiotoxic phenothiazine, causing $QT_c$-interval prolongation that is dosage-related and may give rise to life-threatening ventricular arrhythmias and even to sudden death.
- The **piperazine** group: The phenothiazines with the piperazine side-chains are **high-potency neuroleptics**, with significantly fewer anti-muscarinic, sedative and anti-adrenergic effects. Therefore, they have a greater tendency towards eliciting EPS. Examples include ***fluphenazine*** and *trifluoperazine*. *Prochlorperazine*, however, is rather used as an anti-emetic agent.

Examples of the other important first-generation antipsychotic agents are the butyrophenones, ***haloperidol*** and *droperidol*, and the thioxanthenes, ***flupenthixol*** and ***zuclopenthixol***. The latter group of neuroleptic agents

also possesses 3-ring molecular structures and both of the listed examples also have piperazine side-chains, making them high-potency neuroleptics. ***Haloperidol*** also has neuroleptic properties (high-potency) and a side-effect profile that is similar to the piperazine group of phenothiazines. *Droperidol* is used as a pre-medication before surgery, in the management of postoperative nausea and vomiting, and in combination with *fentanyl* to achieve a state of neuroleptanalgesia (see paragraph 5.1.7). Other examples include *clothiapine* (which is an extremely sedating neuroleptic agent), *pimozide* (a long-acting antipsychotic with additional calcium-blocking properties) and *sulpiride*. *Sulpiride* antagonises the $D_2$-receptors more selectively than many of the other classical neuroleptic agents. *Droperidol* and *pimozide* are associated with $QT_c$-interval prolongation, with a danger of life-threatening ventricular arrhythmias and sudden death.

➲ **Second-generation antipsychotics:** These drugs are also referred to as the **atypical antipsychotics**. As a class these agents display a higher affinity for 5-$HT_{2A}$-receptors than for $D_2$-receptors. These agents display a significantly reduced tendency towards producing EPS and TD, do not have nearly as much influence on serum prolactin levels and are generally better tolerated than the classical drugs. They have also been shown to have favourable effects on the negative symptoms of schizophrenia, at least to some extent. The exact mechanisms that underlie the reduced incidence of extrapyramidal side-effects, combined with the ability to manage both positive and negative symptoms of schizophrenia remain to be fully elucidated. Many theories have been suggested and currently makes for very confusing reading; however, their higher affinity for the serotonergic 5-$HT_{2A}$-receptors, combined with the fact that these drugs may have preferential effects on the dopaminergic receptors of the mesocortical and mesolimbic pathways, may explain some of these observations.

In addition to their tendency to cause weight gain, the atypical antipsychotics are also associated with adverse effects on carbohydrate metabolism, which include glucose intolerance and an increased risk of developing diabetes mellitus, as well as dyslipidaemia (*clozapine* and *olanzapine* have the highest risk of weight gain, diabetes mellitus and dyslipidaemia, while *ziprasidone* and *aripiprazole* have the lowest risk; with *risperidone* and *quetiapine* being considered as having an intermediate risk).

*Clozapine* has a few interesting characteristics that are of note, including its high affinity for the dopaminergic $D_4$-receptor in addition to its affinity for $D_1$-, $D_2$- and other D-receptors. It also blocks serotonergic 5-$HT_{2A}$- and 5-$HT_{2C}$-receptors, as well as other 5-HT-receptors. Furthermore, it blocks $\alpha_1$- and $\alpha_2$-adrenoceptors and has anti-muscarinic and antihistamine ($H_1$-receptor-blocking) effects. This drug has proven to be effective in treatment-resistant schizophrenia, and is used as a *reserve drug* for these and other difficult cases because of its association with rare, but potentially fatal,

**agranulocytosis**. Patients who receive this drug require strict monitoring of their white blood cell counts.

*Amisulpride* is a high-affinity antagonist of $D_2$- and $D_3$-receptors. *Risperidone, olanzapine, quetiapine* and *ziprasidone* may also be used in the management of acute episodes of mania, or the acute treatment of mixed episodes, in patients with bipolar disorder. *Ziprasidone* is also associated with $QT_c$-interval prolongation, with a danger of life-threatening ventricular arrhythmias and sudden death.

- **'Third-generation' antipsychotics:** *Aripiprazole* is the first anti-schizophrenic agent that acts as a **dopamine $D_2$-receptor dualist** and is, therefore, referred to as a 'dopamine system stabiliser': it acts as an agonist where dopamine levels are low (i.e. in the mesocortical pathway) and as an antagonist where these levels are high (i.e. in the mesolimbic pathway). Furthermore, *aripiprazole* is also said to be a dualist at serotonergic 5-$HT_{1A}$-receptors and an antagonist at 5-$HT_{2A}$-receptors. It may also be used as an add-on drug in the acute management of major depressive disorder (MDD), and in the management of manic or mixed episodes in patients with bipolar disorder.

### 5.1.6 Anti-epileptic drug therapy

Convulsions (or seizures) may be caused by clinical problems such as head injuries, pyrexia, hypoglycaemia and alcohol or drug withdrawal. Epilepsy, on the other hand, is characterised by the presence of an epileptogenic lesion somewhere in the brain, and the condition is only diagnosed once non-febrile seizures become recurrent. Therefore, epilepsy may be regarded as a tendency towards having recurrent seizures, although some forms of epilepsy are non-convulsive in nature (e.g. absence seizure and complex partial seizures).

Seizure activity may be categorised as either **partial** (simple, complex, or secondary generalised) or **primary generalised**. The latter includes absence (petit mal) seizures, atonic seizures, myoclonic seizures, and tonic, clonic and tonic-clonic (grand mal) seizures.

Drugs that are capable of inhibiting the abnormal neuronal discharges (i.e. drugs that may interchangeably be referred to as anti-epileptic, antiseizure or anticonvulsant agents) may be divided into three major groups on the basis of their mechanisms of action, namely:

- Drugs that inhibit sodium influx to suppress neuronal action potential: ***Phenytoin***, ***carbamazepine***, *oxcarbazepine* and ***lamotrigine***.
- Drugs that strengthen or enhance the action of GABA and the subsequent opening of chloride channels: The BZDs, barbiturates, *tiagabine* and *vigabatrin*. Refer to note 5.1 for the specific interactions of the BZDs (e.g. ***diazepam***, *clonazepam* and *clobazam*) and the barbiturates (e.g. ***phenobarbitone***) on the $GABA_A$-chloride ionophore. *Vigabatrin* is an

irreversible inhibitor of GABA-transaminase (the enzyme that is responsible for the inactivation of GABA) and *tiagabine* inhibits the neuronal re-uptake of GABA via the GAT-1 transporter (which also inhibits the uptake of GABA into glial cells). *Primidone* may be regarded as a **congener** of ***phenobarbitone*** (it has two active metabolites, of which ***phenobarbitone*** is one, and both of these metabolites, as well as the parent compound, have anticonvulsant effects). ***Phenobarbitone*** is also known as *phenobarbital.*

- Drugs acting through the inhibition of calcium channels: *Ethosuximide* and *pregabalin.*

In addition to the three major groups mentioned above, there are examples of drugs that act through a combination of these mechanisms or through novel mechanisms of action. ***Valproate,*** for example, inhibits sodium channels and enhances the action of GABA; *gabapentin* enhances the action of GABA and inhibits calcium channels, while *felbamate* inhibits the activity of the major excitatory neurotransmitter in the brain, namely glutamate. *Topiramate* enhances the action of GABA, inhibits the action of glutamate and inhibits sodium channels, and *zonisamide* inhibits both sodium and calcium channels. The exact mechanism of action of *levetiracetam* is yet to be revealed.

If possible, it is always preferable to make use of monotherapy. For some types of epilepsy there are several different options and the choice of drug may be determined by a variety of factors, including efficacy in adequately controlling the condition, tolerability, toxicity, patient compliance and cost. ***Phenytoin*** has a narrow therapeutic index and follows zero-order kinetics. A few anti-epileptic drugs have additional indications or uses, which include neuropathic pain (***carbamazepine*** and *pregabalin*), the prophylaxis of migraine headache (***valproate*** and *topiramate*) and effectiveness as mood stabilisers (***carbamazepine*** and ***valproate***).

- Partial seizures may be managed with one of the following drugs: ***Carbamazepine***, *oxcarbazepine*, ***phenytoin***, ***valproate***, ***phenobarbitone***, ***lamotrigine*** or *topiramate*. *Pregabalin*, *gabapentin* or *levetiracetam* may be used as add-on (or adjunctive) therapy. *Vigabatrin* is indicated as an add-on drug for patients with refractory (treatment-resistant) partial seizures and for infantile spasms, but is associated with vision loss.
- Generalised seizures: *Ethosuximide*, ***valproate*** or ***lamotrigine*** is used in the treatment of petit mal epilepsy (i.e. absence seizures). ***Valproate*** and ***lamotrigine*** are both effective in managing atonic and myoclonic seizures. Tonic-clonic seizures may be controlled with ***carbamazepine***, *oxcarbazepine*, ***phenytoin***, ***valproate***, ***phenobarbitone***, ***lamotrigine*** or *topiramate*.

***Lorazepam*** or ***diazepam*** (or any other suitable benzodiazepine, including *midazolam* and *clonazepam*) is the initial drug of choice in the management of status epilepticus. This may be followed by a suitable anti-epileptic drug (e.g.

***phenytoin, phenobarbitone*** or ***valproate***) given intravenously to prevent more seizures from occurring.

Prolonged febrile convulsions in children may be managed with ***diazepam***. In some instances where a risk of recurrent febrile convulsions exists, the prophylactic use of ***phenobarbitone*** or ***valproate*** may be required.

### 5.1.7 General anaesthetic agents

A state of general anaesthesia may be achieved through the use of a variety of systemically administered drugs, which have a strong inhibitory effect on the central nervous system. Anaesthetic agents are used to achieve a state of unconsciousness that is associated with a sufficiently suppressed ability to perceive pain. These agents are either injected intravenously (or intramuscularly in some instances), or administered as volatile liquid inhalants or anaesthetic gases. Analgesia, skeletal muscle relaxation and anterograde amnesia are added benefits and general anaesthetic agents display these additional properties to varying degrees. A suitable anaesthetic agent, or combination of agents, will be selected to achieve the best possible intra-operative conditions, depending on the type and nature of the surgical procedure in question. An in-depth discussion of the complex nature of modern-day anaesthesia practice does not fall within the scope of this text and, therefore, only a brief overview has been included in this chapter.

**Induction agents** are used to rapidly bring about a state of general anaesthesia, which subsequently needs to be maintained for the duration of the surgical procedure. Typically an intravenous anaesthetic agent will be used to *induce* the anaesthesia and inhalants are then utilised as **maintenance anaesthetics**; however, some inhalants are also suitable for use as induction agents. In the case of **total intravenous anaesthesia** (TIVA), on the other hand, an intravenous agent is used to induce and maintain (through continuous intravenous infusion) a state of general anaesthesia. When a combination of pre-medication, skeletal muscle relaxants, induction and maintenance anaesthetics, opioid analgesics and other agents are used to achieve an optimal state of surgical anaesthesia, it is referred to as **balanced anaesthesia**.

In the case of **neuroleptanalgesia** a combination of *droperidol* (a first-generation antipsychotic or neuroleptic agent) and *fentanyl* (a potent μ-receptor agonist) is used to attain an altered state of consciousness during which patients remain calm and able to respond to verbal commands, without responding to stimuli from their surroundings. **Conscious sedation** is the more modern version of the abovementioned, which avoids the use of a neuroleptic agent in favour of a sedative such as *midazolam* in combination with *fentanyl* or a local anaesthetic (several other combinations may also be employed). *Ketamine* may be used to produce a state of **dissociative anaesthesia**.

The volatile and gaseous anaesthetic agents may be described as structurally non-specific drugs that interact with neuronal plasma membranes (refer to

paragraph 1.7); however, more recent evidence also suggests that the volatile agents may strengthen or enhance the actions of GABA through drug-receptor interaction with the $GABA_A$-chloride ionophore, or through drug-receptor interaction with NMDA-receptors (that act as glutamate-gated cation channels) in the case of ***nitrous oxide***. On the other hand the injectable anaesthetic agents act through a variety of mechanisms, including those of the benzodiazepines and barbiturates, which have already been described elsewhere in this chapter. *Ketamine* also antagonises NMDA-receptors (see paragraph 4.13), opioid drugs such as *fentanyl* are powerful μ-receptor agonists, and *propofol* and *etomidate* also strengthen and enhance the effects of GABA at the $GABA_A$-chloride ionophore.

### Inhalant anaesthetics

- ***Nitrous oxide*** ($N_2O$) combined with oxygen produces rapid induction and a quick recovery. It is safe enough for use as an analgesic during obstetric and dental procedures.
- *Halothane* is a halogenated hydrocarbon. It has the potential of being liver-toxic, is very potent and causes vasodilatation, bronchodilatation, decreased blood pressure, and also cardiac arrhythmias.
- *Enflurane*, *isoflurane*, *sevoflurane* and *desflurane* are halogenated ethers. *Sevoflurane* has an excellent drug profile and has become very popular in surgical operating practice. It may be used as an induction agent as well.

### Intravenous anaesthetics

- These agents are generally only suited to the induction of anaesthesia, and do not really produce sufficient levels of skeletal muscle relaxation or pain relief to make them effective for use during surgical procedures as such.
- The intravenous anaesthetic agents are divided into two major groups, namely the barbiturates and the non-barbiturates.

**Barbiturates:**

- *Sodium thiopentone* (or *thiopental*) is ultra-short-acting and highly lipid-soluble. Although the patient recovers within a few minutes, the redistribution of the drug (see paragraph 2.4) causes a prolonged 'hangover' effect. It reduces intracranial pressure (ICP).
- The barbiturates are absolutely contraindicated in porphyria.

**Non-barbiturates:**

- *Ketamine* is a potent hallucinogenic drug, may also be administered intramuscularly, and causes patients to become dissociated from their pain (referred to as **dissociative anaesthesia**).
- *Midazolam* is a BZD and is highly suited to trauma and intensive-care sedation, as well as the induction of general anaesthesia. Another BZD, ***diazepam***, may also be used, is more lipid-soluble, and has an active metabolite. *Midazolam* is therefore more suited to day surgery.

- *Etomidate* should be reserved for patients with asthma or cardiovascular disease and circulatory failure. It also reduces intracranial pressure (ICP) without reducing cerebral perfusion pressure. However, it is contraindicated in porphyria.
- *Propofol* is an induction drug of choice; it has a short half-life, may sustain anaesthesia through continuous intravenous infusion, is highly suited to day surgery, produces a smooth recovery from anaesthesia, and may be used in porphyria.
- The opioid agonists that are used as general anaesthetic agents are all potent, full agonists at the μ-receptors. They are the drugs of choice in cardiac surgery. Examples are *fentanyl, alfentanil, sufentanil* and *remifentanil.*

**Clinical application**

**General remarks:**

- ***Nitrous oxide*** may cause a diffusion hypoxia and therefore necessitates the administration of additional oxygen postoperatively.
- Patients who have received *ketamine* should be safeguarded against unnecessary sensory stimulation because this drug is a potent hallucinogenic agent.

**Specific effects:**

- *Halothane* and *isoflurane* lower the blood pressure, relax bronchial, vascular and uterine smooth muscle, and suppress cardiac functioning.
- *Ketamine* increases the blood pressure through stimulation of the sympathetic nervous system.
- All of the anaesthetic agents suppress the respiratory function, and *halothane* may be hepatotoxic.

The skeletal muscle relaxants that are used in conjunction with the general anaesthetic agents are discussed in paragraph 5.2.5.

### 5.1.8 Other drugs that act on the central nervous system (CNS)

- *Baclofen* is a centrally-acting, selective $GABA_B$-receptor agonist that produces symptomatic relief of spasticity, particularly when associated with lesions of the spinal cord (examples of which include amyotrophic lateral sclerosis, or ALS, and traumatic spinal cord injuries).
- Centrally-acting sympathomimetics (also refer to paragraph 5.2.1): *methylphenidate* and *atomoxetine* are used in the management of attention-deficit/hyperactivity disorder (ADHD); *methylphenidate* and *modafinil* may be used to treat narcolepsy.
- Drugs used in Alzheimer's disease include the reversible cholinesterase (i.e. acetylcholinesterase) inhibitors *donepezil, rivastigmine* and *galantamine* (also refer to paragraph 5.2.3), as well as the NMDA-receptor antagonist *memantine.*

## 5.2 Drugs acting on the peripheral nervous system

Drugs may be used to mimic or inhibit the actions of the peripheral nervous system, i.e. the somatic, sympathetic or parasympathetic nervous system.
Review paragraphs 4.1 to 4.4, 4.6 to 4.8, 4.14 and 12.3.

### 5.2.1 Sympathomimetics

The drugs that **mimic** the action of the sympathetic nervous system may be divided into two broad categories, namely the direct-acting and the indirect-acting sympathomimetics:

- **Direct-acting sympathomimetics:** *Noradrenaline* acts as an agonist at both α- and β-receptors, but stimulates the former more than the latter. ***Adrenaline*** stimulates both α- and β-receptors more than *noradrenaline* does. At smaller dosages α-receptor stimulation with ***adrenaline*** will dominate, causing only the systolic blood pressure to rise (and the pulse pressure to widen). *Isoprenaline* is a non-selective β-receptor agonist. *Dopamine*, in drug form, produces adrenergic receptor stimulation that may be regarded as dosage-dependent (see the clinical application below). *Dobutamine* is a selective $\beta_1$-receptor agonist, with even more selective positive inotropic effects.

  *Etilefrine* is predominantly a $\beta_1$-receptor agonist with additional stimulatory effects at $\alpha_1$- and $\beta_2$-receptors as well, and has a positive effect on blood pressure due to increased venous return, stroke volume and cardiac output. *Phenylephrine* is an $\alpha_1$-receptor agonist that increases peripheral resistance (it is also used as a nasal decongestant). Topically-applied imidazoline derivatives that act as $\alpha_1$-receptor agonists, such as *naphazoline,* ***oxymetazoline*** and *xylometazoline*, may be used as nasal or conjunctival decongestants.
- **Indirect-acting sympathomimetics**: These agents bring about increased concentrations of noradrenaline (NA) in the neuroeffector junctions of the sympathetic nervous system by increasing the release of NA from its nerve endings (e.g. *amphetamine* and tyramine) or by inhibiting its re-uptake (e.g. *cocaine*). Tachyphylaxis (refer to paragraph 1.5.2) may develop rapidly with these drugs because the NA stores will become depleted. *Ephedrine* is a good example of a drug that may bring about tachyphylaxis (it is also considered to be an example of a so-called mixed-acting sympathomimetic because it has both direct-acting and indirect-acting properties). *Pseudoephedrine* is closely related to *ephedrine* but is less potent as a vasoconstrictor and has fewer CNS side-effects. *Phenylpropanolamine* is more indirect-acting as a sympathomimetic and has similar effects to *ephedrine,* but is also less active in the CNS than the latter.

  *Mianserin* is an $\alpha_2$-receptor antagonist, which blocks the negative feedback mechanism via these pre-synaptic receptors (also see figure 4.4)

and may be used in the treatment of depression. The MAOIs and the inhibitors of COMT are indirect-acting sympathomimetics as well.

### Clinical application

- *Noradrenaline* causes both the systolic and diastolic blood pressure to rise, due to its stimulation of α-adrenergic receptors. The increased blood pressure results in a reflex bradycardia. ***Adrenaline***, in bigger dosages, will have a similar effect on the blood pressure. Amongst other indications ***adrenaline*** is used in the management of anaphylactic shock (see note 3.2 and paragraph 12.5.1) and during advanced cardiac life support.
- *Dopamine* in small dosages will stimulate peripheral $D_1$-receptors to produce vasodilatation of intra-cerebral, mesenteric, coronary and renal blood vessels (with increased renal perfusion). Increasing the dosage will add cardiac effects due to $\beta_1$-receptor stimulation. A further increase will then add $\alpha_1$-receptor stimulation, which will ultimately counteract the renal vasodilatation due to systemic vasoconstriction.
- Congestion of the nasal mucosa may be managed with topically-applied or systemically administered vasoconstrictors. These drugs relieve the congestion through their α-adrenergic effects at $\alpha_1$-receptors. Note that topically-applied sympathomimetics may lead to **rebound congestion** when used continuously for more than one week. The orally administered agents, on the other hand, will cause more systemic side-effects. Caution should be exercised when considering these decongestants (especially the systemic agents) in patients with uncontrolled hypertension, ischaemic heart disease and men with enlarged prostate glands, and they are contraindicated in patients who use MAOIs.

Also refer to chapter 6.

### Note 5.2 Sympathomimetic agents, blood pressure and heart rate

- When $\alpha_1$-receptor stimulation dominates the resultant vasoconstriction will cause the peripheral resistance to rise, which in turn will increase both systolic and diastolic blood pressure (BP) readings, as well as the mean arterial pressure (MAP): **MAP = [Systolic BP + (2 × Diastolic BP)] ÷ 3**

  This increase in arterial blood pressure will then result in reflex bradycardia (selective **arterial** vasodilatation, on the other hand, will lower the arterial blood pressure and elicit a reflex tachycardia).
- In the presence of $\beta_1$-receptor stimulation, the positive cardiac effects (refer to paragraph 4.6.2) will increase the force of myocardial contraction (i.e. the ventricular stroke volume, SV), as well as the heart rate (HR). This causes an increased cardiac output (CO): **CO = HR × SV**
- $\beta_2$-receptor stimulation will decrease the peripheral resistance. *Isoprenaline (isoproterenol)* is a potent $\beta_2$-receptor agonist (see paragraph 4.14) that causes a significant decrease in peripheral resistance, which also decreases the diastolic blood pressure and the MAP.

### 5.2.2 Sympatholytics

The effects of the sympathetic nervous system may be terminated or blocked with antagonists at the α- and β-adrenoceptors or their subtypes:

- **α-adrenergic receptor blockers:** The non-selective α-antagonists block both $\alpha_1$- and $\alpha_2$-receptors. *Phenoxybenzamine* is an irreversible, non-selective α-blocker and may be used in the management of phaeochromocytoma; *phentolamine* is a reversible, non-selective α-blocker. The selective $\alpha_1$-receptor blockers are competitive antagonists such as *prazosin, doxazosin* and *terazosin*, and are effective in the treatment of hypertension and to manage the urinary retention in patients with benign prostatic hyperplasia (also see chapter 10). An $\alpha_2$-receptor agonist (see figure 4.4), such as ***methyldopa*** or *clonidine*, may also be used in the treatment of hypertension.
- **β-adrenergic receptor blockers:** This is an important group of sympatholytic drugs, which are classified on **pharmacodynamic** grounds as being either selective or non-selective β-blockers. On **pharmacokinetic** grounds they are classified as being either lipid-soluble or water-soluble. The β-blockers have a wide range of uses, varying from hypertension, angina and cardiac failure to managing the peripheral manifestations of anxiety and in the prophylaxis of migraine attacks. Through competitive antagonism of the $\beta_1$-adrenoceptors, sympathetic nervous system stimulation of the heart is effectively reduced and renin secretion (see figure 12.3) is inhibited.
  - The non-selective β-blockers act as competitive antagonists at both $\beta_1$- and $\beta_2$-receptors. *Propranolol* is lipid-soluble and capable of penetrating the blood-brain barrier (BBB). *Sotalol* is water-soluble.
  - The selective β-blockers act as competitive antagonists at $\beta_1$- receptors only, and are therefore referred to as **cardio-selective** β-blockers. *Metoprolol* and *bisoprolol* are lipid-soluble, and ***atenolol*** is water-soluble.
  - ***Carvedilol*** is a non-selective β-blocker with the added advantage of having vasodilatory effects (i.e. decreasing peripheral resistance), mostly through its additional $\alpha_1$-receptor antagonism. *Labetalol* is another non-selective β-blocker with added $\alpha_1$-receptor blocking effects, but has a shorter half-life than ***carvedilol***, making it highly suited to the emergency management of hypertensive crises and to induce controlled hypotension during surgery.
  - A selective $\beta_2$-receptor blocker would have no clinical application value at all. Contraindications for β-blocker therapy include asthma, chronic obstructive pulmonary disease (COPD), insulin-dependent diabetes mellitus and peripheral vascular disease.
  - Other examples of β-blockers include *acebutolol, nebivolol* and *timolol.*

Also refer to chapter 6 and paragraph 12.3.

### 5.2.3 Parasympathomimetics

The parasympathomimetics may also be divided into direct-acting and indirect-acting agents:

- **Direct-acting parasympathomimetics:** *Carbachol* and *bethanechol* are choline esters. ***Pilocarpine*** is a cholinergic (plant) alkaloid. *Bethanechol* may be used in the management of atonic visceral organs and ***pilocarpine*** is used in the management of glaucoma (see paragraph 12.2). These drugs produce highly selective muscarinic effects (refer to paragraph 4.7.1).
- **Indirect-acting parasympathomimetics:** These drugs inhibit the enzyme cholinesterase (i.e. acetylcholinesterase) **reversibly**, thereby increasing the acetylcholine concentration in the parasympathetic synapses. *Physostigmine* crosses the BBB, while *neostigmine* and *pyridostigmine* do not. The latter two agents may be used in the long-term treatment of myasthenia gravis. Another reversible cholinesterase inhibitor, *edrophonium* is short-acting and is used to diagnose myasthenia gravis. The organophosphate pesticides are **irreversible** inhibitors of cholinesterase.

### 5.2.4 Parasympatholytics

These drugs may be divided into the anti-muscarinic and anti-nicotinic agents (also refer to paragraph 4.7):

- **The anti-muscarinic drugs:** *Atropine* crosses the BBB, causes thickening of all secretions (except for breast milk), and therefore should not be used in the treatment of asthma (see chapter 8). ***Atropine*** may, however, be indicated in the management of symptomatic bradyarrhythmias and poisoning with the organophosphate pesticides.

  Anti-muscarinic drugs that do not cross the BBB include *propantheline*, which may be used to reduce unwanted activity of the urinary bladder and in the management of other conditions that may benefit from antimuscarinic therapy without the unwanted CNS side-effects of ***atropine***. ***Ipratropium bromide*** may be used as a passive bronchodilator in COPD and asthma, since is does not cause thickening of the bronchial secretions (also refer to chapter 8). ***N-butylhyoscine*** may be used in the management of intestinal colic (see paragraph 9.2.3).
- **Anti-nicotinic drugs:** These drugs may be divided into two groups, namely the ganglion blockers and the peripherally-acting skeletal muscle relaxants (which are used in conjunction with the general anaesthetic agents):

- **The ganglion blockers:** These drugs are capable of blocking the nicotinic receptors (of the $N_n$-subtype) of both the sympathetic and the parasympathetic **ganglia** (refer to paragraph 4.7.2 and figure 4.1). They subsequently reduce the outflow of both subdivisions of the autonomic nervous system. This produces a substantial decrease in arterial blood pressure, combined with atropine-like unwanted effects. This limits their use to intra-operative scenarios where controlled hypotension may be required or where a hypertensive crisis needs emergency management during a surgical procedure. *Trimetaphan* is the ganglion blocker of choice, although this class of drugs has become largely obsolete in clinical practice (there are better options available for these indications).
- **The peripherally-acting skeletal muscle relaxants:** These drugs act on the nicotinic receptors of the **motor endplate** and are therefore discussed in the next paragraph.

### 5.2.5 The somatic nervous system and the skeletal muscle relaxants (or neuromuscular blocking agents)

The somatic nervous system utilises acetylcholine (ACh) as its neurotransmitter at the site of the **motor endplate** (refer to paragraphs 4.1 and 4.4). Blocking these nicotinic receptors (of the $N_m$-subtype) will therefore prevent the action potential that is necessary to produce skeletal muscle contraction. Drugs that act as competitive antagonists at these receptors are referred to as non-depolarising skeletal muscle relaxants. *Suxamethonium* (or *succinylcholine*) is a depolarising skeletal muscle relaxant.

- **Suxamethonium:** This drug possesses an intrinsic activity of one (1) and is structurally composed of two molecules of ACh. ACh is usually broken down by cholinesterase (CE) within milliseconds. The drug, however, is broken down by a plasma esterase (pseudocholinesterase). This process may take a few minutes.

  Therefore, the motor endplate will remain in a state of partial depolarisation because it cannot repolarise. This explains the muscle fasciculations (i.e. groups of muscle fibres that contract and twitch involuntarily) that precede the relaxation. The effects of *suxamethonium* cannot be counteracted with another drug because an agonist is already occupying the receptor, and its matching competitive antagonist would be a skeletal muscle relaxant as well. A genetic insufficiency of pseudocholinesterase therefore produces prolonged muscle relaxation (which may last a few hours) and requires mechanical ventilation until the effects of the drug have worn off.
- **The non-depolarising skeletal muscle relaxants:** These drugs have intrinsic activities equal to zero. Their effects may be counteracted with a suitable

agonist, although ACh does not make for a viable drug. The cholinesterase (i.e. acetylcholinesterase) inhibitors are therefore used. *Neostigmine* is the drug of choice, since it does not cross the BBB (neither do the muscle relaxants). *Neostigmine*, however, is non-selective and also increases ACh-concentrations at the sites of the parasympathetic muscarinic receptors. This produces adverse effects that require blocking of the muscarinic receptors with *glycopyrronium bromide* or *glycopyrrolate* (an anti-muscarinic drug that does not cross the BBB either). ***Atropine*** is a cheaper alternative to the latter, but does cross the BBB. *Pyridostigmine* may also be used as an alternative to *neostigmine*.

Examples of the non-depolarising skeletal muscle relaxants are *pancuronium*, *vecuronium*, *alcuronium*, *atracurium*, *cisatracurium*, *mivacurium* and *rocuronium*. They may be divided into two groups based on their chemical structures, namely those with a steroidal structure (i.e. *pancuronium*, *vecuronium* and *rocuronium*), and the benzylisoquinolines that are non-steroidal neuromuscular blocking agents (e.g. *atracurium*, *cisatracurium* and *mivacurium*). *Sugammadex* is a new drug that may be used to effect a rapid reversal of skeletal muscle relaxation that was induced with *vecuronium* or *rocuronium*. It forms an inactive complex with the neuromuscular blocking agent, which is subsequently eliminated by the kidneys. *Sugammadex* cannot be used for the reversal of the non-steroidal neuromuscular blocking agents.

The skeletal muscle relaxants are used to facilitate the endotracheal intubation process; they may be used to prevent laryngeal spasm during intubation and to maintain muscle relaxation during certain operative procedures. Patients who receive skeletal muscle relaxants will require mechanical ventilation due to the relaxation of the respiratory muscles, which is caused by these agents.

### 5.2.6 The local anaesthetic agents

These drugs, upon injection, produce a localised and reversible loss of sensation, which may be accompanied by a loss of function. They achieve this by blocking sodium-ion channels, thus preventing the influx of sodium ions into nerve cells. Depolarisation, therefore, cannot take place and sensation is subsequently suspended. These drugs ionise within the peripheral neurons and are ineffective in the acid surroundings of inflamed tissue or abscesses. Local anaesthetic agents may also be applied topically. They are classified as follows:

- **The amide-type local anaesthetic agents:** These drugs are mostly metabolised in the liver. This group includes *bupivacaine*, *levobupivacaine*, ***lignocaine*** (also referred to as ***lidocaine***), *mepivacaine*, *prilocaine* and *ropivacaine*.

- **The ester-type local anaesthetic agents:** *Cocaine* is an ester of benzoic acid; *procaine, benzocaine* and ***tetracaine*** (also referred to as *amethocaine*) are esters of para-aminobenzoic acid (PABA). These agents are metabolised in the plasma by pseudo-cholinesterase.

***Lignocaine****, tetracaine* and the combination of *lidocaine/prilocaine* are very effective as surface anaesthetics. For tissue infiltration, epidural and spinal anaesthesia, ***lignocaine****, bupivacaine* and *ropivacaine* may be used, for example. When a vasoconstrictor, such as ***adrenaline*** or *noradrenaline*, is added to the local anaesthetic agent the absorption of the anaesthetic agent into the blood circulation will be reduced. This results in a more rapid onset and a longer duration of action.

CHAPTER SIX

# Drugs and the cardiovascular system

**Suggested revision**

***Anatomy and physiology:***

- Basic cardiac physiology, the cardiac cycle and electrical activity of the heart
- The electrocardiogram (ECG), heart rate and rhythm
- Cardiac workload (preload and afterload, including the left ventricular end-diastolic pressure, or LVEDP)
- Ventricular pumping mechanism, stroke volume and cardiac output (including central venous pressure, or CVP, the ejection fraction, pulmonary artery pressure, PAP or $P_{pa}$, and pulmonary capillary wedge pressure, PCWP or $P_{pw}$)
- Neurohormonal pathways that influence cardiac functioning (effects of the sympathetic nervous system, the renin-angiotensin-aldosterone system, or RAAS, and other mechanisms)
- Arterial blood pressure and organ perfusion
- Blood clotting, clotting factors and the fibrinolytic system

***Pathology and pathophysiology:***

- Ischaemic heart disease (IHD): chronic stable angina pectoris and the acute coronary syndromes (i.e. unstable angina, non-ST-segment elevation myocardial infarction, NSTEMI, and ST-segment elevation myocardial infarction, or STEMI)
- Cardiac failure (CF)
- Cardiac arrhythmias (or dysrhythmias)
- Venous thromboembolism (VTE) and arterial thrombus formation
- Essential and secondary hypertension

Note that antihypertensive treatment is discussed in chapter 12.

This chapter aims to give a broad overview of the drug management of the most important cardiovascular conditions encountered in clinical practice, including heart failure, ischaemic heart disease and cardiac arrhythmias (or dysrhythmias). The management of hyperlipidaemia and the use of anticoagulant and antiplatelet therapies are also included.

Heart failure (cardiac failure; or CF) refers to the inability of the heart to meet the metabolic demands and blood flow requirements of the body. The two basic approaches in the management of CF are to strengthen the force of myocardial contraction, and to decrease the cardiac workload. The latter, in turn, will decrease the myocardial oxygen demand. The increased workload is the result of failing myocardial contractibility in the presence of compensatory sympathetic nervous system activity (resulting in tachycardia, improved myocardial contractibility

and increased peripheral resistance) and activation of the renin-angiotensin-aldosterone system (RAAS), which also causes vasoconstriction and an increased peripheral resistance, as well as sodium and water retention.

Drugs that exert positive inotropic effects on the heart (see paragraph 4.6.2) will strengthen the force of myocardial contraction to improve signs and symptoms of hypoperfusion, but this mechanism forces the myocardium to 'work harder' and therefore increases its oxygen demand. Conversely, inhibition of the abovementioned neurohormonal pathways has the advantage of counteracting the detrimental effects of the compensatory vasoconstriction, increased peripheral resistance, and sodium and water retention seen in patients with chronic heart failure, without increasing myocardial oxygen demand. The positive inotropic agents are used in acute settings to maintain adequate vital organ perfusion.

## 6.1 Drugs that strengthen the force of myocardial contraction

For myocardial contractibility to increase (i.e. to produce a positive inotropic effect), the intracellular calcium ion concentration needs to increase. In cardiac myocytes cytosolic $Ca^{2+}$ binds to troponin-C (one of the three subunits of troponin; the other two being troponin-I and troponin-T). The conformational change that follows then facilitates actin-myosin interaction, therefore allowing for the cardiac muscle to contract.

### Drugs that cause an increase in intracellular calcium ions

- The cardiac or digitalis glycosides, such as ***digoxin***, inhibit the $Na^+$-$K^+$-ATPase pump. This causes an accumulation of intracellular sodium ions. The sodium ions subsequently facilitate the intracellular movement of calcium ions through the sodium–calcium exchange mechanism.
- ***Digoxin*** also causes a heightened vagal nerve tone with subsequent negative chronotropic effects. It also has a direct negative dromotropic effect (i.e. it suppresses the SA-node, and also the conduction velocity through the AV-node). These effects oppose those of the sympathetic nervous system on the heart.
- ***Digoxin*** is also used in the management of atrial fibrillation (AF). It has a narrow therapeutic index and requires therapeutic drug monitoring.
- The $\beta_1$-receptor agonists, such as *dobutamine*, facilitate an increase in intracellular cAMP (refer to figure 4.5). This also causes the intracellular calcium ion concentration to be increased. *Dobutamine* and other suitable sympathomimetics are used in the management of acute cardiac failure where target organ perfusion is critically inadequate. *Dopamine* may also be used, especially in patients with low systolic blood pressure readings and cardiogenic shock. However, these drugs will also increase cardiac oxygen demand and myocardial workload.
- The phosphodiesterase (PDE) inhibitors (also refer to figure 4.5), such as ***theophylline***, also facilitate an increase in cAMP and subsequently of intracellular calcium ions. ***Theophylline*** is a non-selective PDE-inhibitor (as is *caffeine*). *Milrinone* is an inhibitor of the PDE-3 isoform of phosphodiesterase.

## 6.2 Drugs that decrease cardiac workload

Decreasing cardiac workload also decreases myocardial oxygen demand. Workload may be decreased through the dilatation of the veins, the arteries, or both. Venous dilatation will decrease central venous pressure, or CVP (i.e. cardiac preload), and dilatation of the arteries will decrease arterial blood pressure and peripheral resistance (i.e. cardiac afterload). However, facilitating selective *arterial* vasodilatation will elicit reflex tachycardia (also refer to note 5.2), due to the fact that the baroreceptors will interpret the drop in arterial blood pressure as hypovolaemia. This would be counterproductive when compared to the goals of the treatment regime.

The most important aspect in the management of cardiac failure, however, is the inhibition of the neurohormonal compensatory mechanisms that give rise to the detrimental effects seen in patients with CF such as fluid overload and oedema, hypoperfusion, and ventricular hypertrophy and cardiac remodelling. Cardio-selective β-blockers (see chapter 5), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (see figure 12.3 and paragraph 12.3), and aldosterone antagonists (see chapter 10) may be employed to achieve an incremental neurohormonal inhibition. In addition, diuretics (see chapter 10) are used to manage the congestion and fluid overload.

## 6.3 The drug management of angina pectoris

An attack of angina pectoris is usually elicited by a situation that gives rise to an increased myocardial oxygen demand in the presence of coronary artery occlusion (implying that the coronary blood circulation is unable to meet the increased demand). The ensuing chest pain is caused by the resultant myocardial ischaemia. Treatment should ideally be aimed at decreasing the cardiac workload (i.e. decreasing the preload, pulse rate and arterial blood pressure) and preventing further occlusion of the affected blood vessel or vessels (e.g. through lowering of the serum cholesterol levels or the prevention of platelet adhesion, since the latter may give rise to coronary artery thrombus formation). Chronic stable angina is one possible manifestation of ischaemic heart disease, or IHD (also referred to as coronary artery disease, or CAD). IHD may also be manifested by unstable angina or myocardial infarction (either NSTEMI or STEMI). These latter manifestations are referred to as the acute coronary syndromes (ACS).

### Drugs that decrease the cardiac preload

- **The diuretics (also refer to chapter 10):** ***Hydrochlorothiazide*** is suitable for the treatment of chronic cardiac failure since its diuretic effects are not very potent. ***Furosemide*** is a powerful loop diuretic that lends itself to the management of acute heart failure, while ***spironolactone*** and *eplerenone* antagonise aldosterone and its effects on the distal convoluted tubule of the nephron. ***Spironolactone*** and *eplerenone* are therefore regarded as potassium-sparing diuretics.
- **The venous dilators:** ***Morphine***, *glyceryl trinitrate* and other nitrates reduce the cardiac preload through direct venous dilatation.

### Drugs that decrease the cardiac afterload

- *Hydralazine* is a direct-acting arteriolar vasodilator and elicits reflex tachycardia. This makes it unsuited for use in the treatment of cardiac failure, unless it is combined with a nitrate such as ***isosorbide dinitrate***, or a β-blocker.
- *Sodium nitroprusside* is also direct-acting, but dilates both arterioles and veins. Therefore, it does not elicit reflex tachycardia.

### Drugs that antagonise the neurohormonal response

- Through inhibition of the angiotensin-converting enzyme (ACE), the so-called ACE-inhibitors, such as ***enalapril*** and *perindopril*, antagonise the RAAS (see paragraph 12.3). This effectively eliminates the vasopressor effects of angiotensin II, and also the sodium and water retention caused by aldosterone. The latter may also be directly antagonised by ***spironolactone*** and *eplerenone.*
- Furthermore, the ACE-inhibitors dilate both the arterial and the venous vascular beds. This effectively prevents a reflex tachycardia as well.
- The angiotensin receptor blockers (ARBs) act as selective antagonists at $AT_1$-receptors (refer to figure 12.3). Examples include *losartan, valsartan* and *candesartan* (also refer to paragraph 12.3).
- The selective $\beta_1$-adrenoceptor antagonists, such as *bisoprolol* and *metoprolol*, as well as ***carvedilol*** (the non-selective β-blocker and $\alpha_1$-adrenoceptor antagonist) may be used to counteract the effects of the sympathetic nervous system in patients with cardiac failure.

### Drugs used in the management of angina pectoris

- **The organic nitrates:** *Glyceryl trinitrate* and ***isosorbide dinitrate*** are widely used organic nitrates (***isosorbide mononitrate*** is an active metabolite of ***isosorbide dinitrate***). These drugs release **nitric oxide** (NO) in vascular endothelial cells and utilise cGMP (cyclic guanosine monophosphate) as a second messenger to facilitate the dilatation of the venous blood vessels. This decreases cardiac preload and LVEDP (to increase myocardial perfusion during ventricular diastole). Unfortunately, when the arterial blood pressure is sufficiently reduced because of the decreased preload and accompanying venous pooling, they elicit a reflex tachycardia. They do also cause arteriolar vasodilatation, but to a much lesser extent. The organic nitrates are therefore usually combined with cardio-selective β-blockers.
- **The calcium-channel blockers (CCBs):** This important group of cardiac drugs, to which *verapamil, diltiazem* and ***nifedipine*** belong (also refer to paragraph 12.3), may be divided into two subgroups:
  - **The 'verapamil group' (i.e. the non-dihydropyridine CCBs):** These are arterial vasodilators, because they block calcium ion influx into the smooth muscle cells of arterial walls, but do not elicit a reflex tachycardia. The reason why they do not, is that they suppress the AV-conduction velocity (conduction through the proximal AV-node is calcium-dependent). *Verapamil* and *diltiazem* should therefore never be combined with β-blockers, as the combination may elicit a conduction block.
  - **The 'nifedipine group' (i.e. the dihydropyridine CCBs):** ***Nifedipine*** also acts as an arterial vasodilator but does not have any direct cardiac effects. Therefore it will elicit a reflex tachycardia. For this reason, it may be combined with a β-blocker. Other examples belonging to this group are *felodipine* and ***amlodipine***.

In addition to a combination of the abovementioned drugs, ***aspirin*** in low dosages (i.e. in the range of 75 to 150 mg daily; if indicated or required, a loading dose of 150 to 300 mg may be given), or another suitable antiplatelet agent (see paragraph 6.6.1) will prevent platelet adhesion.

## 6.4 Drugs that lower serum cholesterol levels

Patients with a history of coronary artery disease, who have suffered a myocardial infarction (MI) or who have familial hypercholesterolaemia (or another form of hyperlipidaemia), will require a reduction in their total serum cholesterol and/or serum triglyceride levels. The low-density lipoprotein, or **LDL-cholesterol** level, in particular, must be lowered, while the high-density lipoprotein, or **HDL-cholesterol** level, should preferably be increased. Drugs that reduce *very* low-density lipoprotein, or **VLDL-levels,** will effectively decrease serum triglyceride levels.

## 6.5 The anti-arrhythmic drugs

An in-depth discussion of the anti-arrhythmic drugs does not fall within the scope of this textbook. It is therefore recommended that a more specialised text be consulted for detailed information.

There are four different classes of anti-arrhythmic agents based on their mechanisms of action and effects on the cardiac action potential, as well as a few atypical agents that cannot be grouped into any one of these classes specifically. Class I agents, for example, are $Na^+$-channel blockers (and are further subdivided into Class Ia, Ib and Ic). All of the β-blockers except for *sotalol* are class II agents. Agents that belong to class III, including *sotalol*, prolong the cardiac action potential by blocking $K^+$-channels, and the class IV agents are $Ca^{2+}$-channel blockers of the non-dihydropyridine group (see insert on page 122). Examples of agents that do not fit into any one of the abovementioned classes are ***atropine***, ***digoxin*** and *adenosine*.

*Disopyramide* is a class Ia agent and may be used for both supraventricular and ventricular arrhythmias. *Quinidine* also belongs to class Ia and has the same indications as *disopyramide*. *Quinidine* is also used to maintain a normal sinus rhythm following successful cardioversion of atrial fibrillation. Intravenous ***lignocaine*** is a class Ib agent and is used in the management of symptomatic ventricular arrhythmias (including intra-operative and peri-arrest settings). The class Ic agents are used for the more severe and sustained forms of paroxysmal supra-ventricular tachyarrhythmias, refractory ventricular tachyarrhythmias and arrhythmias associated with Wolff-Parkinson-White (WPW) syndrome. Class Ic includes *propafenone* and *flecainide*.

The class II agents (i.e. the β-adrenoceptor antagonists, excluding *sotalol*) may be used for tachyarrythmias. *Amiodarone* and *sotalol* are class III agents and may be used in the management of atrial and ventricular dysrhythmias, and also in the treatment of WPW syndrome. The class IV agents, i.e. *verapamil* and *diltiazem*, are used for supraventricular arrhythmias, including atrial fibrillation.

*Adenosine* is a nucleoside that occurs naturally in the body and acts by stimulating adenosine receptors: $A_1$-receptor stimulation slows conduction through the atrioventricular (AV) node and $A_2$-receptor stimulation produces vasodilatation of peripheral and coronary blood vessels. It may be used to convert paroxysmal supraventricular tachycardia back to sinus rhythm and for Wolff-Parkinson-White syndrome. ***Digoxin*** may be used to suppress supraventricular arrhythmias, especially atrial fibrillation or flutter, and ***atropine*** is used to manage symptomatic bradyarrhythmias.

### Drugs that may be used to lower serum lipid levels

- **The bile acid sequestrants (or bile acid-binding resins):** *Cholestyramine* is not absorbed from the intestinal tract, where it facilitates the excretion of bile acids by effectively preventing their reabsorption. This lowers the LDL-cholesterol levels in patients with primary hypercholesterolaemia.

- **The nicotinic acid derivatives:** *Acipimox* reduces the levels of free fatty acids in the bloodstream through the inhibition of lipolysis. This leads to a reduction in VLDL-levels in particular, a rise in HDL-cholesterol levels due to a decrease in its catabolic rate, and a less-pronounced decrease in LDL-cholesterol levels.
- **The 'statins':** The drugs in this group, which includes examples such as ***simvastatin***, *lovastatin* and *pravastatin*, block the synthesis of cholesterol through their inhibition of the enzyme HMG-CoA-reductase (the rate-limiting enzyme in the biosynthesis of cholesterol). They effectively decrease the total serum cholesterol levels, the LDL-levels and the VLDL-levels, and also increase HDL-cholesterol levels to some extent. Other examples are *atorvastatin, fluvastatin* and *rosuvastatin.*
- **The fibrates (or fibric acid derivatives):** These drugs decrease LDL-levels (to a lesser or variable degree) and also triglyceride levels (by decreasing the VLDL-levels) in the bloodstream. They may also increase HDL-cholesterol levels to some extent. Their main indication, however, is to manage hypertriglyceridaemia. Examples are *gemfibrozil*, *fenofibrate* and *bezafibrate.*
- ***Ezetimibe*:** This drug inhibits the absorption of cholesterol from the intestinal tract. *Ezetimibe* may be used on its own, or in combination with a statin to reduce LDL- and total serum cholesterol levels.

## 6.6 Anticoagulant drugs, anti-platelet drugs and fibrinolytic agents

When considering the problem of vascular thrombus formation, a distinction has to be made between arterial and venous thrombi. The underlying pathogenesis differs in that arterial thrombi are primarily platelet-mediated and form on intra-arterial lesions (such as atherosclerotic plaques), while venous thrombi are fibrin clots brought about by venous stasis or vascular trauma. A **thrombus** may be defined as a blood clot inside the cardiovascular system that could occlude a blood vessel at the site on which it has formed. An **embolus**, on the other hand, is a 'plug' (which may be part of a blood clot, or thrombus, or another foreign body) that has travelled through a section of the cardiovascular system to obstruct the flow of blood through a smaller blood vessel than the one from which it originated. Furthermore, the actual vascular **obstruction** that has been caused by a thrombus or embolus is then referred to as **thrombosis** or **embolism** respectively. An often-encountered example of the interplay between thrombosis and embolism is that of a deep-vein thrombosis (DVT) in the lower limb, which gives rise to pulmonary embolism (PE) when a piece of the thrombus breaks loose and travels through the venous circulation and the right side of the heart to become lodged in the pulmonary arterial circulation. This is an example of venous thromboembolism (VTE).

### 6.6.1 The anticoagulants and anti-platelet drugs

The two drugs that are used to prevent venous thromboembolism (VTE) and emboli of cardiac origin (as seen in patients with atrial fibrillation for example)

are *heparin* (unfractionated, or standard, *heparin* and the newer forms of *heparin* with low molecular weight such as *enoxaparin, dalteparin* and *nadroparin*) and *warfarin* (a vitamin K antagonist, or VKA).

*Warfarin* inhibits the hepatic synthesis of clotting factors that depend on vitamin K, namely Factor II (prothrombin), VII, IX and X (as well as protein C and S). This drug is renowned for its long list of potential drug interactions and the variation in individual responses to this drug may be substantial. Careful monitoring and good compliance are essential to the success of anticoagulant therapy with *warfarin*.

Low-molecular-weight heparins (LMWHs) are fractions of standard *heparin* and are becoming increasingly more popular than the unfractionated form. *Heparin* enhances the action of antithrombin III. The two clotting factors that are the most sensitive to the anticoagulant affects of unfractionated *heparin* (UFH) are Factor IIa (thrombin) and Xa, while LMWHs favour Factor Xa. *Fondaparinux* is a synthetic agent that *specifically* inhibits Factor Xa (i.e. the activated form of clotting Factor X). The *heparins* and *fondaparinux* are **indirect** thrombin-inhibitors. *Lepirudin*, on the other hand, is a **direct** inhibitor of thrombin. Refer to figure 6.1.

Patients who receive anticoagulants should be monitored for signs of spontaneous bleeding, including microscopic and macroscopic haematuria, bleeding gums and nosebleeds. Table 6.1 gives an exposition of the most important differences between *heparin* and *warfarin*.

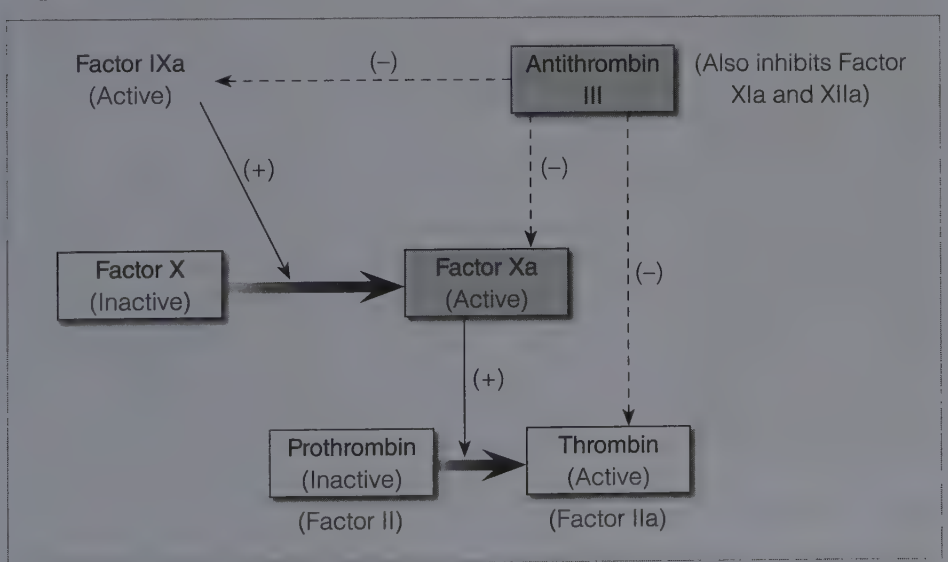



**Figure 6.1 The relationship between Factor Xa, thrombin and antithrombin III**

As already mentioned ***aspirin*** in low dosages may be used to prevent platelet adhesion and therefore also arterial thrombus formation. Other anti-platelet

agents include *dipyridamole* (a vasodilator and anti-platelet agent), *clopidogrel* (which inhibits ADP-mediated platelet aggregation by blocking the ADP-receptors on platelets) and the inhibitors of platelet glycoprotein IIb/IIIa receptor complexes, *abciximab, eptifibatide* and *tirofiban.*

**Table 6.1 The most important differences between *heparin* and *warfarin***

| | Heparin | Warfarin |
|---|---|---|
| **Route of administration** | Parenteral (intravenous or subcutaneous; do not give via intramuscular injection due to the high risk of haematoma formation) | Oral |
| **Biotransformation** | Hepatic | Hepatic |
| **Elimination kinetics** | Zero-order | First-order |
| **Onset of action and $t_{½}$** | Rapid-acting; $t_{½}$ ranges from less than an hour to a few hours and depends on the dosage and route of administration (subcutaneous or intravenous injection) | ≥ 3 days for the full anticoagulant effect to be manifested; $t_{½}$ of approximately 40 hours on average |
| **Placental barrier** | Does not cross the placental barrier; may be used to treat VTE during pregnancy for example | *Warfarin* is contra-indicated during pregnancy |
| **Antidote** | *Protamine sulphate* | Vitamin K and fresh frozen plasma (FFP) |
| **Monitoring** | aPTT (activated partial thromboplastin time) | INR (International Normalised Ratio) and/or PT (prothrombin time); very narrow therapeutic index, which requires frequent monitoring |

### 6.6.2 Fibrinolytic agents

These agents, also referred to as thrombolytic drugs, act as plasminogen activators. They therefore 'dissolve' or lyse blood clots, and may be divided into those that are fibrin non-specific (e.g. ***streptokinase***) and those that are fibrin-specific (e.g. *alteplase* and *tenecteplase*). These agents should only be administered in specialised units where intensive monitoring is available.

CHAPTER SEVEN

# Corticosteroids and the non-steroidal anti-inflammatory drugs (NSAIDs)

**Suggested revision**

***Anatomy and physiology:***

- Structure and functioning of the endocrine system
- The control of endocrine gland functioning, the hypothalamus, pituitary gland (hypophysis) and negative-feedback mechanisms
- CRH (corticotropin-releasing hormone), ACTH (adreno-corticotropic hormone), the adrenal glands and the hormones of the adrenal cortex, and the eicosanoids

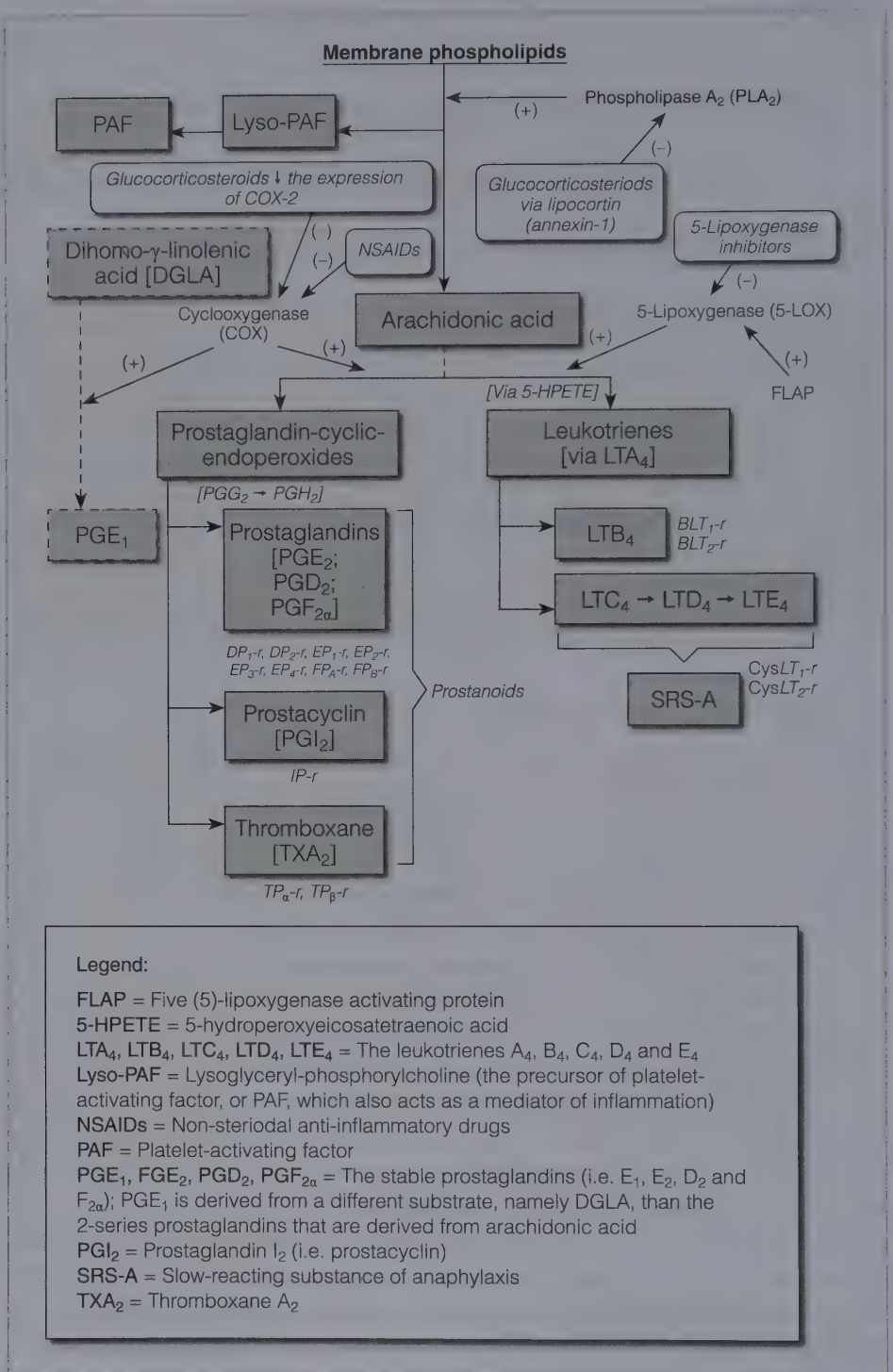
***Pathology and pathophysiology:***

- Cellular injury and the inflammatory process
- Pyrexia (fever), somatic pain and anaphylaxis

## 7.1 Physiological overview

The hormones of the adrenal cortex are collectively referred to as the **adrenocorticosteroids**. This important group of steroid hormones may be divided into three subcategories, namely the **glucocorticosteroids**, which influence various metabolic processes in the body, with cortisol (hydrocortisone) being the most important one; the **mineralocorticosteroids**, which cause sodium and water retention in the distal convoluted tubule of the nephron, with aldosterone being the most significant; and the **adrenal androgens**. The glucocorticosteroids, in particular, are important stress hormones, and when administered in supraphysiological (i.e. higher than the normal physiological levels found in the body) dosages they exhibit therapeutically useful anti-inflammatory, anti-allergic and immunosuppressive (including anti-rheumatic) effects as well.

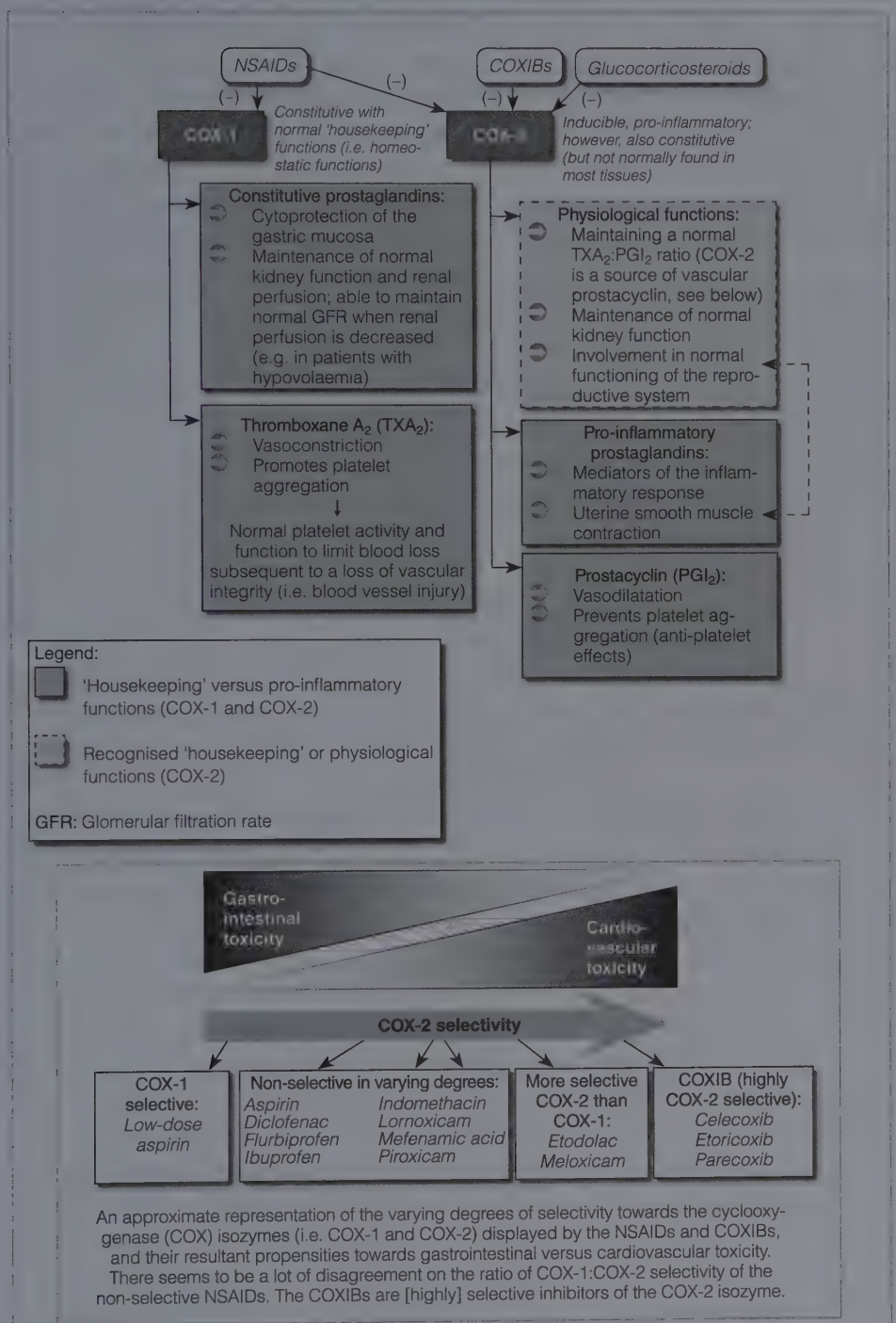
An important physiological cascade produces the clinical syndrome of inflammation. Enzymes catalyse the formation of certain **autacoids** (i.e. *local* hormones or chemical messengers) that mediate the inflammatory process. This cascade of enzymatic and catalytic events is called the **arachidonic acid cascade**; it is named after arachidonic acid, its key substrate. Two major drug groups, the **glucocorticosteroids** and the **non-steroidal anti-inflammatory drugs (NSAIDs)**, have the ability to inhibit the activity of two of the cascade's catalytic enzymes. The cascade and its catalysts, and the enzyme inhibitors acting on them, are diagrammatically represented and elucidated in figure 7.1A.




Legend:

**FLAP** = Five (5)-lipoxygenase activating protein
**5-HPETE** = 5-hydroperoxyeicosatetraenoic acid
**$LTA_4$, $LTB_4$, $LTC_4$, $LTD_4$, $LTE_4$** = The leukotrienes $A_4$, $B_4$, $C_4$, $D_4$ and $E_4$
**Lyso-PAF** = Lysoglyceryl-phosphorylcholine (the precursor of platelet-activating factor, or PAF, which also acts as a mediator of inflammation)
**NSAIDs** = Non-steriodal anti-inflammatory drugs
**PAF** = Platelet-activating factor
**$PGE_1$, $FGE_2$, $PGD_2$, $PGF_{2\alpha}$** = The stable prostaglandins (i.e. $E_1$, $E_2$, $D_2$ and $F_{2\alpha}$); $PGE_1$ is derived from a different substrate, namely DGLA, than the 2-series prostaglandins that are derived from arachidonic acid
**$PGI_2$** = Prostaglandin $I_2$ (i.e. prostacyclin)
**SRS-A** = Slow-reacting substance of anaphylaxis
**$TXA_2$** = Thromboxane $A_2$

**Figure 7.1A The arachidonic acid cascade**




An approximate representation of the varying degrees of selectivity towards the cyclooxygenase (COX) isozymes (i.e. COX-1 and COX-2) displayed by the NSAIDs and COXIBs, and their resultant propensities towards gastrointestinal versus cardiovascular toxicity. There seems to be a lot of disagreement on the ratio of COX-1:COX-2 selectivity of the non-selective NSAIDs. The COXIBs are [highly] selective inhibitors of the COX-2 isozyme.

**Figure 7.1B A comparison between the COX-1 and COX-2 isozymes**

As illustrated, the arachidonic acid cascade plays a vital role, not only in mediating the inflammatory process, but also in the production of certain **eicosanoids** (autacoids that are metabolites, or derivatives, of arachidonic acid) that do not take part in inflammation. Some of the **prostanoids** (see figures 7.1A and 7.1B), the most versatile of the eicosanoids in question, also have normal 'housekeeping and maintenance' functions in the human body. It is therefore necessary to consider the functions of some of these eicosanoids:

- **The prostaglandins:** Prostaglandin synthetase converts the prostaglandin-cyclic-endoperoxides into a series of prostaglandins with diverse actions, including prostaglandin $D_2$, $E_2$ and $F_{2\alpha}$ ($PGD_2$, $PGE_2$ and $PGF_{2\alpha}$). Prostaglandin $E_1$ ($PGE_1$) is derived from another substrate, namely DGLA (see figure 7.1A for more information), and not from arachidonic acid like the abovementioned pro-inflammatory prostaglandins:
  - **$PGE_1$** is responsible for physiological maintenance of key organ structures such as the gastric mucosa, where it acts as an inhibitor of gastric acid secretion (see COX-1). $PGE_1$ also relaxes vascular smooth muscle, but causes contraction of non-vascular smooth muscle, including bronchial and uterine smooth muscle fibres.
  - **$PGE_2$** and **$PGF_{2\alpha}$** are mediators of the inflammatory process. They also sensitise peripheral pain receptors and cause selective **smooth muscle contraction**. For example, uterine smooth muscle contraction in both pregnant and non-pregnant females may be achieved with these prostaglandins. $PGE_2$ causes **vasodilatation** as part of the inflammatory response, and also **bronchodilatation**, depending on which receptors it stimulates (see below). Prostaglandin $F_{2\alpha}$ causes both **bronchoconstriction** and **vasoconstriction**. Both of these eicosanoids increase gastrointestinal motility. $PGD_2$ is a **vasodilator** and inhibits platelet aggregation. The latter also acts as a **bronchoconstrictor**.
  - Note that the arachidonic acid-derived prostaglandins are a diverse group of autacoids that have the ability to exert a multiplicity of effects in most tissues of the body. Together with the prostacyclins and thromboxanes, they are collectively referred to as the **prostanoids**. The latter exert their effects via a series of prostanoid-receptors. $PGE_2$ acts as the natural agonist at the EP-receptor, for example, and its effects on certain tissues are dependent on the specific receptor-subtype (i.e. $EP_1$, $EP_2$, $EP_3$ or $EP_4$) that it interacts with (e.g. $PGE_2$ acts as a bronchoconstrictor at $EP_1$-receptors, but as a bronchodilator at $EP_2$-receptors). Other examples of prostanoid-receptors, most of which also have receptor-subtypes, are the DP-, FP-, IP- and TP-receptors (for $PGD_2$, $PGF_{2\alpha}$, $PGI_2$ and $TXA_2$ respectively).

- **Prostaglandin $I_2$ (prostacyclin):** The enzyme prostacyclin synthetase converts prostaglandin-cyclic-endoperoxides to prostacyclin ($PGI_2$), which in turn **activates adenylyl cyclase** to produce a **vasodilatory effect** on blood vessels. It also prevents platelet aggregation under normal circumstances. Together with $PGE_2$, $PGI_2$ plays an important role in maintaining pulmonary and renal blood flow, as well as glomerular filtration (see COX-1). These eicosanoids are vital in maintaining the patency of the **ductus arteriosus** until such time as its closure is needed or desired.
- **Thromboxane $A_2$ ($TXA_2$):** This metabolite of arachidonic acid is found in blood platelets, where its role is to promote platelet aggregation. It also causes vasoconstriction and therefore produces effects opposite to those of $PGI_2$.

Furthermore, **cyclooxygenase** (COX) has three **isoforms** (or isozymes), labelled COX-1, COX-2 and COX-3:

- **COX-1** is present in most tissue cells of the body and catalyses the formation of the prostanoids (prostaglandins and thromboxane) that are involved in **normal 'housekeeping and maintenance' functions**, including the regulation of renal perfusion during stressful episodes (including trauma), platelet aggregation and haemostasis, and the protection of the gastric mucosa through increased mucous secretion and decreased gastric acid secretion (this is known as its cytoprotective effect on the GIT). Thus, COX-1 has normal physiological functions and is **always present** (it is said to be constitutively expressed).
- **COX-2** is responsible for **inflammation**, since it is **induced** (i.e. it is not always present in the body) by inflammatory triggers such as cellular hypoxia and tissue injury. Of note is the fact that COX-2 is, however, also involved in the regulation of renal perfusion. COX-2 is also responsible for the formation of the prostaglandins that cause uterine contractions. More recently it has become increasingly evident that COX-2 has normal physiological, or constitutive, functions as well, whether it be directly or via the maintenance of a normal thromboxane $A_2$-to-prostacyclin ratio (see note 7.1), or both. The development of a new class of non-steroidal anti-inflammatory agents, namely the selective COX-2 inhibitors (or COXIBs), originally promised to bring about anti-inflammatory actions (by selectively inhibiting the COX-2 isozyme, since the latter was then thought to only be inducible by inflammatory stimuli) without producing any of the unwanted side-effects that are associated with the inhibition of the constitutively-expressed COX-1 isozyme with its normal physiological, or 'housekeeping' functions. Therefore, it was hoped that the COXIBs would act as selective anti-inflammatory and analgesic agents, without bringing

about NSAID-induced gastrointestinal toxicity or unwanted (in specific settings) anti-platelet activity.

The benefits of being a selective inhibitor of COX-2 turned out to be very relative indeed. COXIBs have been implicated in life-threatening hypersensitivity reactions, rare but potentially fatal skin rashes, as well as gastrointestinal (albeit less likely than with the non-selective NSAIDs) and significant cardiovascular (and cerebrovascular) adverse reactions. As already mentioned COX-2 also plays a physiological role in the maintenance of normal kidney function. Also refer to figure 7.1B.

Furthermore, it should be noted that the COXIBs are *not* more effective in relieving pain and inflammation than the traditional, non-selective NSAIDs.

➲ **COX-3** is the likely isoform of cyclooxygenase found in the central nervous system (i.e. in brain tissue). It is because ***paracetamol*** does not inhibit either of the other two isozymes peripherally that scientists have come to believe that the COX-3 isoform exists.

**Note 7.1 Why do the COXIBs bring about an increased risk for significant cardiovascular and cerebrovascular adverse reactions?**

As illustrated in figure 7.1B the two cyclooxygenase isozymes, i.e. COX-1 and COX-2, are responsible for, amongst others, the production of thromboxane $A_2$ ($TXA_2$) and prostacyclin ($PGI_2$) respectively. $TXA_2$ acts as a **vasoconstrictor** and **promotes** platelet aggregation, while $PGI_2$ is a **vasodilator** that **prevents** platelet aggregation (i.e. it has anti-platelet effects). Therefore, selectively inhibiting COX-2, and therefore also inhibiting the production of $PGI_2$, will give rise to an imbalance in the normal physiological ratio of $TXA_2$:$PGI_2$. Thromboxane $A_2$ will then be in relative oversupply and will, therefore, favour vasoconstriction, the aggregation of platelets and a resultant tendency towards the occurrence of thrombotic events such as stroke and myocardial infarction (especially in patients with other predisposing risk factors for such events).

The other group of eicosanoids that are of clinical and pharmacological significance are the **leukotrienes**. The enzyme 5-lipoxygenase (other forms such as 12-lipoxygenase also exist) converts arachidonic acid to leukotrienes (LTs) **in inflammatory cells** (including macrophages, mast cells, basophils and eosinophils) in response to inflammatory stimuli. Three of these leukotrienes, leukotriene $C_4$, $D_4$ and $E_4$ (or $LTC_4$, $LTD_4$ and $LTE_4$) that are formed via the unstable intermediate leukotriene $A_4$ ($LTA_4$), are the main constituents of the so-called slow-reacting substance of anaphylaxis, or SRS-A, and play a vitally important role in the pathophysiology of both **anaphylaxis** and **bronchial asthma**.

Therefore, these leukotrienes also mediate inflammation. They are potent bronchoconstrictors, even more so than histamine, and play an important role in the pathogenesis of **allergic rhinitis** as well. When bronchoconstriction is initiated by allergenic triggers, leukotrienes $C_4$, $D_4$ and $E_4$ are released, upon which they interact with leukotriene receptors (known as ***cys*LT$_1$-receptors**, since these three leukotrienes contain the amino acid **cysteine** in their chemical structures). Stimulation of *cys*LT$_1$-receptors mediates the following **airway effects**: bronchoconstriction, airway inflammation and oedema, as well as an increase in bronchial mucous secretion and viscosity. Refer to figure 7.1A. A lesser known *cys*LT$_2$-receptor also exists.

The unstable $LTA_4$ may also, via a different metabolic pathway, be converted to leukotriene $B_4$ ($LTB_4$), which is mainly produced in neutrophils and acts as a potent chemotactic agent (i.e. it attracts leukocytes to areas of cellular injury as part of the inflammatory process). $LTB_4$ acts on its own specific leukotriene receptors, namely the BLT-receptors (i.e. $BLT_1$ and $BLT_2$). Also refer to figure 7.1A.

## 7.2 The glucocorticosteroids

These steroid hormones interact with **intracellular receptors** (refer to paragraph 3.7) to facilitate the synthesis of **lipocortin**, which inhibits phospholipase $A_2$ (see figures 7.1A and 7.2). In doing so, they prevent the activation of the arachidonic acid cascade, and therefore the formation of both the prostaglandin-cyclic-endoperoxides, and of the leukotrienes. The glucocorticosteroids also inhibit the expression of COX-2 and, therefore, they directly suppress the formation of the pro-inflammatory prostaglandins as well. Furthermore, they are capable of inhibiting a variety of other inflammatory mediators, including (as figure 7.1A illustrates) platelet-activating factor, or PAF, and a number of pro-inflammatory **cytokines** (also see figure 7.2 and the definition of cytokines in the glossary). The onset of their anti-inflammatory action via the inhibition of $PLA_2$, however, is rather slow, due to their mechanism of action that requires the induction of gene transcription for the synthesis of lipocortin, or annexin-1 (see figure 7.2).

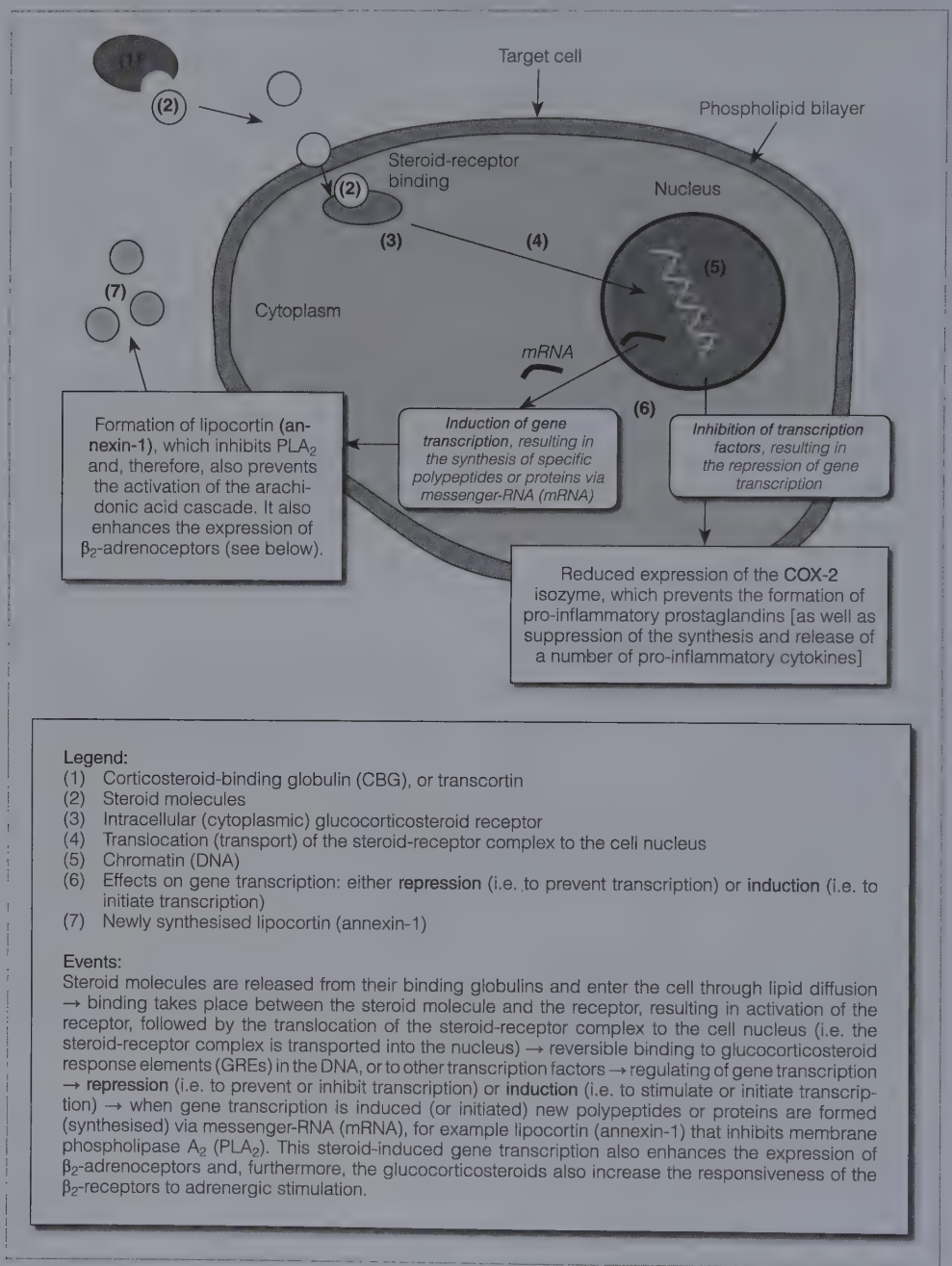



**Figure 7.2 The mechanism that underlies the anti-inflammatory action of the glucocorticosteroids**

These drugs have a significant clinical application value in that they have the ability to act as anti-inflammatory, immuno-suppressive (including anti-

rheumatic) and anti-allergic agents. They suppress cell-mediated immunity through their intense effects on peripheral white blood cells, and are of benefit in the management of auto-immune reactions. The glucocorticosteroids have the following effects on **circulating blood cells**:

- They **increase** the concentration of circulating erythrocytes, thrombocytes and neutrophils (some authors prefer to refer to the latter as **polymorphonuclear (PMN) leukocytes**), as well as the blood haemoglobin (Hb) concentration.
- They **decrease** the number of circulating lymphocytes as well as monocytes, basophils and eosinophils. These cells are re-distributed into the lymphoid tissue.

Furthermore, the glucocorticosteroids prevent the degranulation (and resultant release of histamine) of eosinophils, basophils and mast cells, they inhibit the normal functioning of tissue macrophages, and they may even prevent antibody production (in high dosages). They can cause vasoconstriction and decrease capillary permeability, as well as stabilise lysosomal membranes and, therefore, inhibit the release of proteolytic enzymes from these organelles.

A very important aspect of glucocorticosteroid treatment is the fact that these drugs have numerous side-effects, many of which influence metabolic processes in the body. Some of these side-effects, or adverse reactions are a drug-induced (or iatrogenic) Cushing's syndrome, osteoporosis and steroid diabetes. Refer to table 7.1 for a summary of the most important side-effects that are associated with glucocorticosteroid therapy, as they relate to the various metabolic and other actions of these drugs.

**Table 7.1 The effects and associated side-effects of the glucocorticosteroids**

| Metabolic and other actions and effects of the glucocorticosteroids | Important side-effects or adverse reactions that are associated with glucocorticosteroid therapy |
|---|---|
| (↑) gluconeogenesis; (↓) peripheral glucose utilisation → (↑) blood glucose levels (to protect glucose-dependent tissues)<br>(↑) lipolysis → (↑) free fatty acids | **Endocrine-metabolic:** increased insulin-resistance; steroid diabetes (may worsen the degree of blood glucose control in patients with diabetes mellitus or precipitate diabetes in patients who have other predisposing risk factors); negative nitrogen balance |

| | |
|---|---|
| Both naturally-occurring and therapeutically-employed glucocorticosteroids have a negative feedback effect on the secretion of CRH (corticotropin-releasing hormone) from the hypothalamus, and of ACTH (adrenocorticotropic hormone) from the anterior pituitary gland. Extended glucocorticosteroid therapy at supraphysiological (i.e. pharmacological) dosages will, therefore, cause suppression of the normal secretion of corticosteroids, and will eventually result in atrophy of the adrenal cortex | Redistribution of body fat: obesity of the trunk, fat-loss in the extremities, buffalo hump and moon facies (i.e. a moon face) → iatrogenic Cushing's syndrome; (↑) appetite and weight gain<br>Growth retardation in children<br>Acute adrenal insufficiency (secondary to the suppression of the hypothalamic-pituitary-adrenal (HPA) axis and a subsequent sudden withdrawal of glucocorticosteroid therapy) |
| Catabolic and anti-anabolic effects on connective tissue, bone, lymphoid tissue, muscle tissue, peripheral fat and the skin | **Cardiovascular:** hypertension (through various mechanisms including sodium and water retention); oedema (secondary to sodium and water retention) → congestive cardiac failure (CCF) |
| (↑) production of pepsin and gastric acid | **Gastrointestinal:** peptic ulceration |
| (↑) catabolism of bone tissue and antagonism of the effects of vitamin $D_3$ on the absorption of calcium from the intestinal tract; (↑) renal excretion of calcium; long-term therapy will (↓) osteoblast activity and (↑) osteoclast activity → loss of trabecular bone | **Musculoskeletal:** weakness and wasting of skeletal muscle tissue (steroid myopathy); osteoporosis (with an increased risk of bone fractures); avascular necrosis of the head of the femur; inhibition of bone growth in children |
| Unwanted inflammation, allergic and other hypersensitivity reactions, organ transplant rejection and auto-immune reactions may be suppressed | **Skin:** thinning of the skin, red cheeks, easy bruising, stretch marks (striae), acne and hirsutism (abnormal male-pattern body and facial hair in women), impaired wound healing |
| | **Eye:** raised IOP (intra-ocular pressure); glaucoma; cataract formation |
| | **Neuropsychological:** benign intracranial hypertension; elevated mood, excitability, euphoria, psychosis, or even depression |
| | **Fluid and electrolyte balance:** sodium and water retention (sodium reabsorption and potassium loss); hypokalaemia |
| | **Immune system:** (↑) susceptibility to infection; suppression of cell-mediated immunity; inhibition of normal macrophage function; inhibition of the degranulation of eosinophils, basophils and mast cells, (↓) number of circulating lymphocytes and suppression of T-helper cell function; (↓) leukocyte accumulation at sites of tissue injury and inflammation |

**Notes:**

1. The therapeutic effects and the side-effects, or adverse reactions, of the glucocorticosteroids are all dependent upon their dosage and duration of use. The iatrogenic Cushing's syndrome is generally seen after an extended duration of treatment with large dosages of glucocorticosteroids.
2. Suppression of the hypothalamic-pituitary-adrenal (HPA) axis is usually only significant when the duration of treatment exceeds 10 days of continuous therapy (opinion differs and some authors quote a 'safe' duration of treatment as being 7-14 days, or even as long as three weeks). In chronic treatment HPA-axis suppression and systemic toxicity may be limited to some extent by alternate-day therapy.
3. Sodium and water retention is an aldosterone-dependent effect on the distal convoluted tubule of the nephron; sodium is reabsorbed in exchange for potassium and hydrogen ion ($H^+$) excretion (i.e. a 'loss' of potassium and hydrogen ions ensues). The sodium and water retention potential of the various corticosteroid preparations vary. *Cortisone* and ***hydrocortisone***, in addition to their glucocorticosteroid effects, also have mineralocorticosteroid effects through their binding to intracellular aldosterone receptors. Some of the synthetic glucocorticosteroids such as *methylprednisolone* and *dexamethasone* have negligible or no mineralocorticosteroid effects (i.e. they do not cause any sodium and water retention, while aldosterone itself has almost exclusive mineralocorticosteroid effects and very few glucocorticosteroid effects).

***Hydrocortisone*** is the naturally occurring, active form of cortisone (secreted by the adrenal cortex), and causes significant sodium and water retention. Newer, synthetic glucocorticosteroids have been developed to limit the extent of the sodium and water retention, and to elicit more powerful therapeutic effects in the body. The medium-, or intermediate-acting corticosteroids include ***prednisone*** and *prednisolone* (they exhibit less sodium and water retention potential than ***hydrocortisone***), as well as *methylprednisolone*, which causes insignificant salt retention. ***Prednisone*** is converted to *prednisolone* in the body. Long-acting corticosteroids, such as ***betamethasone*** and *dexamethasone*, have more potent anti-inflammatory effects and do not cause sodium and water retention (salt retention may elicit or exacerbate hypertension, eventually culminating in congestive cardiac failure). The newer, synthetic preparations also have fewer androgenic effects (i.e. hirsutism, acne and the amenorrhoea seen in female patients with Cushing's syndrome), than the naturally occurring glucocorticosteroids.

Clinical uses of the glucocorticosteroids include adrenal replacement therapy (in physiological dosages), various respiratory diseases (see chapter 8), inflammatory and autoimmune diseases, the treatment of transplant rejection, several skin conditions, cerebral (brain) oedema and nephrotic syndrome, as well

as the stimulation of lung maturation in the unborn foetus (when premature delivery is anticipated earlier than 34 weeks of gestation).

**Clinical application**

- Owing to the significant metabolic effects of the glucocorticosteroids, and if no contraindications exist, it is generally recommended that patients on long-term therapy follow a special diet that is high in protein content, as well as being low in sodium and high in potassium content.
- Closely monitor arterial blood pressure, blood glucose levels, renal function, serum electrolytes and blood lipid levels.
- Calcium and vitamin D supplementation may be required.
- Observe the skin for bruising and take into consideration that the glucocorticosteroids may impair wound healing, suppress the inflammatory response and increase the risk of opportunistic infections.
- Do not withdraw long-term therapy abruptly and consider the option of alternate-day dosing. It is also preferable to administer glucocorticosteroids in the morning.
- Owing to the suppression of the HPA-axis, which is brought about by long-term therapy at supraphysiological dosages, patients who suffer serious illness, traumatic injury, moderate or severe stress, and/or who require surgery, need to receive increased dosages of their glucocorticosteroids during such times of increased demand. Optimal functioning of the HPA-axis may stay suppressed for up to 12 months after discontinuation of long-term therapy.
- Patients should be made aware of the fact that they need to alert healthcare professionals to their glucocorticosteroid therapy (e.g. their family practitioner, pharmacist and dentist).

## 7.3 The NSAIDs

From the abovementioned discussion of the arachidonic acid cascade, it follows that the prostaglandins are important mediators of inflammation, they may act as vasodilators, they stimulate the temperature-regulating centre in the hypothalamus to produce fever and they sensitise peripheral pain receptors. They also cause uterine contractions, implying dysmenorrhoea or the facilitation of labour. This is the reason why the inhibition of prostaglandin synthesis produces the following clinical effects:

- Anti-inflammatory effects
- Analgesia, especially in the presence of well-defined musculoskeletal pain, headache and dental pain
- Antipyretic effects
- Constriction of blood vessels in certain vascular beds, which is of particular importance in patients with renal pathology, or patients who are dehydrated, since renal perfusion may be compromised. (Note that both the COX-1

and COX-2 isozymes are responsible for the synthesis of prostaglandins [including $PGI_2$] that help to regulate and maintain renal blood flow, especially in the presence of increased concentrations of circulating vasoconstrictors such as the catecholamines and angiotensin II.)

- Relief of dysmenorrhoea (and the suppression of preterm labour)

Inhibition of the COX isozymes will have the following effects:

- **COX-1 inhibition:** The effects should mostly be viewed as unwanted, as erosions or ulcerations of the gastric mucosa may occur, or even decreased kidney perfusion in the presence of physical stress or trauma. However, one effect that may be utilised therapeutically is decreased platelet aggregation, especially in the prevention of arterial thrombus formation.
- **COX-2 inhibition:** The COX-2 isozyme is not normally found in most tissues and is mainly expressed during periods of stress, when it is newly formed and released. COX-2 inhibition, therefore, results in the suppression of the inflammatory process, antipyretic and analgesic effects, and decreased uterine contractions. Also refer to figure 7.1B.
- **COX-3 inhibition:** ***Paracetamol*** has antipyretic and analgesic properties only. It may be considered to be a *selective COX-3 inhibitor*. Since COX-3 is restricted to the brain, musculoskeletal (peripheral) inflammation cannot be influenced with this drug.

The NSAIDs are particularly useful in the management of mild to moderate musculoskeletal pain, dental pain, fever and inflammation, as well as dysmenorrhoea, postpartum pain and pain of vascular origin. The 'older'-type NSAIDs are **non-selective cyclooxygenase inhibitors**. The newer-type NSAIDs, on the other hand, have progressed towards a very high degree of COX-2 selectivity and are, therefore, referred to as the **selective COX-2 inhibitors**, or COXIBs (refer to figure 7.1B for an illustration of the varying degrees of selectivity towards the COX-isozymes that are displayed by the NSAIDs and COXIBs).

The selection of available NSAIDs belong to a variety of different chemical classes, including the propionic acid derivatives (e.g. ***ibuprofen*** and *naproxen*), indole acetic acids (e.g. *indomethacin*), fenamates (e.g. *mefenamic acid*), and many more (with examples such as *diclofenac* and *meloxicam*). Patients may respond differently to drugs from the different chemical classes and even to different drugs from the same chemical class. The COXIBs include *celecoxib* and *etoricoxib*. *Meloxicam* is an example of an NSAID that displays a preference for the COX-2 isozyme (i.e. it has an increased selectively towards inhibiting COX-2, but is not a highly-selective inhibitor like the COXIBs).

### Non-selective NSAIDs that exhibit varying degrees of selectivity towards the COX-isozymes

- ***Aspirin*** (acetylsalicylic acid, or ASA) inactivates cyclooxygenase irreversibly (through acetylation). At low daily dosages (of less than 100 mg, for example) it selectively inhibits the COX-1 isozyme and therefore inhibits platelet aggregation irreversibly as well. Platelets do not have nuclei and are therefore unable to synthesise a new supply of the cyclooxygenase enzyme. In platelets COX-1 is responsible for the formation of thromboxane $A_2$ ($TXA_2$).
- Except for the inhibition of prostaglandin synthesis, ***aspirin*** may also cause **direct damage** to the gastric mucosa. It has a $pK_a$ of 3.5, implying that it would mostly be found in its un-ionised form (see paragraph 2.2.1) in the stomach, from where it will penetrate the protective mucosal layer, diffuse into the intracellular compartment and ion trapping will take place. In overdose, ***aspirin*** causes hyperventilation and respiratory alkalosis at first, followed by compensatory metabolic acidosis. This may be accompanied by hyperthermia. High-dose ***aspirin*** follows **zero-order** kinetics. A serious overdose may well prove to be fatal.
- Other examples:
  - *Piroxicam* has a very long half-life and a high relative risk of gastrotoxicity.
  - *Indomethacin* may also be used to induce the closure of a **patent ductus arteriosus** in premature infants; as well as to suppress preterm labour (see chapter 10). It is a strong anti-inflammatory agent.
  - Examples of NSAIDs that may be administered intravenously are *ketorolac* and *lornoxicam*. *Ketorolac* is suitable for short-term, postoperative pain management and may be used to reduce the dosages of opioid analgesics required for effective pain management in this setting (it is therefore said to be an 'opioid-sparing' analgesic). Other injectable NSAIDs are also used in this setting.
  - *Mefenamic acid* is used in the management of fever in children. Both *mefenamic acid* and *naproxen* have been used with success in the management of painful menses. ***Ibuprofen*** is very widely used as an analgesic and antipyretic agent, and it has a somewhat lower relative risk of gastrotoxicity when compared to many of the other non-selective NSAIDs. The latter is also effective in the management of dysmenorrhoea.
  - More examples: *diclofenac, flurbiprofen, ketoprofen, nabumetone* and *sulindac*. *Diclofenac* and *ketorolac* may also be used to manage biliary and ureteral colic, and the NSAIDs (and COXIBs) are widely used as pain relievers in rheumatoid and osteoarthritis.

### NSAIDs that exhibit a higher degree of selectivity for COX-2 inhibition

- *Meloxicam* inhibits COX-2 with relatively more selectivity than its selectivity for COX-1.
- *Meloxicam*, therefore, has fewer gastrointestinal side-effects.
- *Etodolac* and *nimesulide* are also considered to be (relatively) selective inhibitors of the COX-2 isozyme.

## The (highly) selective COX-2 inhibitors (the COXIBs)

- These drugs exhibit a very high degree of selectivity for COX-2.
- *Celecoxib*, *etoricoxib* and *parecoxib* are well-known examples.
- They were originally believed to be *the* solution to eliminating the unwanted gastrointestinal, renal and platelet-inhibiting side-effects of the NSAIDs while, at the same time, acting as selective anti-inflammatory agents. They do have significantly fewer gastrointestinal effects; however, they have similar renal side-effects and display an actual increase in cardiovascular toxicity, compared to the non-selective COX-inhibitors (i.e. the NSAIDs). They do not offer any protection against thrombotic events because they do not inhibit normal platelet functioning. See text, as well as figure 7.1B and note 7.1. Combining low-dose ***aspirin*** with a COXIB, for the added advantage of the platelet-inhibiting action of the former, will unfortunately cancel out the relative 'gastro-protective' advantage of the latter.
- *Parecoxib* is administered parenterally (both intramuscularly and intravenously), making it especially useful in the management of postoperative pain.
- *Rofecoxib*, *valdecoxib* and *lumiracoxib* have all been withdrawn from the market.

## Clinical application

- The problem of gastrotoxicity necessitates the monitoring of the patient for any signs of gastritis or upper gastrointestinal tract bleeding, or both. Other signs and symptoms include dyspepsia, abdominal discomfort, diarrhoea, nausea and vomiting.
- The inhibition of platelet aggregation necessitates monitoring the patient for bleeding tendencies. Microscopic haematuria may be detected early on with regular urinalysis, using test-reagent strips. The anti-platelet effects of the non-selective NSAIDs will increase the likelihood of bleeding episodes in patients who are also receiving anticoagulant therapy (e.g. *warfarin*).
- Patients with impaired renal function or hypovolaemia require careful monitoring, due to the danger of decreased kidney perfusion. Do not use the NSAIDs (or COXIBs) indiscriminately in patients who suffered severe burn wounds or who sustained multiple traumatic injuries. Sodium and water retention, and the resultant oedema, may aggravate hypertension, counteract antihypertensive treatment, and precipitate congestive cardiac failure in patients who are at risk.
- It is generally recommended that patients take orally-administered NSAIDs with a meal; preferably not on an empty stomach.
- The gastrotoxicity of these drugs may be aggravated by the simultaneous use of alcohol.

## 7.4 Paracetamol

***Paracetamol*** is also called *acetaminophen*. This drug has antipyretic properties and is very widely used for mild to moderate pain. It is considered to be very safe at therapeutic dosages for limited periods of time, even during pregnancy and lactation. As already explained, ***paracetamol*** is not effective as an anti-inflammatory agent at all. It is well tolerated with very few side-effects. The successful formulation of a ***paracetamol*** solution for intravenous infusion has broadened it usefulness considerably. The intravenous formulation may even be used in the management of postoperative pain, as an opioid-sparing analgesic.

In an acute overdose, however, ***paracetamol*** is a very dangerous and potentially lethal drug. It undergoes hepatic biotransformation and one of its lesser intermediary metabolites is toxic. Normally this toxic metabolite would be conjugated with glutathione. However, when glutathione stores become depleted during an overdose, this toxic metabolite (known as *N*-acetyl-para-benzoquinone imine, or NAPQI) accumulates and causes liver cell necrosis. The hepatotoxicity may be accompanied by acute renal failure. *N-acetylcysteine* is used as the antidote in the management of acute ***paracetamol*** overdose or poisoning.

***Paracetamol*** is the analgesic and antipyretic of choice in paediatrics. It is also well tolerated in this population and has a favourable side-effect profile compared to the alternatives (e.g. ***ibuprofen*** and *mefenamic acid*). However, alternating ***paracetamol*** and one of the latter NSAIDs every four hours is a commonly-encountered practice in the management of febrile conditions in children. ***Aspirin*** is contraindicated in children due to the risk of Reye's syndrome.

CHAPTER EIGHT

# Drugs and the respiratory system

**Suggested revision**

***Anatomy and physiology:***

- The upper and lower airway or respiratory tract
- Lung volumes and capacities
- The mechanism of breathing and respiratory control
- Functional respiratory units, the air-blood barrier and gaseous exchange in the lungs
- Pulmonary blood circulation and the ventilation–perfusion ratio
- The transport of oxygen and carbon dioxide in the bloodstream

***Pathology and pathophysiology:***

- Bronchial asthma and allergic rhinitis
- Chronic obstructive pulmonary disease (COPD)

The pharmacotherapeutic approach to the treatment of bronchial asthma may also be applied to other airway conditions that are associated with bronchoconstriction, or bronchospasm, and a resultant decrease in pulmonary or respiratory function. Drug treatment may be aimed at relieving the major symptom (i.e. dyspnoea due to such bronchoconstriction or bronchospasm), or to modify (i.e. 'control') the disease process through anti-inflammatory and anti-allergic action. Therefore, these therapeutic approaches may also be applied to the management of chronic obstructive pulmonary disease (COPD), and the latter also applies to the treatment of allergic rhinitis.

## 8.1 The bronchodilators

These drugs cause relaxation of the bronchial smooth muscle, and therefore facilitate bronchodilatation. The bronchial smooth muscle contains both muscarinic and $\beta_2$-adrenergic receptors. This provides for two possible mechanisms of drug action, namely **active** bronchodilatation and **passive** bronchodilatation:

- **The selective $\beta_2$-receptor agonists:** These drugs are selective agonists at the adrenergic $\beta_2$-receptors (also referred to as the $\beta_2$-adrenoceptors) of the bronchial smooth muscle when they are inhaled directly into their biophase (i.e. when a *localised* effect is achieved on the smooth muscle of the lower

respiratory tract). When administered intravenously (or even by mouth) they lose their selectivity and will produce cardiac ($\beta_1$-receptor) and other systemic effects as well. Examples of short-acting agents are ***salbutamol*** (also known as *albuterol*), *fenoterol, hexoprenaline* and *terbutaline*. By increasing the concentration of cAMP, these drugs act as active bronchodilators. Therefore, it can be said that they act as physiological antagonists of the **spasmogens** causing the bronchoconstriction. Patients should be monitored for tachycardia, palpitations, skeletal muscle tremors and an increase in arterial blood pressure.

In contrast to the short-acting $\beta_2$-agonists, which have an average onset of action of approximately half an hour (or less), and a duration of action in the range of four to six hours, the long-acting $\beta_2$-agonists will have a slower onset and more sustained duration of action, lasting up to 12 hours. Examples of the latter are *salmeterol* and *formoterol*.

- ***Theophylline***, a methylxanthine, is a systemic bronchodilator with a **narrow therapeutic index**. Therapeutic drug monitoring is therefore required. It differs from the abovementioned drugs in that it inhibits the enzyme phosphodiesterase (refer to figure 4.5). This produces non-selective β-receptor effects through an increase in the cAMP concentration. It is a second-line drug. *Caffeine* is a methylxanthine as well and may be used as an alternative to *aminophylline* in the prevention of apnoea of prematurity (AOP). *Aminophylline* is theophylline ethylene diamine, which is more water soluble and may be administered intravenously. In addition to their systemic β-adrenergic effects, the methylxanthines also have a stimulatory effect on the CNS, resulting in increased levels of alertness, and can cause gastric irritation.
- **Anti-muscarinic drugs**: The short-acting drug of choice is ***ipratropium bromide***, since it does not cause thickening of the bronchial secretions. Blocking the muscarinic receptors will inhibit acetylcholine-induced bronchoconstriction, and implies that adrenergic stimulation of $\beta_2$-adrenoceptors in the bronchial smooth muscle will not be opposed by parasympathetic outflow from the vagus nerves. This results in bronchodilatation. Therefore, ***ipratropium bromide*** is a **passive bronchodilator**. *Tiotropium bromide* is a long-acting muscarinic antagonist. Both drugs are of particular importance in the management of COPD, and because they are poorly absorbed following inhalation they cause very few systemic side-effects.

Enhanced bronchodilatation may be achieved when combining ***ipratropium bromide*** with a short-acting, selective $\beta_2$-agonist, such as ***salbutamol*** or *fenoterol*, due to the synergism between their mechanisms of action.

## 8.2 Disease modifiers

The inhaled glucocorticosteroids, such as ***budesonide, beclomethasone***, *ciclesonide* and *fluticasone*, are much safer for long-term use than systemic corticosteroids. They will alter the course of the disease process and are life-saving in the long run. They will, however, not manage acute bronchospasm, but will decrease bronchial hyper-reactivity and the risk of a relapse. Nasal sprays are also available for the management of allergic rhinitis. In addition to ***budesonide, beclomethasone*** and *fluticasone*, *mometasone* and *triamcinolone* are also available for the latter indication. Inhaled glucocorticosteroids may give rise to oral thrush (i.e. oral candidiasis) and patients are therefore encouraged to rinse their mouths with clean water following the use of their steroid inhalers. These drugs are the main anti-inflammatory agents used in the management of asthma. Refer to chapter 7 for additional information on the glucocorticosteroids.

The **leukotriene receptor-antagonists** (refer to chapter 7 for a discussion on the leukotrienes, including their biosynthesis) may be effective in controlling exercise- and aspirin-induced asthma, and may also be used in the chronic treatment of asthma. Examples are *zafirlukast* and *montelukast*. They are competitive antagonists of the *cys*$LT_1$-receptor, they have the advantage of oral administration, and *montelukast* is even available as a sprinkle and in chewable tablet form for paediatric use.

*Zileuton* is a 5-lipoxygenase (5-LOX) inhibitor and therefore acts as a leukotriene synthesis inhibitor (refer to figure 7.1A for additional information on the role of 5-LOX in the arachidonic acid cascade). *Zileuton* has the added advantage of also inhibiting the formation of leukotriene $B_4$ ($LTB_4$).

The so-called mast cell stabilisers, such as *sodium cromoglycate* (also known as *cromolyn sodium*) and *ketotifen*, may be used in (allergic) asthma prophylaxis, as well as for the prevention and treatment of allergic rhinitis. These drugs act by stabilising the plasma membranes of mast cells. This prevents these cells from degranulating and releasing histamine and other spasmogens. The term 'mast cell stabiliser' is actually somewhat limiting because *sodium cromoglycate,* and the closely related *nedocromil sodium,* have effects on a number of other cells that form part of the inflammatory response as well, and *ketotifen* also acts as an antagonist at $H_1$-receptors.

## Note 8.1 Cough suppressants, expectorants, mucolytic agents, and nasal decongestants

***Cough suppressants (also referred to as antitussive agents):***
The fact that the cough reflex fulfils an important protective function should always be kept in mind when one considers using a cough suppressant. Coughing clears the back of the throat and lower respiratory tract (i.e. the trachea, bronchi and bronchioles) of secretions and foreign particles. Care should be taken to only suppress dry, irritating and non-productive coughs, and only once this has been established as being safe and desirable. Coughing that is due to bronchoconstriction or bronchospasm (which may be found in asthmatic patients for example) should be managed with appropriate bronchodilators and infections of the lower respiratory tract should be suitably treated with antimicrobial agents (see chapter 11). Drugs that are capable of suppressing this reflex include the opioid analgesics and opioid derivatives, such as *dextromethorphan*, *pholcodine*, *codeine phosphate*, *methadone* and *noscapine*.

***Expectorants and mucolytic agents:***
These are drugs that promote the coughing up of sputum by decreasing the viscosity of the bronchial secretions. This may ease a productive cough by making it easier for the patient to expel the mucus from the lower respiratory tract. There are two ways of achieving this through pharmacological intervention, namely:

- By using **expectorants** to increase the volume of bronchial secretions and produce a more fluid-like mucus (i.e. increased secretions with a decreased viscosity). *Guaiphenesin*, *sodium citrate* and *ammonium chloride* are examples of expectorants. For obvious reasons the use of cough mixtures that contain an expectorant as well as an antitussive agent, or combined with an antihistamine, should rather be avoided.
- By using **mucolytic agents**, such as *carbocisteine*, *bromhexine* and *N-acetylcysteine*. These drugs are capable of changing the structure of the mucus itself, resulting in decreased viscosity. *Dornase alfa* (recombinant human DNase) is used in patients with cystic fibrosis.

Maintaining an optimal hydration status and the use of steam inhalations will also assist in decreasing mucous viscosity.

***Nasal decongestants:***
A congested (i.e. a 'blocked' or 'stuffy') nose is the result of vasodilatation and oedema of the nasal mucosa, which may be accompanied by inflammation, depending on the cause. Vasoconstrictors will therefore alleviate the congestion. These decongestants are $\alpha_1$-adrenergic agonists that may be applied topically or taken systemically (see chapter 5). Anti-inflammatory treatment with topical glucocorticosteroids may also be required, as well as suitable antihistamines, in the case of allergic rhinitis (also refer to paragraph 12.5.1). For the latter *sodium cromoglycate* nasal spray may also be used.

CHAPTER NINE

# Drugs and the gastrointestinal tract

**Suggested revision**

**Anatomy and physiology:**

- Basic structure and functioning of the organs which make up the gastrointestinal, digestive or alimentary tract and its accessory organs
- Ingestion of food and propulsion through the digestive tract
- Gastric and intestinal secretions
- Mechanical and chemical digestion
- Absorption
- Defecation
- The enteric nervous system and autonomic nervous system control of the motility and secretions of the gastrointestinal tract

***Pathology and pathophysiology:***

- Gastro-oesophageal reflux disease (GORD)
- Peptic ulcer disease
- Constipation and diarrhoea

## 9.1 Physiological overview

Foodstuffs that are ingested by mouth pass through the oesophagus to reach the stomach, which primarily acts as a 'receptacle', but is also capable of absorbing certain particles into the bloodstream. ***Aspirin*** and *ethanol* in particular may be well-absorbed through the stomach lining. The stomach is capable of breaking down ingested food, both physically and chemically, although chemical digestion in the stomach is primarily targeted at ingested proteins (i.e. the process of protein digestion begins in the stomach). The stomach also turns ingested food into creamy, paste-like chyme, which is subsequently passed into the duodenum.

Goblet cells make up the epithelial lining of the stomach and secrete protective alkaline mucus (to protect the stomach wall against the effects of gastric acid). The stomach lining also contains secretory **gastric glands** that are found in deep indentations called gastric pits. These gastric glands are responsible for producing the gastric secretions known as gastric juice. Different cells make up the gastric glands, including **parietal cells**, chief cells and mucous neck cells. The parietal cells are responsible for the secretion of **hydrochloric acid** (*HCl*, or stomach acid) and intrinsic factor (which is required for the absorption of vitamin $B_{12}$), the chief cells secrete pepsinogen and the mucous neck cells contribute to the

secretion of protective mucus. Gastrin, a hormone that is secreted by specialised endocrine cells in the pyloric antrum of the stomach, is a powerful stimulant for the secretion of gastric acid and pepsinogen.

**Note 9.1**

- Parasympathetic nervous system stimulation increases gastric secretions (gastrin, pepsinogen, gastric acid and intrinsic factor). Pepsinogen (inactive) is subsequently converted to the protein-digesting enzyme pepsin. Gastrin (which is also triggered by the presence of food in the stomach), in turn, will cause more gastric juice to be secreted.
- **Autacoids** are involved in balancing gastric acid and mucous secretions. Stimulation of the **$H_2$-receptors** of parietal cells by histamine increases acid secretion. Cytoprotective **prostaglandins**, however, increase mucous secretions (as well as bicarbonate secretion) and decrease acid secretion. Refer to chapter 7.
- Mucous secretion has an important protective function, since *HCl* and pepsin in the stomach are quite capable of digesting the stomach wall itself, in the absence of sufficient alkaline mucus.

After a well-balanced meal, **gastric emptying** takes about four hours to complete (up to six hours in the case of a very fatty meal). GIT motility then propels food through the remainder of the gastrointestinal tract. **Intestinal transit time** (movement through the **small intestine**) lasts another six hours.

## 9.2 Drugs that influence the functioning of the gastrointestinal tract

Drugs may be used to influence the gastrointestinal tract (GIT) in the following ways:

- Increasing gastric emptying and GIT motility.
- Favourably influencing the ratio of acid-to-mucus secretion in the stomach and neutralising gastric acid.
- Alleviating diarrhoea and intestinal colic (intestinal cramping).
- Relieving constipation.

### 9.2.1 Gastro-oesophageal reflux disease (GORD)

Patients who suffer from gastro-oesophageal reflux disease (GORD) suffer from acid heartburn (dyspepsia) due to the reflux of stomach acid into the distal part of the oesophagus.

Drug management is aimed at decreasing the amount of stomach acid that enters the distal oesophagus, usually by increasing the rate at which the stomach empties into the duodenum, and relieving the discomfort caused by the

heartburn. Note that the distinction between the management of GORD and peptic ulceration given here, is purely arbitrary and that the drugs mentioned here and in paragraph 9.2.2 may be used to treat either condition.

### Drugs used to treat dyspepsia

- **Simple antacids** such as those that contain aluminium and magnesium neutralise the hydrochloric acid in the stomach and are quite effective as **pain relievers**. The magnesium-containing antacids cause diarrhoea, while the aluminium-containing ones cause constipation. The combination of magnesium and aluminium will therefore constitute the antacid of choice (e.g. a combination of ***aluminium hydroxide*** and ***magnesium trisilicate***). The divalent cations (i.e. $Al^{2+}$ and $Mg^{2+}$), however, will interact with **chelating agents** such as the tetracycline and fluoroquinolone antimicrobials (see chapter 11), and several other drug interactions are possible.
- Combining an antacid with an **alginate** may actually **prevent reflux**, in that the alginate literally forms a 'floating gel' on top of the gastric contents.
- *Calcium carbonate* and *sodium bicarbonate* may also be used as simple antacids. However, care should be taken with these agents, since *calcium carbonate* may interfere with normal acid-base balance and cause metabolic alkalosis, or it may elicit rebound gastric acid secretion, making it suitable for short-term use only, while *sodium bicarbonate* should be used with caution in patients who require a restricted sodium-intake.
- *Dimethicone* and *simethicone* may relieve a 'bloated feeling' by acting as antiflatulent or defoaming agents. They may also be of benefit in the management of intestinal colic in infants and children.

### Pro-kinetic drugs

- ***Metoclopramide*** (refer to paragraph 12.1.2) acts as an agonist at gastrointestinal 5-$HT_4$-receptors, thus increasing the rate of gastric emptying and peristalsis. *Domperidone* has a similar mechanism of action, but differs from ***metoclopramide*** in that it does not cross the BBB.
- *Cisapride* is another 5-$HT_4$-receptor agonist, which is unrelated to the above-mentioned two drugs. It has the disadvantage of causing potentially serious cardiac side-effects such as ventricular dysrhythmias (by causing $QT_c$-interval prolongation), especially when its own metabolism is inhibited (through various drug interactions, for instance). Access to this drug has been restricted and it should be used with extreme caution.
- *Bethanechol* is a parasympathomimetic drug, which selectively stimulates muscarinic receptors. In the gastrointestinal tract this causes smooth muscle contraction, but produces relaxation of the sphincters. *Bethanechol* therefore stimulates the functional contraction of the gastrointestinal tract (i.e. it increases intestinal motility). A different approach with a similar outcome on the motility of the GIT would be to use *neostigmine* (refer to paragraph 5.2.3).
- ***Erythromycin*** also has pro-kinetic properties (refer to paragraph 11.3.4).

### 9.2.2 Peptic ulcer disease

To alleviate the accompanying discomfort and heartburn, simple antacids (as described in paragraph 9.2.1) are used. Recurring peptic ulcers have been positively linked to the presence of *Helicobacter pylori*, a gram-negative bacterium with a spiral shape, in the submucosal layers of the stomach and duodenum. Peptic ulcers may also be caused by severe physical trauma (including major surgery and severe burn wound trauma) and the presence of critical illness, or they may be NSAID-induced (as described in chapter 7).The mainstay of the drug treatment is to lower the acidity of the stomach secretions, in other words, to increase the stomach pH. This allows the ulcer to heal while being protected from the damaging effects of being exposed to stomach acid. The other option, although usually combined with the former, is to cover the surface of the ulcer with a protective coating that effectively prevents stomach acid from damaging the stomach lining any further. *Sucralfate* is capable of achieving this.

Drugs that increase gastric pH fall into two categories, namely the $H_2$-receptor antagonists and the proton-pump inhibitors (or PPIs). In order of effectiveness (in the treatment of peptic ulceration) the PPIs constitute the most effective drugs by far. They are followed by the $H_2$-receptor blockers and, lastly, by *sucralfate* (that actually does not have an acid-lowering mechanism of action). In the case of a recurring peptic ulcer, where *H. pylori* have been implicated, the so-called **triple therapy** should be used.

**The proton-pump inhibitors (PPIs)**

- These drugs enter the parietal cells of the gastric glands found in the gastric pits of the stomach lining, where they subsequently **inhibit** the $H^+$-$K^+$-ATPase pump (i.e. the 'proton pump' that is specifically responsible for the $H^+$-secretion into the lumen of the gastric pits where these cations combine with the secreted $Cl^-$ from a separate pump to form *HCl*). This effectively prevents the secretion of gastric acid from the gastric pits into the lumen of the stomach.
- Therefore, these drugs are highly effective in increasing the stomach pH, rapidly relieving the symptoms and achieving good cure rates.
- Well-known examples of PPIs are *omeprazole*, *esomeprazole* (the *S*-isomer of *omeprazole*), *lansoprazole*, *pantoprazole* and *rabeprazole*.

**The $H_2$-receptor antagonists (or blockers)**

- Blocking the gastric $H_2$-receptors of parietal cells will reduce stomach acid secretion. Ulcer healing rates are significant but not nearly as good as those obtained through the use of the PPIs.

- ***Cimetidine***, *ranitidine, famotidine* and *nizatidine* are examples of these selective $H_2$-receptor blockers.
- ***Cimetidine*** has the disadvantage of sometimes producing unwanted anti-androgenic side-effects in male patients (it has a fairly small affinity for androgen receptors). It also has a higher likelihood of multiple drug interactions through its inhibition of cytochrome P450 isozymes (see paragraph 2.5.2).

**Cytoprotective drugs**

- These drugs are referred to as cytoprotective because they protect the cells of the stomach lining against the corrosive effects of stomach acid. In addition, misoprostol also promotes perfusion of the gastric mucosa because it is an analogue of **prostaglandin $E_1$ ($PGE_1$)**.
- *Sucralfate*, as already mentioned, forms a protective layer that covers the exposed surface of the ulcer and, in doing so, produces cure rates that are comparable to those obtained with the $H_2$-receptor antagonists. It should preferably be taken one hour before meals, since it is activated by stomach acid.
- Wherever *sucralfate* is combined with any of the simple antacids, the antacid should be taken half an hour after taking the *sucralfate* (i.e. on an empty stomach as well).
- ***Misoprostol*** is of particular use in preventing the gastrotoxic effects of the NSAIDs (see chapter 7). It influences the ratio of acid-to-mucus secretion favourably by increasing gastric mucus secretion while decreasing acid secretion. Care should be taken with this drug, however, since $PGE_1$ causes uterine contractions (see chapter 7), may be used for termination of pregnancy or the induction of labour, and should therefore be avoided during pregnancy.
- *Bismuth compounds* may also be used.

**'Triple therapy'**

- A combination of a PPI, *clarithromycin* and ***amoxicillin*** will eradicate *H. pylori* and reduce the incidence of recurring peptic ulcers.
- Patients who are allergic to penicillin may receive ***metronidazole*** instead of ***amoxicillin***. Alternatively ***amoxicillin*** may be combined with ***metronidazole*** instead of *clarithromycin*.
- In resistant cases a *bismuth compound* may be combined with ***doxycycline***, ***metronidazole*** and a PPI.

## 9.2.3 Diarrhoea and intestinal colic

It is preferable to investigate the cause of diarrhoea instead of merely administering anti-diarrhoeal agents at random. The opioid agonists usually have constipation as a side-effect (see chapter 5). This has brought about the development of the non-analgesic opioid derivatives that are used particularly for the treatment of diarrhoea. ***Loperamide*** is an excellent and widely used example. Together with

*diphenoxylate* they act as **anti-motility agents** on the intestinal tract. Other possible options in the management of diarrhoea include *bismuth compounds* and *kaolin-pectin* combination formulations.

**Anti-motility agents**

- ***Loperamide*** and *diphenoxylate* are synthetic, non-analgesic opioid derivatives. They stimulate pre-synaptic opioid receptors in the enteric nervous system. This inhibits the release of acetylcholine, with a subsequent reduction in peristaltic movement. Therefore, these drugs decrease intestinal motility (i.e. they have an anti-propulsive effect).
- These drugs are generally not recommended for paediatric use.
- Unlike ***loperamide***, *diphenoxylate* may have central nervous system effects at higher dosages. A small amount of ***atropine*** is combined with *diphenoxylate* to limit its abuse potential.

***Hyoscine N-butylbromide*** *(or* ***N-butylhyoscine****)* is an anti-cholinergic drug (refer to paragraph 5.2.4) that may be used for its **antispasmodic** action, not only on the gastrointestinal tract, but also on the biliary tract and the genitourinary tract. It is of value in the management of intestinal colic (cramping). Other examples of anti-cholinergic agents that may be used for their antispasmodic action are *dicycloverine* (also known as *dicyclomine*) and *propantheline bromide*. *Dicycloverine* also has a direct antispasmodic action. *Mebeverine* is a selective anti-spasmodic drug that may be useful in situations where anti-cholinergic agents are contraindicated. *Mebeverine* is a derivative of *papaverine*, which may also be used.

### 9.2.4 Constipation

Patients who are constipated, or who require evacuation of the bowel prior to colorectal surgery or invasive diagnostic investigations of the colon, may be given a laxative. Laxatives decrease intestinal transit time by increasing the rate of intestinal peristalsis. Generally speaking, laxatives should only be used to treat acute episodes of constipation, to clean out the bowel or to assist in the elimination of certain drugs in the event of overdose or poisoning.

However, chronic use is possible in the case of the bulk-forming laxatives. The other groups of laxatives are the osmotic laxatives, the irritants, the faecal or stool softeners, and liquid paraffin. Dietary fibre and the intake of sufficient quantities of water remain vitally important in the effective management of constipation and healthy bowel habits. Oral laxatives should *not* be used in the management of faecal impaction.

## Bulk-forming laxatives

- These are indigestible substances that are hydrophilic and facilitate the retention of water in the lumen of the intestine, forming bulk, and therefore stimulating peristaltic movements. *Psyllium seed* is a good example. These laxatives should preferably be taken with a large glass of water so as to hydrate the preparation properly.
- Dietary fibre (including bran), *methylcellulose, ispaghula seed* and *husks*, and *sterculia* are other examples of bulk-forming laxatives.
- They usually start working within three days.
- Because they are hydrophilic they may even be used in the management of diarrhoea and to regulate colostomy flow.

## Osmotic laxatives

- These laxatives increase the osmotic pressure in the intestine, which results in fluid being retained inside the intestinal lumen. Except for ***lactulose*** these laxatives should really only be used for short-term relief (e.g. *magnesium hydroxide*) or rapid evacuation of the bowel (e.g. during preoperative preparation of the bowel).
- ***Lactulose*** is the osmotic laxative of choice. It is a disaccharide, composed of fructose and galactose, which cannot be hydrolysed in the small intestine. Colonic bacteria subsequently break down the disaccharide molecules to non-absorbable acetic acid and lactic acid (anions). The anions then cause water retention in the intestinal lumen.
- However, in preparation for bowel surgery, products containing purgatives such as *polyethylene glycol*, *sodium sulphate* or *sodium phosphate* may be used.
- Purgatives will produce an effect within a few hours following oral administration, but will act more rapidly following rectal administration.

## Irritants or contact laxatives

- These laxatives stimulate or irritate the colon directly, thus increasing intestinal motility. Many well-known laxatives, such as *bisacodyl*, *caster oil* (not recommended) and ***senna*** (***sennosides A*** and ***B***), belong to this group.
- They usually start working within 6 to 12 hours (or within as little as two hours following rectal administration).
- These stimulant laxatives are most often associated with laxative abuse. They are generally only indicated for short-term use.

### Stool softeners (emollient laxatives)

- Also known as surfactant laxatives, they allow water to penetrate faecal material and therefore soften the faeces.
- They are particularly useful in patients where unnecessary abdominal straining should be avoided. Dioctyl sodium sulfosuccinate (*docusate*) is a good example.

### Liquid paraffin

- *Liquid paraffin* acts as an intestinal lubricant. It is composed of hydrocarbons that are not broken down or absorbed from the gastrointestinal tract.
- It may interfere with the absorption of lipids and lipid-soluble vitamins, and could cause anal seepage. It should be used with caution.

CHAPTER TEN

# Drugs and the genitourinary and reproductive system

**Suggested revision**

***Anatomy and physiology:***

- The structures and organs of the urinary tract
- Normal micturition and urinary bladder control (urinary continence)
- Renal functioning and urine formation
- The male and female reproductive organs
- Male and female sexual functioning, including spermatogenesis, oogenesis and the menstrual cycle
- Conception, pregnancy and childbirth

***Pathology and pathophysiology:***

- Gout
- Benign prostatic hyperplasia (BPH)
- Urinary incontinence
- Sexual disfunctioning

## 10.1 Diuretics

These drugs **increase the urine volume** by increasing urine production. For most of the commonly used diuretics, the principal mechanism that underlies their action in the nephron is based on the prevention of sodium reabsorption at various tubular sites. Such agents are therefore also referred to as natriuretics (because they increase the excretion of sodium in the urine). Other possible diuretic mechanisms include an osmotic diuresis (e.g. *mannitol,* which prevents the reabsorption of water from the proximal convoluted tubule of the nephron by exerting an osmotic effect), the carbonic anhydrase (also see figure 3.1) inhibitors (e.g. ***acetazolamide,*** which inhibits the carbonic anhydrase enzyme to effectively bring about diuresis by preventing the reabsorption of $NaHCO_3$ from the proximal convoluted tubule) and the aldosterone antagonists (e.g. ***spironolactone***). The aldosterone antagonists are also discussed in paragraphs 6.2 and 12.3. The natriuretic agents include the loop diuretics and the thiazides.

## 10.2 Gout

Gout is a disorder of **purine metabolism** and implies that there are increased levels of uric acid in the bloodstream. Purines are converted to hypoxanthine, which will in turn be converted to xanthine and finally to uric acid (as illustrated in figure 3.2). The primary problem may be an increased rate of uric acid production or a decreased rate of uric acid secretion. Urate crystals are deposited in connective tissue and articular cartilage, causing acute gouty arthritis.

Uric acid may be excreted through glomerular filtration (about 90%) or active tubular secretion into the proximal convoluted tubule (the remaining 10%). About 5% of tubular uric acid is reabsorbed into the bloodstream.

### The loop diuretics

- These are 'high-ceiling' diuretics with dosage-dependent effects.
- ***Furosemide***, a powerful loop diuretic, inhibits the $Na^+/K^+/2Cl^-$ symporter in the thick ascending limb of the loop of Henle.
- ***Furosemide*** is very useful in the management of acute heart failure, since it also has haemodynamic effects when administered intravenously. It has the ability to dilate renal blood vessels, as well as the venous capacitance vessels and therefore decreases cardiac preload.
- Other examples of loop diuretics are *bumetanide* and *torasemide* (also referred to as *torsemide*).
- Loop diuretics may cause a variety of electrolyte disturbances, including hyponatraemia, hypokalaemia and hypomagnesaemia.

### The thiazide and 'thiazide-like' diuretics

- The thiazide diuretics primarily inhibit the $Na^+/Cl^-$ symporter in the early portion of the distal convoluted tubule of the nephron. They also enhance the reabsorption of $Ca^{2+}$. They are highly suited to the long-term treatment of hypertension, since they also have a direct effect on arteriolar smooth muscle, where they facilitate vasodilatation.
- As opposed to the loop diuretics, the thiazides are 'low-ceiling' diuretics (i.e. their dosage-response curve is flat). ***Hydrochlorothiazide*** is one of the most frequently prescribed diuretics in clinical practice.
- *Chlorthalidone* and *indapamide* are not thiazides but have very similar effects and uses, and may therefore be referred to as 'thiazide-like' diuretic agents.
- These agents may also cause important electrolyte disturbance, which include hyponatraemia and hypokalaemia.

### The potassium-sparing diuretics

- These diuretics may be divided into two groups, namely those that influence the aldosterone-dependent cation exchange mechanism (which normally facilitates the reabsorption of $Na^+$ in exchange for $K^+$-secretion via intracellular mineralocorticoid receptors) and those that influence the influx of $Na^+$ via epithelial sodium channels (which may simply be described as an 'aldosterone-independent' cation exchange mechanism). Their site of action is the late portion of the distal convoluted tubule and the collecting duct.
- Under normal circumstances, an increased sodium ion concentration in the filtrate that reaches the distal convoluted tubule will facilitate the cation exchange mechanisms to reabsorb sodium ions ($Na^+$) in exchange for potassium ions ($K^+$). This explains the common side-effect of most diuretics that do not 'spare' potassium, namely hypokalaemia.
- ***Spironolactone*** acts as a competitive antagonist of aldosterone at the mineralocorticoid receptor. This drug is a synthetic steroid and has anti-androgenic side-effects that may limit its use. It may cause gynaecomastia, benign prostatic hyperplasia (BPH) and impotence in men, menstrual irregularities in women, and may also be used to treat hirsutism and polycystic ovarian syndrome. Another aldosterone antagonist, *eplerenone*, does not have nearly the same intensity of these anti-androgenic side-effects. These are diuretics that influence the aldosterone-dependent process and reduce the absorption of $Na^+$ and the secretion of $K^+$ at their site of action.
- *Amiloride* and *triamterene* are examples of diuretics that influence the 'aldosterone-independent' process. They are found in a number of fixed-dosage combination products together with ***hydrochlorothiazide***. The two drugs in such a combination product will then augment one another's diuretic effects, and the *amiloride* or *triamterene* will prevent a loss of potassium ions in the late distal convoluted tubule and collecting duct.
- Patients who receive the abovementioned combination diuretics will require monitoring of their serum potassium levels, since hyperkalaemia may actually develop. The potassium-sparing diuretics should also not be combined with ACE-inhibitors (see paragraph 12.3) or potassium supplements, and should be avoided in patients with renal insufficiency due to the danger that a potentially life-threatening hyperkalaemia may develop.

## 10.3 Drugs and the reproductive system

Contraceptive agents, drugs used to treat infertility and hormone replacement therapy (HRT) do not fall within the scope of this textbook and only a brief overview has been included here. Readers are advised to consult an appropriate text on family planning, obstetrics and gynaecology.

### 10.3.1 The female reproductive system

The hormonal contraceptive agents are a group of drugs that are used to prevent fertilisation or in some cases the implantation of fertilised ova (as is the case

with emergency contraception). These agents may be taken orally, injected intramuscularly, or used to impregnate contraceptive devices.

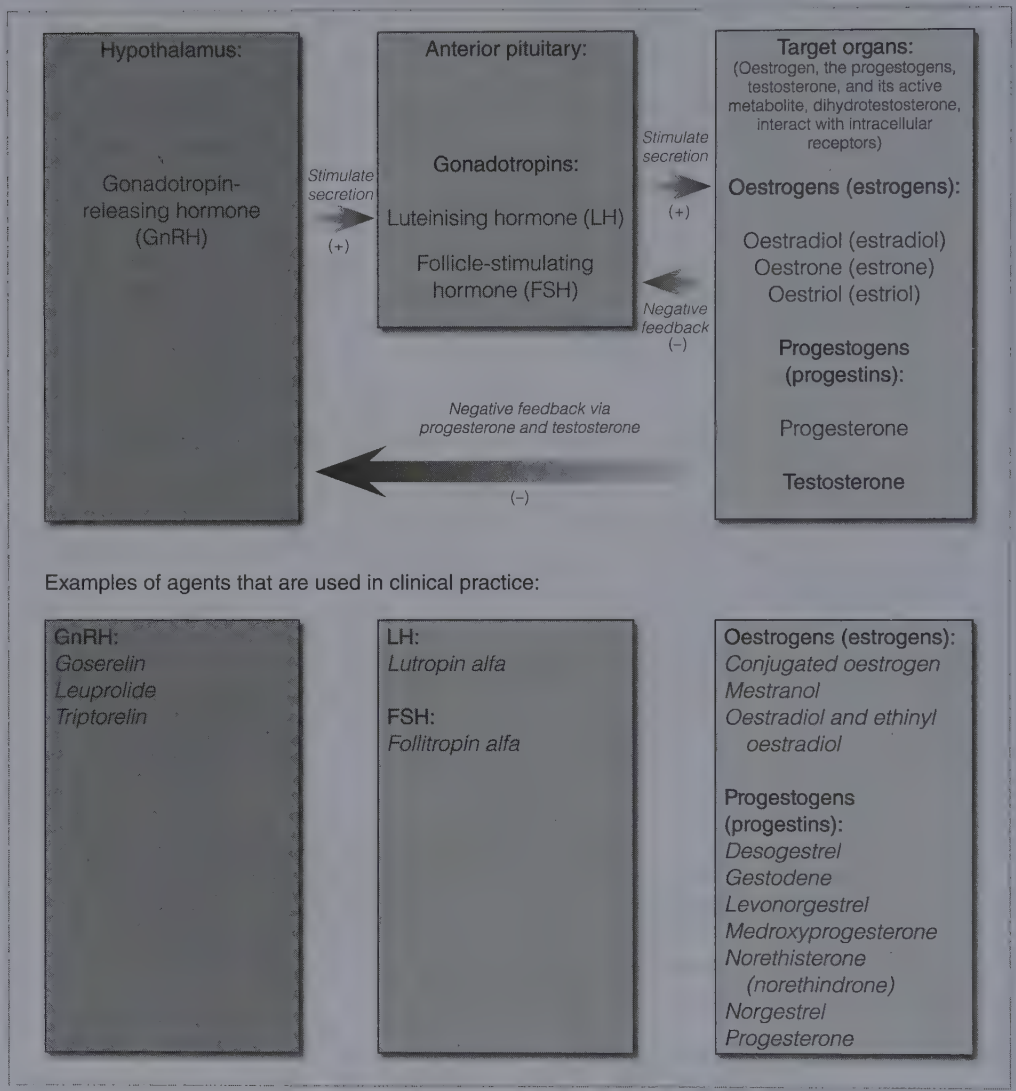



**Figure 10.1 The gonadotropins and female sex hormones**

Both oestrogen and the progestogens (progestins) may be used as contraceptive agents. They decrease the circulating levels of luteinising hormone (LH) and follicle-stimulating hormone (FSH) through negative feedback (see figure 10.1). In this way oestrogen inhibits the secretion of FSH and therefore suppresses the development of the ovarian follicle, while progestogen effectively prevents ovulation by inhibiting the secretion of LH.

- **Progestogen-only contraceptives:** These agents also have an effect on the endometrial lining of the uterus, namely to bring about changes in the endometrium that make it difficult for implantation to take place. Furthermore, they cause cervical mucus to thicken, thus making it more difficult for sperm to pass through.

  Two progestogens are available as long-acting formulations for intramuscular injection, namely ***medroxyprogesterone acetate*** and ***norethisterone enantate***, and progestogens are also used as emergency (or postcoital) hormonal contraceptives, as well as to impregnate hormonal intrauterine devices (IUDs).
- **Combination oral contraceptives:** Also referred to as 'combined pills', these agents normally contain a synthetic oestrogen (e.g. ***ethinyl oestradiol*** or *mestranol*), in combination with a progestogen (e.g. *norethisterone,* ***levonorgestrel,*** *desogestrel, gestodene,* etc.).

The oestrogens and progestogens may also be used in hormone replacement therapy (HRT), endometriosis and other indications.

### Drugs used in the management of gout

**Acute attack of gouty arthritis:**

- The severe pain, caused by joint inflammation, of an acute attack may be managed by means of a nonsteroidal anti-inflammatory drug (refer to chapter 7).
- *Colchicine* has an anti-inflammatory action in gouty arthritis. It is often combined with drugs that are used in the chronic management of gout, since such drugs may elicit acute attacks (see below). *Colchicine* inhibits the formation of $LTB_4$ (see figure 7.1A, as well as paragraph 7.1).
- Note that the abovementioned drugs do not influence serum uric acid levels, but rather manage the symptoms of an acute attack.

**Chronic therapy:**

- The aim of chronic treatment is to lower the serum uric acid levels, either by inhibiting uric acid production, or by improving the renal excretion thereof.
- ***Allopurinol*** is an analogue of hypoxanthine, and competes with this substrate in the process of purine metabolism. The enzyme xanthine oxidase (XO) converts ***allopurinol*** to alloxanthine, an active metabolite, which in turn inhibits XO, and therefore reduces the synthesis of uric acid.
- Alloxanthine competes with uric acid for transport via the acid secretion carriers, and could therefore elicit an acute attack of gout.
- On the other hand, uric acid excretion may be increased by blocking the acid secretion and reabsorption carriers of the proximal convoluted tubule of the nephron.
- *Probenecid* blocks both carrier systems and could also, in the short term, elicit an acute attack of gout.

### 10.3.2 The male reproductive system

The urinary retention caused by benign prostatic hyperplasia (enlargement of the prostate gland or BPH) may require the use of $\alpha_1$-receptor antagonists such as *terazosin* (also see paragraph 5.2.2) and *alfuzosin*. By blocking the $\alpha_1$-receptors in the lower urinary tract, relaxation of the smooth muscle of the prostate, prostatic urethra and bladder neck may be achieved.

Testosterone is reduced to dihydrotestosterone, a more active androgynous hormone, by the enzyme 5α-reductase. Dihydrotestosterone is responsible for the regression of the male hairline, an increase in body hair and the enlargement of the prostate. Therefore, the 5α-reductase inhibitor *finasteride* will be of benefit in the management of BPH as well.

*Sildenafil* is a selective inhibitor of the enzyme phosphodiesterase-5 (PDE-5), which converts the active second messenger, cGMP, to its inactive form, 5'-GMP (similar to what is illustrated in figure 4.5). *Sildenafil* therefore facilitates relaxation of the smooth muscle of the corpus cavernosum and may be used in the management of erectile dysfunction (impotence) in men. Examples of other selective cGMP-specific PDE-5 inhibitors are *tadalafil* and *vardenafil*. Another option in the management of erectile dysfunction is the $PGE_1$-analogue *alprostadil* (see chapter 7).

CHAPTER ELEVEN

# The antimicrobial treatment of infections and infestations

**Suggested revision**

***Microbiology and immunology:***

- Prokaryotic versus eukaryotic cells
- Bacteria, fungi, viruses and parasites
- Bacterial endotoxins and exotoxins
- The immune system, first-, second- and third-line body defences
- Antibody and cell-mediated immunity

**Note 11.1**

**Important note on the spectrums of activity of the various antimicrobial agents presented in this chapter:** It is a well-known fact that resistance to antimicrobial agents is ever-increasing and becoming more widespread as time goes by. Resistance patterns also differ from one population, region or geographical area to the next. Furthermore, the opinions of experts and authors differ, sometimes significantly, on the subject of susceptibility and resistance of specific pathogens to certain groups of antimicrobial agents, or to individual agents within these groups. Therefore, the spectrums of activity and/or gaps in such spectrums that are presented in this chapter are purely illustrative and only meant to cast some light on the characteristics and possible uses of some of the more well-known and commonly-encountered agents used in clinical practice, and should not be viewed as a definitive guide to their antimicrobial activity.

## 11.1 Introduction and general remarks

Drugs with chemotherapeutic action have the ability to eradicate cells that are responsible for infectious diseases (i.e. pathogenic micro-organisms) or the neoplastic cells that make up cancerous growths. Therefore, using the term 'chemotherapy' implies that cells, whether bacteria, fungi, viruses, parasites or cancer cells, will be destroyed. The chemotherapeutic agents that are used in oncology (as a cancer treatment modality) are referred to as oncochemotherapeutic agents (oncostatic or antineoplastic drugs). The chemotherapeutic agents used in the fight against infectious diseases are referred to as antimicrobial agents (i.e. 'anti-micro-organism'). These agents

are generally referred to as antibiotics, although, strictly speaking, this term is used incorrectly. Antibiotics are substances that are derived from, or produced by, certain micro-organisms that cause harm to other micro-organisms at low concentrations. Some antimicrobial agents are true antibiotics, but many more are synthetic agents, and can therefore not be called antibiotics in the true sense of the word. (***Benzylpenicillin***, also referred to as penicillin G, is an example of a natural antibiotic.) The term 'antimicrobial agents' will more accurately encompass all drugs or agents (i.e. antibiotics and synthetic agents) used in the fight against harmful pathogenic organisms, although antibiotics are also produced by pharmaceutical companies. It is even more accurate to use the terms 'antibacterial', 'antiviral', 'antiparasitic' or 'antifungal' when referring to the appropriate antimicrobial agents.

For all practical purposes, medically significant micro-organisms may be divided into four important groups, namely bacteria, fungi, viruses and parasites. Parasites may be subdivided into internal and external ones. **Internal parasites** (or endoparasites) comprise the protozoa and the helminths (cestodes, nematodes and trematodes). The **external parasites** (or ectoparasites) are arthropods such as mites and lice that are found in or on the surface areas of the body. These parasites are not true microscopic organisms, but may actually be visible to the naked eye (i.e. they are macroscopic). A few atypical bacteria could perhaps warrant the introduction of separate categories of pathogenic organisms. These are the *Chlamydiae*, *Rickettsiae* and the *Mycoplasma* organisms. They differ from other bacteria in that the *Chlamydia* organisms and the *Rickettsiae* are non-viral, obligate intracellular organisms, while the *Mycoplasma* organisms, as opposed to other bacteria, do not have cell walls. Infections are caused by bacteria, fungi, viruses and endoparasites; infestations are caused by ectoparasites.

### 11.1.1 Absolute and relative toxicity

Antimicrobial drugs aim to destroy the pathogenic micro-organisms that invade the body and cause infections. Preferably, however, the ideal antimicrobial drug should not bring any harm to body cells and tissues in the process of eradicating the disease-causing micro-organisms. Antimicrobial drugs that display a greater degree of **absolute selective toxicity** almost exclusively harm micro-organisms, while those that display less absolute and more **relatively selective toxicity** could bring harm to patients themselves. Absolute toxicity may be achieved by utilising, and even exploiting, the actual biological differences between the tissue cells of humans (and other hosts) and those of the micro-organisms in question.

One of the differences between human and bacterial cells, for instance, is the fact that bacteria have cell walls, while tissue cells have plasma membranes. Also, bacteria synthesise their own **folic acid** from a **ρ-aminobenzoic acid (PABA)** containing substrate (see figure 11.1). Humans, on the other hand, obtain folic acid through dietary intake.

### 11.1.2 Antimicrobial spectrum and resistance

In terms of antimicrobial **spectrum** these agents may be divided into three categories:

- **Narrow-spectrum antimicrobials:** Only a few types or species of micro-organisms are sensitive to these agents. In the case of antibacterial agents this usually implies that they are mostly effective against gram-positive organisms only.
- **Extended-spectrum antimicrobials:** This term is mostly used to describe an intermediary spectrum that may, for example, include gram-positive bacteria with the addition of only a few selected gram-negative organisms.
- **Broad-spectrum antimicrobials:** A wide variety of different bacteria, both gram-positive and gram-negative, are sensitive to these antimicrobials. Unfortunately they are also particularly prone to bringing harm to non-pathogenic organisms that usually colonise areas such as the gut and vagina. Destroying these non-pathogenic organisms usually results in an excessive growth of opportunistic organisms such as *Candida albicans*.

**Resistance** to antimicrobial agents implies that organisms that were previously sensitive to the agents in question become resistant to their effects, or they were never covered by a specific agent's spectrum of activity to begin with. In the case of bacteria the resistance may be the result of genetically induced changes in the organism, the inability of the antimicrobial drug to penetrate the bacterial cell wall or unscrupulous and inappropriate use of antimicrobials in clinical practice. Dosages may be inappropriately small or treatment periods ineffectively short.

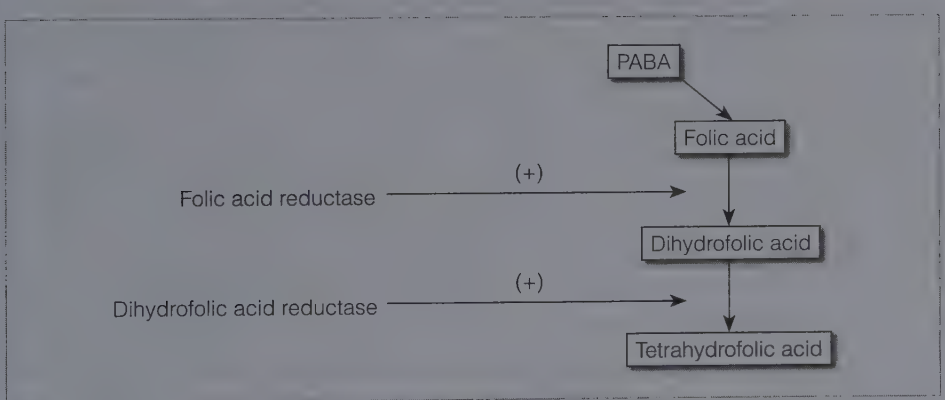



**Figure 11.1 Folic acid metabolism**

**Clinical application**

Antimicrobials should also not be prescribed when definite indications for their use do not exist. The value of proper laboratory microscopy, culture and sensitivity testing, or reliance on strict empirical evidence, cannot be overstated. Antimicrobial treatment in community settings should always commence with first-line agents of the correct spectrum. Reserve antimicrobials should only be used in the case of life-threatening, systemic infections with highly resistant organisms or those that are notoriously difficult to kill. Another way of approaching antimicrobial therapy is to prescribe the drug with the narrowest possible spectrum which includes the causative organism, whenever this is known, or to prescribe broad-spectrum antimicrobials in serious cases where the pathogens have not yet been identified.

### 11.1.3 MIC, MBC, CDKR and PAE

Antimicrobials may be used to kill microbes (bactericidal agents kill bacteria, for instance), to inhibit their reproduction and growth without killing them (bacteriostatics will inhibit the growth and reproduction of bacteria and fungistatics will influence fungi in the same way), or even to prevent infectious disease (e.g. using antimicrobial prophylaxis to control outbreaks of infectious diseases).

**MIC** is the **minimum inhibitory concentration** that the antimicrobial drug needs to attain to effectively inhibit further multiplication of the micro-organism. However, successful antimicrobial treatment with bactericidal agents relies heavily on intact host defence mechanisms as well. The host's immune system must eventually eliminate the invading bacteria. The **MBC** is the **minimum bactericidal concentration**, i.e. the plasma concentration at which the antimicrobial will kill bacterial cells in the body. Bactericidal agents are usually preferable to bacteriostatics.

Certain bactericidal agents exhibit a **concentration-dependent killing rate (CDKR)**, thus determining that high plasma concentrations will achieve effective bactericidal activity against specific bacteria or certain strains of bacteria. Bactericidal agents may also exhibit a **PAE**, or **post-antibiotic effect**. This implies that susceptible micro-organisms will exhibit a persistent inhibition of their multiplication, in some cases for several hours after their exposure to sufficient concentrations of the antimicrobial agent and after plasma levels have decreased to below the therapeutic range.

Antimicrobial effects may also be **time-dependent**, as opposed to the above-mentioned effects, which are **dosage- or concentration-dependent**. This means that the therapeutic effects are dependent upon the micro-organisms' exposure time to sufficient concentrations of the antimicrobial agents in question. The combination of time-dependent and dosage-dependent effects will determine

the frequency of administration and the size of the dosages of the antimicrobial agent to be administered. Figure 11.2 illustrates the relationship between MIC, MBC, CDKR and PAE, using the fluoroquinolones, aminoglycosides and β-lactams as examples.

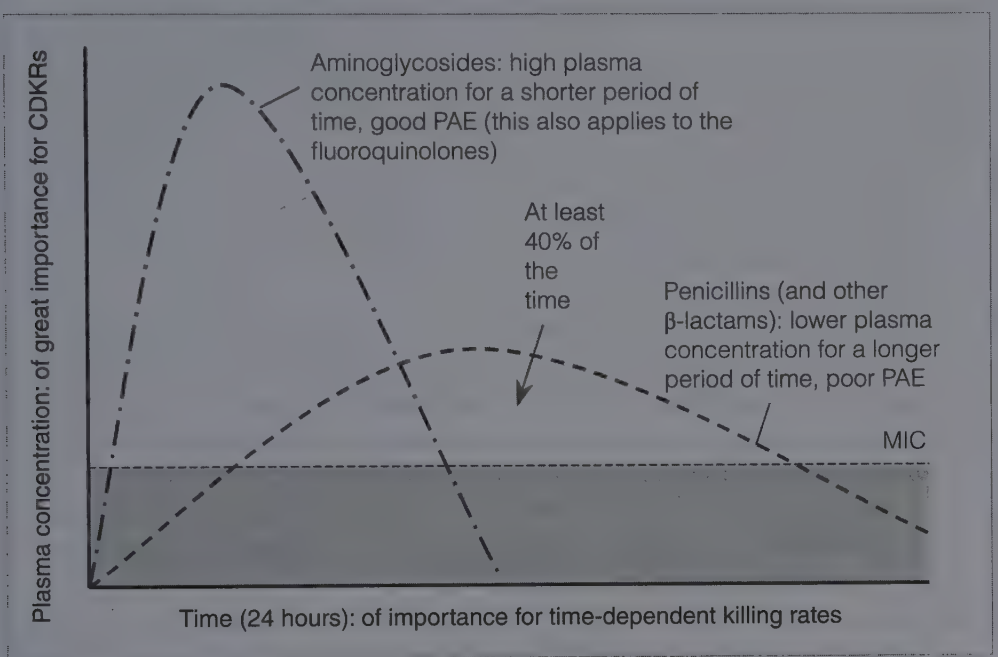



**Figure 11.2 The relationship between MIC, MBC, CDKR and PAE**

### 11.1.4 Peak and trough levels

In some instances it may become necessary to monitor the **peak** and **trough** serum levels of certain **antimicrobial agents**, especially in the case of the **aminoglycosides** (refer to paragraph 11.3.11) and *vancomycin* (refer to paragraph 11.3.6). The principles described here may also be applied to monitoring the serum levels of other drugs that have narrow therapeutic indices and toxic effects. The two parameters in question are:

- **$C_{min}$:** This is the trough serum level (or minimum serum concentration) and is measured (i.e. the blood sample is obtained and sent for laboratory analysis) directly prior to administering the next dosage of the drug.
- **$C_{max}$:** In the case of the aminoglycosides, for example, the maximum serum concentration (or peak serum level) is measured one hour after administering an intravenous or intramuscular bolus dosage, or one hour after initiating an intravenous infusion.

### 11.1.5 Monotherapy versus combination antimicrobial therapy

Many uncomplicated infections that are caused by highly susceptible and community-acquired organisms simply require monotherapy (use of a single antimicrobial agent) with agents that have the correct spectrum and kinetic properties. In more complicated cases the concomitant use of two or more antimicrobial agents (i.e. combination therapy) will usually be required. Combining antimicrobials in a treatment regime, however, does not merely imply choosing drugs with the appropriate spectrum. Combining antimicrobials may have additive, synergistic, antagonistic and indifferent consequences:

- **Additive effects:** This implies that the combination produces effects that are equal to the sum of those that would have been obtained with the individual agents on their own.
- **Synergism:** The combination produces effects that are greater than the sum of the effects that would have been obtained with the individual agent alone.
- **Antagonistic effects:** When the combination of two or more agents produces effects that are less than the sum of the individual agents used on their own. The combination, therefore, has no clinical benefit. The antagonism may in fact render the combined agents completely ineffective. For this reason the penicillins and tetracyclines should never be combined in a single treatment regime.
- **Indifference:** The combination is no more effective than any one of the agents used to their maximal potential as monotherapy.

### 11.1.6 Choosing antimicrobial agents

Some of the more important factors to take into consideration when deciding on the most appropriate antimicrobial therapy for a specific patient in a given clinical situation include, but are not limited to, the following:

- Spectrum, gaps in the spectrum and kinetics, including the suitability of monotherapy versus combination antimicrobial therapy
- Nature of the causative organisms, resistance, including the presence of multiple drug-resistant organisms, and mixed infections
- Severity and seriousness of the infection and the patient's medical condition (including decreased kidney or liver functioning)
- Safety aspects, adverse reactions and special circumstances such as pregnancy and lactation in female patients
- Convenience, **compliance** and cost-effectiveness

Furthermore, some specific factors that relate to the patient's condition and the nature of the infection also need to be considered when necessary. These include:

- **The immune status of the patient:** As already mentioned, intact body defence mechanisms are required to effectively fight off microbial invaders, especially where bacteriostatics, fungistatics or antiviral agents are used. Patients who are immunocompromised (e.g. the elderly, diabetics, patients with cancer or HIV infection, etc.) therefore require longer treatment or larger dosages of the antimicrobial agents, or both.
- **The presence of abscesses:** Effective treatment requires surgical debridement or draining of the abscess, since antimicrobials penetrate these areas very poorly.
- **The treatment of bacterial meningitis:** The blood-brain barrier is notoriously difficult to penetrate with chemical substances. However, in the presence of bacterial meningitis, when the meninges are inflamed (and therefore more permeable), agents that would normally not penetrate the barrier may gain access to the cerebrospinal fluid space.
- **A history of recent travel:** Persons who have visited foreign destinations and exotic locations may have been exposed to tropical diseases and endemic infections that require treatment regimes differing from those for infections commonly acquired within the community of concern.

## 11.2 The classification of antimicrobial agents

There are several classes or groups of antimicrobial agents available. Only the major groups will be discussed in more detail. These are given below.

**Antibacterials:**

- The **beta-lactams** (β-lactams)
  - Penicillins
  - Cephalosporins (and the structurally-related cephamycins and carbacephems)
  - Carbapenems
  - Monobactams
- The macrolides and ketolides
- Lincosamides
- *Fusidic acid*
- Glycopeptides
- ***Chloramphenicol***
- The tetracyclines and glycylcyclines
- The streptogramins
- The oxazolidinones
- Aminoglycosides and spectinomycin
- The fluoroquinolones
- ***Co-trimoxazole***

- Antimycobacterial drugs
- ***Metronidazole***
- Miscellaneous antibacterial agents

**Antifungals:**

- The polyene antibiotics
- Azole derivatives
- Allylamine drugs
- *Griseofulvin*
- Miscellaneous antifungal agents (including *tolnaftate*, *amorolfine*, *undecenoic acid* and *flucytosine*)

**Antiparasitics:**
Antiparasitic agents against:

- Protozoal infections:
  - Lumen- and tissue-dwelling
  - Blood- and tissue-dwelling
- Helminth infections:
  - The nematodes
  - Cestodes and trematodes
- Ectoparasitic infestations

**Antivirals:**
Antiviral agents against:

- Influenza
- Herpes simplex and varicella-zoster virus infections, and cytomegalovirus infections
- Human immunodeficiency virus (HIV)
- Hepatitis B and C infections

## 11.3 Antibacterial agents

### 11.3.1 Penicillins

***Benzylpenicillin*** (penicillin G) is the original penicillin. Although numerous antimicrobial agents have been developed and synthesised in the decades following the discovery of penicillin, penicillin G remains the antibiotic of choice in the treatment of bacterial infections with susceptible organisms that fall within its spectrum. However, it is considered to be a narrow-spectrum antibiotic since it eradicates a relatively small number of bacterial species only. When the organisms in question are susceptible the spectrum of penicillin G is as follows:

- **Gram-positive cocci** (streptococci, staphylococci and pneumococci), specifically the **staphylococci** that do not produce **penicillinase** (or **β-lactamase**), as well as sensitive strains of enterococci.
- **Gram-negative cocci** (*Neisseria meningitidis*). The emergence of gonococcal resistance to the penicillins now necessitates the use of alternative antibacterial agents.
- **Gram-positive bacilli** (the gram-positive anaerobic bacilli, i.e. *Clostridium tetani* and *C. perfringens*, and the anthrax bacillus. *C. difficile* is resistant to penicillin).
- The **spirochetes** of Vincent's angina (*Treponema vincentii*) and syphilis (*T. pallidum*), as well as *Leptospira*.

Penicillin G has a few shortcomings that limit its usefulness in clinical practice. Addressing these shortfalls has led to the development of a wide range of highly useful penicillins. These are:

- **The depot formulations for parenteral injection:** Penicillin G has a short plasma $t_{½}$ of approximately 30 minutes. *Procaine penicillin G* and ***benzathine penicillin G*** have much longer half-lives but attain lower plasma concentrations, and should therefore only be used when the infective organisms are highly susceptible to the effects of the narrow-spectrum penicillins. Another option is to administer *probenecid* concomitantly with the penicillin. *Probenecid* blocks the organic acid secretion carriers in the proximal convoluted tubules of the nephron (see chapter 10), and therefore effectively decreases the renal tubular excretion of penicillin (also refer to paragraph 2.6.2). This prolongs its plasma half-life. The increased $t_{½}$ is of particular importance when one considers that most of the β-lactams, including penicillin, exhibit **time-dependent** killing rates.
- **Penicillin V:** Penicillin G is acid-labile, meaning that it is unstable and broken down in gastric acid upon oral administration. This problem has been overcome by the formulation of ***phenoxymethylpenicillin*** (penicillin V), which is acid-stable and has the same spectrum as penicillin G.
- **Extended-spectrum penicillins:** Owing to its narrow spectrum, penicillin G has limited usefulness, especially in the case of hospital-acquired bacterial infections where resistant *Staphylococcus* strains and gram-negative bacilli are the infective organisms. The aminopenicillins (i.e. *ampicillin* and ***amoxicillin***, both of which are acid-stable) have an extended spectrum that includes, in addition to the spectrum of penicillin G, the following organisms:

  **Gram-negative bacilli:**
  - *Haemophilus influenzae*
  - *Salmonella* species

- *Shigella* species (*ampicillin*)
- *Proteus mirabilis*
- *Escherichia coli*
- *Helicobacter pylori* (***amoxicillin***)

**Other:**

- *Listeria monocytogenes* (*ampicillin*)
- Enterococci
- ***Amoxicillin***, in particular, is very active against pneumococci

This extended spectrum allows for the use of the aminopenicillins in both paediatric and geriatric practice settings, where *H. influenzae* is often to blame for upper respiratory tract infections, meningitis, etc. ***Amoxicillin*** and *ampicillin* differ kinetically in that *ampicillin* is not as readily absorbed after oral administration as ***amoxicillin***. Furthermore, *ampicillin* follows some degree of biliary excretion in addition to its renal clearance, whereas most of the other penicillins are only excreted via the kidneys through a combination of glomerular filtration and active tubular secretion. Therefore *ampicillin* is also indicated in the management of biliary tract infections. ***Amoxicillin*** penetrates tissue fluid areas readily, is well-absorbed from the gut, and may be taken with meals.

*Piperacillin* (an ureidopenicillin) also has the same spectrum as the aminopenicillins, but with the addition of even more clinically significant gram-negative bacilli, including:

- *Klebsiella pneumoniae* and other enterobacteria (from the family ***Enterobacteriaceae***), especially in combination with tazobactam (a β-lactamase inhibitor). The latter also increases its effectiveness against *Acinetobacter*, staphylococci and *H. influenzae*.
- *Pseudomonas aeruginosa*
- *Bacteroides fragilis* (a gram-negative anaerobic bacillus)

*Piperacillin* is therefore classified as an anti-pseudomonal agent and is acid-labile. It is a reserve antibiotic for hospital-acquired pneumonia and other serious infections with gram-negative bacteria, especially in critical care settings. In the case of such serious and life-threatening infections, *piperacillin* should be combined with a second agent from the aminoglycoside group (e.g. *amikacin* or *gentamicin*).

➲ The **penicillinase-resistant** penicillins and **β-lactamase**-inhibitors: Penicillin G and V, and also ***amoxicillin***, *ampicillin* and *piperacillin*, are sensitive to penicillinase and β-lactamase, and will be destroyed by these enzymes.

To address this problem the so-called penicillinase-resistant penicillins (PRPs) were developed, the first of which was *methicillin*. *Methicillin* is acid-labile and can therefore not be administered orally (however, it is not used anymore). *Cloxacillin* and ***flucloxacillin*** (examples of isoxazolyl penicillins)

are acid-stable PRPs. In most instances, however, PRPs are only effective when the penicillinase-producing organism is *Staphylococcus aureus*.

Another way of dealing with bacterial β-lactamase is to add clavulanic acid to ***amoxicillin*** to produce ***co-amoxiclav***. Similarly, sulbactam may be combined with *ampicillin*, and tazobactam with *piperacillin*. Clavulanic acid, sulbactam and tazobactam have the ability to inhibit bacterial β-lactamase, without being antimicrobial agents themselves. They act as substitute substrates for the β-lactamase enzymes. This allows for the *ampicillin*, ***amoxicillin*** or *piperacillin* to then eradicate the infective organisms in question. ***Co-amoxiclav*** has the added advantage of also being effective against anaerobes, and the common causative organisms in respiratory infections, i.e. *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* (or *Branhamella catarrhalis*), which all fall within its spectrum.

In the case of MRSA (methicillin-resistant *Staphylococcus aureus*) infections, however, the organism in question has altered its **penicillin-binding protein (PBP)**. This implies that no β-lactam will be effective against the organism, and alternative antimicrobials will need to be chosen and utilised (these could include ***co-trimoxazole***, the glycopeptides, *tigecycline*, the fluoroquinolones, *quinupristin-dalfopristin*, *linezolid* and the aminoglycosides).

**Adverse effects:** The penicillins may cause drug-induced hypersensitivity reactions, including type I reactions (i.e. urticaria, bronchospasm and anaphylactic shock). The cephalosporins may elicit cross-hypersensitivity reactions in patients who are allergic to the penicillins. *Ampicillin* may elicit a maculopapular skin rash in patients with viral mononucleosis (glandular fever). This rash is not indicative of a penicillin allergy. *Clostridium difficile* **superinfections** may cause **pseudomembranous colitis** (the overgrowth of *C. difficile* may cause severe, bloody diarrhoea, which may even develop into a life-threatening condition).

**Clinical application**

- The depot formulations of penicillin G can only be administered intramuscularly, since they are less soluble, and intravenous administration may cause emboli.
- Where food interactions exist the drugs should preferably be taken an hour before starting a meal (or 30 minutes at the very least), or two hours after completing one.
- Penicillins must not be applied to the skin since this may cause sensitisation.
- When surgical patients have a history of penicillin allergy, *cefazolin* (the first-generation parenteral cephalosporin) is often prescribed as a prophylactic measure for the prevention of *Staphylococcus aureus* infection.

- According to Sommers (2000: 271), a 12% possibility of cross-hypersensitivity between the penicillins and the cephalosporins exists. The first dosage of the cephalosporin, therefore, should be given by slow intravenous injection while carefully monitoring the patient for any adverse reactions. However, the cephalosporins are contraindicated in patients who have experienced type I hypersensitivity reactions towards the penicillins.
- When pseudomembranous colitis develops, the causative drug (i.e. the penicillin, which may quite possibly be *ampicillin*, or a cephalosporin, or *clindamycin*) must be discontinued.
- *C. difficile* overgrowth may be treated with orally administered *vancomycin* or with ***metronidazole*** to eradicate the causative organism and relieve the diarrhoea.

### 11.3.2 Cephalosporins (and the structurally-related cephamycins and carbacephems)

This group of β-lactams may be divided into four generations. Their killing rates are also time-dependent, but at a higher MIC than those of the penicillins. The spectrum of the cephalosporins differs from one generation to the next, but follows the following basic rule of thumb:

- **First-generation:** Effective against gram-positive cocci. *Cephalexin* has a spectrum similar to that of penicillin G and V, although the cephalosporins are not effective against the enterococci, MRSA or *Listeria monocytogenes*.
- **Second-generation:** Effective against gram-negative cocci and, to some extent, increased activity against gram-negative bacilli.
- **Third-generation:** Effective against gram-negative bacilli (organisms belonging to the family *Enterobacteriaceae*) and *Pseudomonas*, but less active than the first-generation agents against staphylococci and other gram-positive cocci.
- **Fourth-generation:** Possibly more effective (and with an extended spectrum of activity) than the third-generation against the *Enterobacteriaceae* and *Pseudomonas*. *Cefepime* is a fourth-generation cephalosporin with good anti-pseudomonal activity.

The **first-generation** oral cephalosporins are inferior to the penicillins. The first-generation parenteral *cefazolin*, however, is resistant to penicillinase-producing *Staphylococcus*, and is still widely used as a prophylactic antimicrobial in cardiac and orthopaedic surgery. Other examples include *cephradine* and *cefadroxil*.

The **second generation** is a diverse group and includes *cefuroxime* (available in an oral formulation and a parenteral formulation), which is comparable to ***co-amoxiclav*** in many respects, and *cefoxitin*, which is a parenteral **prophylactic** antimicrobial against faecal anaerobic organisms (*B. fragilis*) and certain enterobacteria involved in abdominal sepsis. *Cefoxitin* is a cephamycin, which

is structurally-related to the cephalosporins. Other examples include *loracarbef* (a structurally-related oral carbacephem), *cefprozil* and *cefaclor.*

The **third generation** includes *cefpodoxime*, *cefotaxime* and ***ceftriaxone***, which penetrate membranes and barriers well and cover most gram-negative bacilli, with the exception of *Pseudomonas*, in their spectrum. *Ceftazidime* is a third-generation anti-pseudomonal cephalosporin. Most of the third-generation cephalosporins are only available as parenteral formulations and should be reserved for serious and life-threatening infections with susceptible organisms. ***Ceftriaxone*** has a long $t_{½}$ and follows biliary excretion (as does *ampicillin*). *Cefpodoxime* has a spectrum similar to that of ***co-amoxiclav*** (as does *cefuroxime*). ***Ceftriaxone*** acts excellently against the gonococci.

### 11.3.3 The carbapenems and monobactams

*Imipenem* and *meropenem* are **carbapenems**. These are β-lactams with exceptionally broad spectrums. They are effective against a wide range of aerobic and anaerobic gram-positive and gram-negative bacteria, but not against MRSA and *Clostridium difficile*. *Pseudomonas aeruginosa* may also develop resistance to *imipenem*. *Imipenem* is combined with cilastatin to prevent the drug from being degraded by renal dehydropeptidase I. Another carbapenem, *ertapenem*, has a somewhat more limited spectrum of activity and cannot be used for pseudomonal infections. High plasma concentrations (i.e. in the presence of impaired renal clearance of the drug or the use of very high dosages) of *imipenem*, specifically, have been associated with seizures.

*Aztreonam* is a **monobactam**, with a spectrum limited to aerobic gram-negative bacilli (*Enterobacteriaceae* and *Pseudomonas*), which are eradicated exceptionally well. It is not active against gram-positive organisms or anaerobes.

### 11.3.4 The macrolides and ketolides

The macrolides, such as ***erythromycin***, are alternatives to penicillin G (especially in cases of respiratory infections caused by gram-positive bacteria) where penicillin allergy or penicillin resistance exists. ***Erythromycin estolate,*** in particular, also stimulates **motilin** receptors in the gastrointestinal tract. It therefore also acts as a pro-kinetic drug to stimulate peristalsis. Other macrolides include *roxithromycin*, *azithromycin* and *clarithromycin.*

The added bonus is that ***erythromycin***, in addition to having more or less the same antibacterial spectrum of penicillin G, is also effective against a number of additional organisms, including a few atypical ones. These are:

- *Bordetella pertussis*
- *Moraxella catarrhalis* (*Branhamella catarrhalis*)
- *Chlamydia trachomatis, Chlamydophila pneumoniae* and *C. psittaci*

- *Corynebacterium diphtheriae*
- *Legionella pneumophila*
- *Mycoplasma pneumoniae*
- *Rickettsiae* (tick-bite fever)
- *Listeria monocytogenes*
- *Campylobacter jejuni*
- ***Erythromycin*** may also be used in the treatment of acne.

Important gaps in the spectrum of erythromycin are *H. influenzae* (which has poor susceptibility to ***erythromycin***), enteric gram-negative bacilli, and the gram-negative anaerobic organisms. Therefore it is not really suitable in paediatric or geriatric practice settings. With the development of the newer macrolides, however, the following improvements have been made:

- *Azithromycin* (an azalide, or nitrogen-containing macrolide) is effective against *H. influenzae* and has such a long half-life that it generally only requires once-daily administration for three consecutive days to make up a full course of treatment.
- *Clarithromycin* is also effective against *H. influenzae* and has the added benefit of antibacterial activity against *Helicobacter pylori* (the organism that is implicated in recurrent peptic ulceration).

**Clinical application**

**Problems** with ***erythromycin*** that may be encountered in clinical practice settings are:

- Severe abdominal cramping, nausea and vomiting, in part caused by its prokinetic effects.
- The development of bacterial resistance while the patient is under treatment.
- An allergic hepatitis (intra-hepatic cholestatic jaundice) may be elicited. However, it is reversible if the drug is discontinued.

These problems are more likely to occur with the use of ***erythromycin estolate***.

*Telithromycin* is a **ketolide** and has a similar spectrum of activity to *clarithromycin* and *azithromycin*. However, it is particularly useful in the management of respiratory tract infections with organisms that are otherwise resistant to the macrolides, or other antimicrobial classes. These include multi-drug-resistant *Streptococcus pneumoniae*, or MDRSP (including penicillin-resistant *S. pneumoniae*, or PRSP), *H. influenzae, M. catarrhalis, Mycoplamsa pneumoniae* and *Chlamydophila* (or *Chlamydia*) *pneumoniae*.

### 11.3.5 Clindamycin and fusidic acid

Both *clindamycin* (a lincosamide) and *fusidic acid* (*sodium fusidate*) are effective against penicillinase-producing *Staphylococcus aureus* and probably also against MRSA. *Clindamycin* is particularly useful in the treatment of osteomyelitis since it penetrates avascular bone very well. *Clindamycin* eradicates a wide variety of anaerobic organisms, with the notable exception of *Clostridium difficile*. This means that **pseudomembranous colitis** may occur as a result of *C. difficile* overgrowth (see paragraph 11.3.1). *Clindamycin* is a derivative of *lincomycin*. *Clindamycin* may also be combined with *primaquine*, as an alternative to ***co-trimoxazole***, in the treatment of *Pneumocystis jirovecii* (*carinii*) pneumonia in patients with AIDS.

**Clinical application**

Resistance against *fusidic acid* may develop during the course of treatment. It should therefore rather be given in combination with ***erythromycin***, which has the same problem with bacterial resistance. Topically applied *clindamycin* may also be used in the treatment of acne.

### 11.3.6 Vancomycin and teicoplanin

*Vancomycin* is a **glycopeptide**. It has a large molecule that is incapable of penetrating the outer membrane of gram-negative bacteria. *Vancomycin* is also highly water-soluble and is therefore not really absorbed from the gastrointestinal tract. Thus, when taken orally, it will eradicate susceptible intestinal flora only. *Vancomycin* is reserved for life-threatening infections with staphylococci, MRSA and resistant *Streptococcus pneumoniae*. A huge drawback is that this drug may cause an irreversible loss of hearing (it is nephro- and ototoxic). *Vancomycin* is administered by slow intravenous infusion, since rapid injection results in histamine release due to the degranulation of mast cells. *Teicoplanin* is a newer glycopeptide that is more lipid-soluble and may be administered intramuscularly.

### 11.3.7 Chloramphenicol

This is a highly lipid-soluble agent, and therefore is extremely capable of penetrating biological membranes and barriers. It has a very broad spectrum, which includes gram-positive and gram-negative organisms, both aerobic and anaerobic, and is extremely useful in the treatment of bacterial meningitis, brain abscesses and typhoid fever. Unfortunately, drug toxicity limits the clinical usefulness of this drug as shown below.

- ***Chloramphenicol*** may cause two types of bone marrow suppression:
  - **Reversible bone marrow suppression:** This is toxic in nature, dosage-dependent, and may be reversed by decreasing the dosage or discontinuing the drug.
  - **Irreversible bone marrow suppression:** This is allergic in nature, and therefore not dosage-dependent. It causes aplastic anaemia, with a concurrent decrease in the leucocyte (the granulocytes are of particular importance) and platelet counts.
- In neonates, ***chloramphenicol*** causes the so-called grey baby syndrome. These babies' livers lack sufficient amounts of the enzyme glucuronyl transferase, which is required for the conjugation of ***chloramphenicol***. The subsequent build-up of ***chloramphenicol*** in the bloodstream causes cardiovascular collapse with central cyanosis (the 'grey baby'). However, this effect is dosage-dependent.

**Clinical application**

- Patients receiving ***chloramphenicol*** should be monitored for signs of bone marrow suppression (i.e. anaemia, agranulocytosis and thrombocytopenia).
- Serum ***chloramphenicol*** levels need careful monitoring in neonates and premature infants.
- **Topically applied *chloramphenicol*** penetrates the **eye** very well and is often used in the treatment of bacterial eye infections.

### 11.3.8 The tetracyclines and glycylcyclines

The tetracyclines have a very broad spectrum, although a few significant organisms such as certain strains of staphylococci and streptococci, the enterococci, as well as important gram-negative organisms such as *Pseudomonas aeruginosa* and members of the *Enterobacteriaceae* (*Proteus* in particular) often exhibit a resistance towards them (in fact, *Proteus* and *Pseudomonas aeruginosa* are considered to be intrinsically resistant). They are very useful in the treatment of 'pimples and plague' since the following organisms fall within their spectrum:

- **'Pimples':** *Propionibacterium acnes* and *Staphylococcus epidermidis*, which have been implicated in the pathogenesis of acne.
- **'Plague':** The following organisms may be sensitive to one or more of the tetracyclines:
  - *Brucella* (Malta fever, or brucellosis, in combination with *streptomycin*, or ***doxycycline*** in combination with ***rifampicin***)
  - *Chlamydia trachomatis* and *Chlamydophila psittaci*
  - *Campylobacter jejuni*

- *Francisella tularensis*
- Granuloma inguinale
- *Haemophilus influenzae* and *H. ducreyi* (chancroid)
- *Mycoplasma pneumoniae*
- *Legionella pneumophila*
- *Rickettsiae*
- *Treponema pallidum* (syphilis) and other spirochetes
- *Vibrio cholerae*
- *Yersinia pestis* (plague) and *Y. enterocolitica*

- Additional organisms which respond well to ***doxycycline*** and are of particular interest:
  - *Helicobacter pylori*, which has been implicated in recurring peptic ulceration
  - Chloroquine-resistant strains of *Plasmodium falciparum* (African *falciparum* malaria)

The tetracyclines are chelating agents of multivalent cations. *Tetracycline* has a short half-life and must be administered six-hourly. *Minocycline* may be taken twice daily and ***doxycycline*** on a daily basis. *Tetracycline* primarily follows renal excretion, *minocycline* follows both renal and biliary excretion and ***doxycycline*** follows biliary excretion only.

The **glycylcyclines** are tetracycline analogues, currently represented by *tigecycline*. This drug is administered intravenously and has a very broad spectrum. It has the added advantage over the tetracyclines of being active against strains of many organisms that have become tetracycline-resistant, as well as important organisms that do not fall within their spectrum of activity. These include:

- *Legionella pneumophila*
- *Enterobacteriaceae* (however, *Proteus* remains intrinsically resistant)
- Staphylococci, including MRSA and strains that are resistant to *vancomycin*, and streptococci
- Enterococci, including vancomycin-resistant enterococci (VRE)
- Multi-drug-resistant strains of *Acinetobacter*
- Gram-positive and gram-negative anaerobes

*Tigecycline* is also not effective against *Pseudomonas aeruginosa* due to its intrinsic resistance.

**Clinical application**

- The tetracyclines cause lesions of bone and teeth because they are chelating agents. To prevent permanent tooth lesions, infants and children between the ages of four months and eight years should preferably not receive tetracyclines. Lesions of the deciduous teeth may be prevented by avoiding tetracyclines during the second and third trimesters of pregnancy and the first 12 months after birth.
- **Dietary interaction:** With the exception of *minocycline* and ***doxycycline*** the older tetracyclines are poorly absorbed when taken together with dairy products, antacids and other foodstuffs that contain multivalent cations in high concentrations. However, none of the orally-administered tetracyclines should be taken together with antacids.
- *Candida albicans* superinfections of the gastrointestinal tract and vagina occur quite readily.

### 11.3.9 The streptogramins

A combination of two streptogramins, namely *quinupristin* and *dalfopristin* (combined for their synergistic effect) is proving to be very effective against a range of **multi-drug-resistant** gram-positive bacteria, and also selected gram-negative organisms. These are:

- MRSA, as well as MRSE (methicillin-resistant *S. epidermidis*)
- *Streptococcus pneumoniae*, which is penicillin- and macrolide-resistant
- *Enterococcus faecium* (but **not** *E. faecalis*), which is resistant to *vancomycin*
- *Clostridium perfringens*
- *Moraxella catarrhalis*
- *Neisseria meningitidis* and *N. gonorrhoea*
- *Legionella pneumophila*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*

The *quinupristin-dalfopristin* combination drug is administered by intravenous infusion only. It should be reserved for serious and life-threatening infections with multi-drug-resistant, gram-positive organisms such as MRSA, PRSP (penicillin-resistant *S. pneumoniae*) and VREF (vancomycin-resistant *E. faecium*).

### 11.3.10 The oxazolidinones

*Linezolid* may be used as a reserve antimicrobial agent against serious infections caused by multi-drug-resistant, aerobic gram-positive organisms, such as MRSA, MDRSP (multi-drug-resistant *Streptococcus pneumoniae*) and VREF.

### 11.3.11 Aminoglycosides and spectinomycin

These antimicrobial agents constitute a significant and very important group of antibacterial agents, which includes examples such as *gentamicin*, *tobramycin*, *neomycin*, ***streptomycin***, *amikacin*, *kanamycin* and *netilmicin*. These drugs are highly polar and therefore not really absorbed from the GIT. Oral administration of *neomycin*, for example, may be used for bowel preparation prior to colorectal surgery. They do not cross the BBB unless inflamed meninges (as found in meningitis) allow them passage across this barrier.

The aminoglycosides are reserved for serious and life-threatening gram-negative infections since their spectrum is as follows:

- *Enterobacteriaceae* (gram-negative enteric bacteria)
- *Pseudomonas aeruginosa* (except for *kanamycin* and ***streptomycin***)
- *Staphylococcus aureus* (including MRSA) and *S. epidermidis* (especially *gentamicin* and *tobramycin*, but never as monotherapy)
- *Mycobacterium tuberculosis* (***streptomycin*** is used in TB treatment)

The gaps in their spectrum are clinically significant:

- Anaerobic bacteria, both gram-positive and gram-negative
- Streptococci and enterococci (although in synergistic combination with a suitable penicillin or *vancomycin*, the activity of *gentamicin* and ***streptomycin*** against these organisms will be enhanced)

**Clinical application**

- Because the aminoglycosides exhibit a significant PAE, in combination with a CDKR, and because they are so toxic, the current trend is to administer the entire daily dosage once every 24 hours. This lessens the toxic side-effects when compared to divided daily dosages that are administered every eight or 12 hours.
- The duration of the course of treatment also determines the degree of toxicity seen with these drugs. Other factors to consider in terms of aminoglycoside toxicity are high plasma concentrations, patients receiving high dosages, their use in infants and the elderly, and the presence of impaired kidney function.
- When serum concentrations with these drugs rise exceedingly high, they may cause skeletal muscle paralysis. **Apnoea** will set in when the respiratory muscles become paralysed. This dangerous side-effect may be counteracted by administering *neostigmine*.
- *Neomycin* is too toxic to use systemically, but topical eye, ear and skin preparations contain this antibiotic.

The aminoglycosides are nephro- and ototoxic. Hearing loss is largely irreversible. They have a narrow therapeutic index and the monitoring of serum levels (see paragraph 11.1.4) would constitute prudent practice. The aminoglycosides exhibit concentration-dependent bactericidal activity and a significant PAE (see paragraph 11.1.3).

*Spectinomycin* is an aminocyclitol antibacterial agent that is specifically used in the treatment of drug-resistant gonorrhoea.

### 11.3.12 The fluoroquinolones

The fluoroquinolones may be divided into three groups or 'generations', albeit arbitrary and open to debate. Many of these agents have been withdrawn from the market over the years. The fluoroquinolones differ from the original quinolones in that a fluorine atom has been added to their chemical structure. The original quinolones are represented by the **urinary tract antiseptics**, *nalidixic acid* and *pipemidic acid*. Another urinary tract antiseptic, unrelated to the quinolones but often encountered in clinical practice, is *nitrofurantoin*.

The **'first-generation' fluoroquinolones** are represented by *norfloxacin*, which is much less potent than the other fluoroquinolones. Their main indications are urinary tract infections and gonorrhoea. The **'second-generation' fluoroquinolones** exhibit a spectrum of activity and accompanying gaps in the spectrum, which are very similar to those of the aminoglycosides, with the advantage of also being available in preparations for oral administration. ***Ciprofloxacin***, *ofloxacin* and *levofloxacin* are therefore effective against the staphylococci (including MRSA), the gram-negative enterobacteria (including *E. coli, Salmonella, Shigella, Enterobacter* and *Yersinia*) and *Pseudomonas aeruginosa*. However, they are not ideally suited to the treatment of upper respiratory tract infections because of their limited efficacy against the streptococci (with the exception of *levofloxacin*). Furthermore, they are effective against *Haemophilus influenzae* and *H. ducreyi, Legionella pneumophila, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Moraxella catarrhalis* and *Neisseria gonorrhoea*. These agents are useful in the treatment of urinary tract infections (UTIs). They also cover the common causative organisms that are responsible for bacterial enteritis in their spectrum (including *Campylobacter* and *Vibrio*).

*Moxifloxacin* and *gemifloxacin* are **'third-generation' fluoroquinolones**. These drugs exhibit improved antimicrobial action against gram-positive organisms, especially the pneumococci and streptococci.

**Adverse effects:** The quinolones exhibit an affinity for growing cartilage and should generally not be administered to children under the age of 18 years, or to pregnant and lactating women. They are also associated with an increased risk of developing tendonitis, with the possibility of tendon rupture. Furthermore, *levofloxacin, moxifloxacin* and *gemifloxacin* have been associated with prolongation of the $QT_c$-interval, as seen on the electrocardiogram (ECG). The fluoroquinolones are chelating agents. They should therefore not be taken together with antacids or dairy products (as for the tetracyclines).

### 11.3.13 Co-trimoxazole

***Co-trimoxazole (trimethoprim-sulphamethoxazole***, or ***TMP-SMX***) combines two different antimicrobial agents that inhibit folic acid synthesis in susceptible micro-organisms. These two agents are *trimethoprim* (TMP) and *sulphamethoxazole* (SMX). *Trimethoprim* (a diaminopyrimidine) is a non-competitive inhibitor of the enzyme dihydrofolic acid reductase, which catalyses the conversion of dihydrofolic acid to tetrahydrofolic acid. On the other hand, *sulphamethoxazole* (a sulphonamide) competes with PABA (para-aminobenzoic acid) for the enzyme that facilitates the uptake of PABA into the folic acid molecule.

The two agents, therefore, inhibit two consecutive steps in the micro-organism's folic acid metabolism pathway (refer to figure 11.1). This is referred to in pharmacological terms as the **sequential blocking** or inhibition of a metabolic process. The ensuing deficiency in folic acid kills the micro-organism, but causes little harm to humans since we derive our folic acid from our dietary intake.

***Co-trimoxazole*** has a very broad spectrum that includes gram-positive and gram-negative bacteria, as well as some protozoa (e.g. *Toxoplasma gondii*). It is **not** effective against *Pseudomonas aeruginosa,* anaerobic organisms or the enterococci. However, it is exceptionally effective against the fungal pneumonia, **PCP**, seen in AIDS sufferers (and other patients with compromised immune systems), and caused by *Pneumocystis jirovecii* (*P. carinii*). Since it contains a sulphonamide, ***co-trimoxazole*** is absolutely contraindicated in **porphyria**.

### 11.3.14 Antimycobacterial agents

It does not fall within the scope of this text to discuss these antimicrobial drugs in any detail. However, a brief overview of the most important agents used in the treatment of tuberculosis (TB) and leprosy follows.

**Anti-TB drugs:** Tuberculosis (caused by *Mycobacterium tuberculosis*) is never treated with a single antimycrobacterial agent. The available drugs are divided into first- and second-line agents on the basis of their safety and effectiveness. With the exception of ***streptomycin***, an aminoglycoside, all of the first-line anti-TB drugs are potentially hepatotoxic (i.e. toxic to the liver) and administered orally. The potential for liver toxicity necessitates the careful monitoring of liver function in patients with an increased risk, especially those with pre-existing liver disease. ***Streptomycin*** is administered intramuscularly and is vestibulotoxic.

- **First-line drugs:**
  - ***Isoniazid (INH)*:** This is probably the most potent and important anti-TB drug available, and is also the safest to use. Furthermore, ***INH*** may

be used in effective prophylaxis against tuberculosis. ***Isoniazid*** should preferably be administered together with vitamin $B_6$, as a preventative measure against peripheral neuropathy.

- ***Ethambutol:*** Vision disturbances may occur with the use of this drug, although these disturbances are generally reversible when the drug is discontinued. This drug is not recommended for use in children under the age of eight years, where accurate measurement of their visual acuity is not possible.
- ***Rifampicin:*** Also known as *rifampin,* this is a rifamycin antibacterial agent. Great care should be taken with this drug when treating patients with pre-existing liver disease since a fatal dysfunction may develop. ***Rifampicin*** is also very potent and may be used as an alternative to ***INH*** for chemoprophylaxis against tuberculosis. It is a potent liver microsomal enzyme inducer as well. Bodily fluids (saliva, sputum, sweat, tears and urine) are coloured orange by ***rifampicin***. ***Rifampicin*** **is also used as a prophylactic drug in the prevention of meningococcal and *H. influenzae* meningitis** and as an alternative agent in the treatment of infections such as leprosy, Legionnaire's disease, serious and resistant staphylococcal infections, and brucellosis.
- ***Pyrazinamide:*** This drug displays a dosage-related liver toxicity and pyrazinamide-induced hyperuricaemia. Therefore, it is preferable to monitor serum uric acid levels and liver function, if possible.
- ***Streptomycin:*** This aminoglycoside is considered by some authors to be a second-line agent, but it also serves as an alternative first-line agent and as add-on therapy during re-treatment. ***Streptomycin*** is especially toxic to the vestibular apparatus, and the ensuing damage is permanent.

Treatment is usually divided into two stages. During the first stage, four different drugs (i.e. ***isoniazid***, ***rifampicin***, ***pyrazinamide*** and ***ethambutol***) are administered for a period of two months. Due to drug resistance, monotherapy is never attempted. During the second stage, only two drugs (i.e. ***isoniazid*** and ***rifampicin***) are used, but the course of treatment will typically last another four months. In the case of children under the age of eight years, only three drugs are used during the initial phase of treatment, since ***ethambutol*** is not recommended in this age group.

- **Second-line drugs:** These agents are generally more toxic than the first-line agents and are reserved for the treatment of multi-drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). In the case of **MDR-TB**, there is resistance against both ***isoniazid*** and ***rifampicin***. In the case of **XDR-TB**, the situation is even more detrimental with a multi-drug-resistant organism having developed additional resistance against the fluoroquinolones and at least one of the injectable second-line

agents as well. A diverse selection of second-line agents are available and much more aggressive treatment regimens are used at this level.

The second-line agents include *ethionamide, capreomycin, cycloserine, terizidone, rifabutin* (another rifamycin antibacterial agent), fluoroquinolones (especially *ofloxacin, levofloxacin* and *moxifloxacin*), other aminoglycosides such as *kanamycin* and *amikacin*, and *para-aminosalicylic acid (PAS)*.

**Anti-leprosy drugs:** The causative organism is *Mycobacterium leprae*. A combination of ***rifampicin***, *clofazimine* and *dapsone* (a sulfone) is used. Other effective agents are *minocycline, clarithromycin* and the fluoroquinolones (*ofloxacin* in particular). Treatment should be individualised.

### 11.3.15 Metronidazole

***Metronidazole*** is a nitroimidazole derivative and is highly effective against the following organisms:

- **Bacteria:**
  - The anaerobic gram-negative bacilli (such as *Bacteroides fragilis*), anaerobic gram-positive bacilli (including *Clostridium difficile* and other *Clostridium* species) and anaerobic cocci (e.g. *Peptostreptococcus*)
  - *Helicobacter pylori* (as part of combination therapy)
- **Protozoa:**
  - *Entamoeba histolytica* (amoebic dysentery)
  - *Giardia lamblia*
  - *Trichomonas vaginalis*

Many authors classify ***metronidazole*** as an antiprotozoal agent, although it has very important antibacterial activity against most obligate anaerobic bacteria as well. Another nitroimidazole, *tinidazole*, is closely related to ***metronidazole*** and has similar uses.

***Metronidazole*** suppositories are effective as a prophylactic measure since the drug is well-absorbed from the rectum. The drug has very few side-effects, but does have a significant interaction with alcohol. The normal metabolism of alcohol in the body is illustrated in figure 11.3.

***Metronidazole*** is an inhibitor of the enzyme aldehyde dehydrogenase. The implication is that acetaldehyde will accumulate in the bloodstream with subsequent nausea and vomiting, and also other symptoms of the 'acetaldehyde syndrome' (including vasodilatation with a resultant reflex tachycardia, flushing and throbbing headaches). *Disulfiram*, used in the treatment of chronic alcoholism, has a similar mechanism of action. Patients receiving ***metronidazole*** treatment should therefore be warned not to combine their treatment with any form of alcohol.

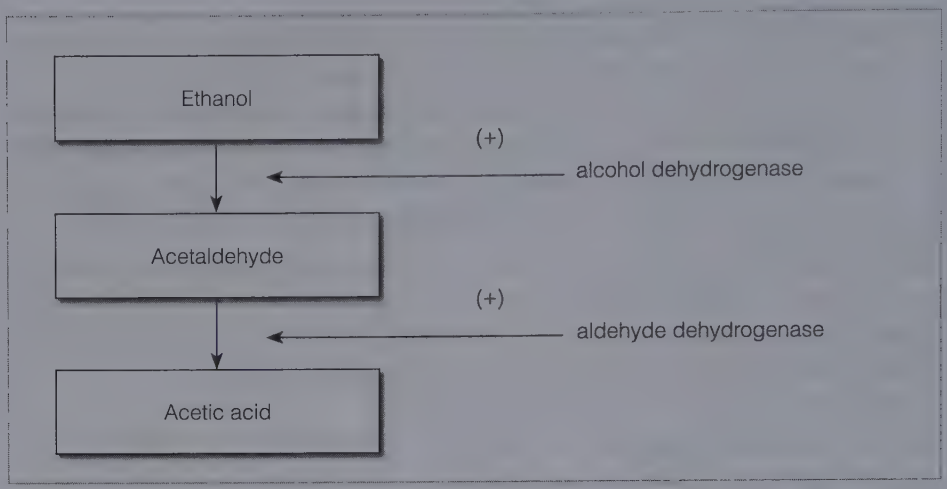



**Figure 11.3 Alcohol metabolism in the human body**

### 11.3.16 Miscellaneous antibacterial agents

*Fosfomycin* is active against a variety of gram-positive and gram-negative bacteria, but is specifically indicated in the treatment of uncomplicated urinary tract infections and for surgical prophylaxis prior to transurethral procedures.

*Bacitracin* is only used topically because of its nephrotoxicity and is mostly active against gram-positive bacteria. *Mupirocin* is also used topically and has good activity against the gram-positive cocci (including MRSA). *Mupirocin* is rapidly metabolised and inactivated when given systemically. Another topical antibacterial agent, with significant systemic toxicity (dosage-related neurotoxicity and nephrotoxicity), is *polymyxin B*, which has good activity against gram-negative bacteria (including *Pseudomonas aeruginosa*).

## 11.4 Antifungal drugs

For drug-treatment purposes, fungal infections (mycoses) may be categorised as being either superficial (e.g. dermatophyte infections, i.e. 'ringworm') or systemic. Commonly encountered superficial (or mucocutaneous) infections are tinea pedis (athlete's foot), tinea capitis (on the scalp), tinea corporis (on the body), tinea cruris ('jock itch'), tinea barbae (barber's itch) and others, as well as moniliasis (also referred to as candidiasis) of the skin (i.e. skin infections caused by *Candida albicans,* or less frequently by other *Candida* species).

### 11.4.1 Topical antifungal drugs

Several antifungal agents may be employed to effectively manage dermatophytoses (tinea infections) of the skin. These include *undecenoic acid*

(and *zinc undecenoate*) and *tolnaftate*. The azoles (see paragraph 11.4.5) and *terbinafine* (an allylamine) can also be used, and are effective against candidiasis as well. Topical ***nystatin*** may be used for mucocutaneous candidiasis, such as oropharyngeal and vulvovaginal thrush. Fungal infections of the nails (onychomycoses) may be treated topically with *amorolfine*.

### 11.4.2 Systemic antifungal drugs against superficial infections

Systemic drugs may be used to treat superficial infections. *Griseofulvin* is effective against most dermatophyte infections and is highly lipophilic (it should preferably be taken together with a fatty meal). Disadvantages of *griseofulvin* include the fact that this drug may exhibit cross-sensitivity with penicillin, it is contraindicated in patients with porphyria, and it is not effective against systemic fungal infections. The azoles (see paragraph 11.4.5) and *terbinafine* may also be administered systemically. Systemic treatment with *terbinafine* is very effective against onychomycoses (dermatophyte infections of the nails), and requires a much shorter period of treatment than *griseofulvin* does.

### 11.4.3 The polyene antibiotics

This group of antifungal agents includes ***nystatin*** and *amphotericin B*. These drugs are not readily absorbed from the gastrointestinal tract, making the oral suspensions and lozenges suitable for the treatment of moniliasis of the gastrointestinal tract only. ***Nystatin*** is the drug of choice when treating oral candidiasis (oral thrush), but cannot be used for systemic treatment.

*Amphotericin B* may also be administered intravenously for effective treatment of most systemic fungal infections. However, the conventional colloidal formulation is a very toxic drug, especially nephrotoxic, which exhibits several adverse effects. The newer liposomal *amphotericin B* displays significantly reduced toxicity (the adverse effects associated with the drug occur less frequently and are not as severe as those seen with the conventional formulation). **Intrathecal** administration may be required for the treatment of fungal meningitis.

### 11.4.4 Flucytosine (5-FC)

This drug is rather toxic and may cause liver damage and bone marrow suppression. It has a narrow spectrum compared to *amphotericin B* and is used as part of combination therapy against organisms such as *Cryptococcus neoformans* (cryptococcal meningitis), systemic candidiasis and chromoblastomycosis.

### 11.4.5 The azoles

These are broad-spectrum antifungal agents. The group may be subdivided into:

- **The imidazoles:** ***Metronidazole***, used in the treatment of infections caused by anaerobic bacteria and certain protozoa, is a nitroimidazole (see paragraph 11.3.15). The imidazoles used in the treatment of fungal infections, however, include *econazole*, ***clotrimazole***, *ketoconazole* and *miconazole*. These are the azoles of choice in the management of dermatophyte infections and mucocutaneous candidiasis. Other examples are *bifonazole* and *tioconazole*.
- **The triazoles:** This group includes antifungal agents such as ***fluconazole*** and *itraconazole*. These are important **systemic** drugs and not the first choice in the treatment of dermatophyte infections. *Voriconazole* is an example of a newer, broad-spectrum triazole and may be used for invasive aspergillosis, serious infections cause by fluconazole-resistant *Candida* species (including species such as *C. krusei*), and other serious infections with susceptible fungi.

### 11.4.6 Echinocandins

This is a new class of antifungal agents, including *caspofungin* and *micafungin*, which are active against invasive candidiasis and aspergillosis.

## 11.5 Antiparasitic drugs

Important pathogenic parasites include the following:

- Protozoa, such as those that cause amoebic infections, the malaria parasites and *Toxoplasma gondii*
- The helminths, including the *Schistosoma* species that cause bilharziasis, and the intestinal worms
- Ectoparasitic infestations (i.e. pediculosis and scabies)

### 11.5.1 Malaria

In South Africa, malaria prophylaxis and treatment is aimed at *Plasmodium falciparum*, which is the most prevalent malaria parasite within our borders, as well as being the cause of cerebral malaria. The other three species are *P. malariae, P. ovale* and *P. vivax*. *Chloroquine* used to be an important prophylactic agent, but resistance is an ever-increasing problem. Only a few endemic areas around the world are still infested with malaria parasites that are chloroquine-sensitive. For sub-Saharan Africa, south-east Asia and Brazil, for example, *chloroquine* (or *chloroquine-proguanil*) prophylaxis is no longer recommended.

**It is imperative that appropriate and up-to-date guidelines be followed for the chemoprophylaxis or treatment of malaria, whenever either of these is required.** (Also refer to http://cdc-malaria.ncsa.uiuc.edu/ on the Internet for more information on endemic areas and resistance patterns pertaining to malaria.)

**Malaria prophylaxis:** It is important not only to use prophylactic agents against the malaria parasite, but also to take preventative measures against being bitten by the female *Anopheles* mosquito itself. *Mefloquine, atovaquone-proguanil* and ***doxycycline*** are the important prophylactic drugs in areas where chloroquine-resistance prevents it from being used. *Primaquine* may also be appropriate in areas where *P. vivax* predominates. ***Doxycycline*** is the drug of choice for areas with multi-drug-resistant malaria.

**Clinical application**

**The treatment of malaria:**
***Chloroquine*** may be used in uncomplicated cases of non-falciparum malaria, or where *P. falciparum* and *P. vivax* are not resistant to the drug, in which case *mefloquine* is an alternative drug. Other treatment options include:

- ***Artemether-lumefantrine***
- ***Quinine*** with ***doxycycline*** or *clindamycin*
- The combination ***sulfadoxine-pyrimethamine*** (another example of the sequential blocking of folic acid metabolism)
- *Primaquine* is used as part of the treatment regimen for infections with *P. vivax* and *P. ovale*
- *Quinidine*, *halofantrine*, *amodiaquine* and *artesunate* are other treatment options

People residing in endemic regions should not use prophylactic drugs at all, so as to limit resistance against the anti-malarial agents. Rescue treatment must be instituted in the event of such a person contracting malaria.

### 11.5.2 Bilharziasis (schistosomiasis)

The drug of choice is ***praziquantel***. It effectively eradicates all of the *Schistosoma* species that infect humans during all the stages of the lifecycle of these parasites. It is also the drug of choice in the treatment of cysticercosis of the central nervous system.

### 11.5.3 Intestinal worms

- ***Mebendazole*** is a broad-spectrum anthelmintic drug and is effective against a wide variety of intestinal worms (including pinworms, roundworms, hookworms, whipworms and tapeworms). ***Albendazole*** has a similar

spectrum, and is more effective against the intestinal threadworm, *Strongyloides stercoralis*. ***Albendazole*** is also used in the treatment of neurocysticercosis and hydatid disease (echinococcosis). *Niclosamide* is effective against tapeworms (cestodes). ***Praziquantel*** may be used as an alternative to *niclosamide*. Other drugs that may be used include *piperazine* (an alternative in the treatment of roundworm and pinworm infections) and *ivermectin* (for filarial infections, strongyloidiasis and other infections that may include roundworms, pinworms and whipworms).

- **Adjunctive agents:** When treating intestinal worm infections, the additional administration of suitable laxatives and the combination pro-kinetic/anti-emetic drug ***metoclopramide*** may be desirable.

### 11.5.4 Scabies and pediculosis

Drugs that are capable of eradicating the scabies mite, as well as lice, include ***benzyl benzoate*** (an emulsion for topical application) and ***permethrin***. ***Monosulfiram*** (which may be applied to the skin as an ointment or may be contained in a soap), effectively acts as a prophylactic measure against outbreaks of scabies, but is not effective in treating already-established infestations. *Crotamiton* is an effective alternative against scabies and also alleviates the itching associated with this infestation. A shampoo containing *gamma benzene hexachloride* may be used to treat pediculosis (lice). *Ivermectin* may be a suitable systemic alternative to the conventional treatment of scabies and pediculosis.

## 11.6 Antiviral drugs

Because viruses are intracellular organisms, which use host cell genetic material for their own replication, the antiviral drugs that act as non-selective inhibitors of viral replication are also toxic to human beings.

In cases of influenza, *amantadine, zanamivir* and *oseltamivir* may be of benefit. Infections with the herpes viruses may respond favourably to ***aciclovir***, *famciclovir, valaciclovir* and *penciclovir*. *Ganciclovir* and *valganciclovir* may be used in cases of cytomegalovirus infections. In the case of chronic hepatitis B virus (HBV) infection, ***lamivudine***, *adefovir,* ***tenofovir*** and *entecavir* are possible treatment options, while *ribavirin* is used as part of combination therapy in the treatment of chronic hepatitis C virus (HCV) infection.

An array of antiviral drugs against the human immunodeficiency virus (HIV) is available and these agents are referred to as the antiretroviral (ARV) agents. There are various classes of antiretroviral agents, some of them still in clinical development, and they inhibit different steps in the virus' replication. The standard of care is to make use of a combination of three (or possibly four) different drugs, the so-called highly-active antiretroviral therapy, or HAART.

**Treatment regimens are usually selected in accordance with recognised treatment guidelines; however, there is an emerging trend towards viral load and resistance testing to help clinicians in choosing an appropriate HAART-regimen for individual patients.**

The antiretroviral agents include:

- **Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs):** ***Zidovudine*** (AZT), ***stavudine*** (d4T), ***lamivudine*** (3TC), ***didanosine*** (ddI), *abacavir* (ABC) and *emtricitabine* (FTC) are examples of NRTIs; ***tenofovir*** (TDF) is a nucleotide reverse transcriptase inhibitor (NtRTI).
- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs):** This class includes ***nevirapine*** (NVP) and ***efavirenz*** (EFV).
- **Protease inhibitors (PIs):** Examples of protease inhibitors include *saquinavir, nelfinavir, indinavir, fosamprenavir,* ***lopinavir-ritonavir*** (i.e. ritonavir-boosted *lopinavir*), *atazanavir* and *darunavir. Ritonavir* may also be used to 'boost' any of the other PIs (i.e. increase their half-lives and trough serum concentrations through its potent inhibition of CYP3A4).
- **Other ARVs:** The fusion inhibitor, *enfuvirtide*, the integrase inhibitor, *raltegravir*, and the CCR5-antagonist, *maraviroc* (for CCR5-tropic HIV-1 infection specifically), are alternative treatment options.

# Selected clinical applications

## 12.1 Nausea and vomiting

### 12.1.1 Physiological overview

The vomiting centre, which is situated in the medulla oblongata, controls the act of vomiting (or emesis). This centre may be stimulated via (1) peripheral receptors and afferent fibres of the vagal nerve and sympathetic nervous system, (2) higher brain centres (within the cerebral cortex), (3) the vestibular apparatus of the inner ear, or (4) a second medullary centre involved in emesis, namely the chemo-emetic trigger zone (CTZ). Vomiting is usually preceded by a feeling of nausea. However, the feeling may also occur without subsequent vomiting.

#### *The vomiting, or emesis centre*

This medullary centre lies within the **blood–brain barrier (BBB)**, and therefore responds to the following impulses:

- Impulses from higher brain centres within the cerebral cortex, including those that are produced by nauseating sights, sounds and smells.
- Afferent nerve impulses from the gastrointestinal tract, or other visceral organs that are innervated by the vagal nerve or the sympathetic nervous system, including distension, irritation and infection of the stomach and duodenum. Vagal impulses reach the vomiting centre via the **solitary tract nucleus**. These impulses include nauseating tastes.
- Stimuli from the vestibular apparatus (or labyrinth) in the inner ear, the cause of motion sickness, stimulate the vomiting centre directly.

The vomiting centre controls the complex of events and motor mechanisms involved in the vomiting act.

**Receptors:** The vomiting centre contains muscarinic acetylcholine receptors (of the $M_1$, or neural, subtype) and histamine receptors (of the $H_1$ subtype). Stimulation of these receptors induces nausea and vomiting. The stimulatory pathway via the vestibular apparatus, which utilises the $M_1$ receptors, is of particular importance here.

### *The chemo-emetic trigger zone (CTZ)*

This area reacts to chemical substances in the bloodstream, since it is situated **outside of the BBB**, and therefore comes into contact with circulating stimulants. Chemical substances that are capable of inducing nausea and vomiting through stimulation of the CTZ include:

- Certain drugs such as ***digoxin***, ***morphine***, *apomorphine*, ***theophylline***, *ergotamine* and *levodopa* (a dopamine agonist)
- The oestrogens, taken as oral contraceptives or produced during pregnancy
- Cytotoxic and cytostatic agents used in cancer chemotherapy (the cytotoxic drug *cisplatin* is a particularly potent emetic)
- Metabolic by-products (derived from the uraemic state, caused by renal failure, and diabetic ketoacidosis)
- The by-products of radiation therapy (caused by the destruction of neoplastic and other rapidly dividing tissue cells)

Afferent nerve fibres extend from the CTZ to the vomiting centre to induce nausea and vomiting once chemical substances activate the former.

**Receptors:** Dopamine receptors (of the $D_2$ subtype) and 5-hydroxytryptamine receptors (of the 5-$HT_3$ subtype). Stimulation of these receptors induces nausea and vomiting. Dopamine is the most important neurotransmitter in this pathway. Another important receptor found in the *area postrema* (in which the CTZ is located) is the neurokinin-1 ($NK_1$) receptor.

### *Peripheral activation*

As indicated above, stimulation of **peripheral receptors** or the mucosal lining of the stomach and duodenum may also induce vomiting through peripheral (vagal) stimulation of the vomiting centre.

**Receptors:** 5-$HT_3$-receptors are found at the origins of vagal nerve afferents in the gastrointestinal tract, as well as the synapses of the **solitary tract nucleus**. Stimulation of these receptors will activate vomiting via this peripheral pathway.

The following aspects are important to note:

- The **solitary tract nucleus** comprises afferent nerve fibres from three different cranial nerves that synapse in the medulla oblongata. These are the fibres of the **gustatory pathway**, which produce the cognition of taste. A branch of the facial nerve (N.VI), the lingual branch of the glossopharyngeal nerve (N.IX) and the vagus nerve (N.X) synapse in this nucleus, from which nerve fibres then extend to reach the thalamus, the hypothalamus, the limbic system and the vomiting centre. Vagal afferents from various visceral organs also run through the solitary tract nucleus.

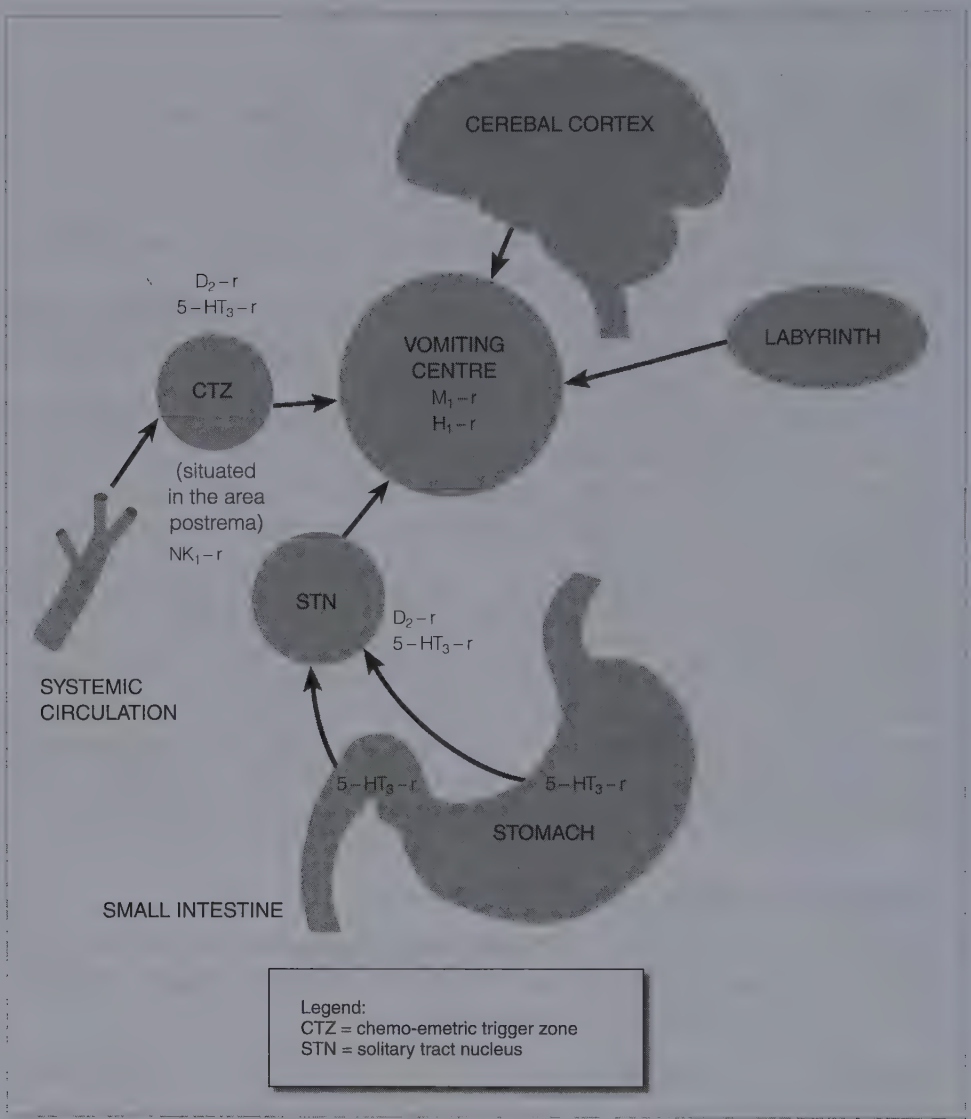



**Figure 12.1: Receptors and pathways that activate the vomiting centre in the medulla oblongata**

- The visceral pain, irritation and/or distension caused by conditions such as cholelithiasis (gallstones) and renal calculi (kidney stones), or acute myocardial infarction (AMI), stimulate the vomiting centre via vagal afferent (and therefore the solitary tract nucleus) and sympathetic nerve fibres.
- Conditions of the inner ear, including infective conditions and disturbances of motion and balance (like **Ménière's disease**), stimulate the vomiting centre via afferent fibres from the labyrinth (or vestibular apparatus).

- Increasing the rate of gastrointestinal motility with **prokinetic** drugs may be of benefit during episodes or nausea and vomiting since the normal rate of gastric emptying and peristaltic movement is speeded up. Two receptors that are of particular importance in this regard are presynaptic $D_2$-receptors and **intestinal** 5-$HT_4$ receptors. Blocking these $D_2$-receptors will increase the release of ACh from parasympathetic neurons in the GIT, causing an increased stimulation of $M_3$ receptors in the gut. Stimulation of 5-$HT_4$ receptors also facilitates the release of ACh. $M_3$ receptor stimulation will increase smooth muscle contraction and the rate of propulsion in the oesophagus, stomach and intestines.
- **Entero-endocrine** (or enterochromaffin-like) **cells** in the glands of the gastric mucosa secrete various locally acting hormones and hormone-like substances that include histamine and serotonin (5-HT). Cytotoxic drugs cause the release of 5-hydroxytryptamine from these entero-endocrine cells with subsequent stimulation of the 5-$HT_3$-receptors at vagal afferents in the stomach.
- Anti-emetic drugs are best administered as a **prophylactic** measure. Administering 8 mg of parenteral *ondansetron* immediately prior to highly emetogenic oncochemotherapy, followed by two more dosages of 8 mg at two- to four-hourly intervals, for example, has proven to be highly effective in the prevention of chemotherapy-induced nausea and vomiting. Combining *ondansetron* with a long-acting corticosteroid like *dexamethasone* does increase the effectiveness of the anti-emetic prophylaxis. In addition, a benzodiazepine like ***diazepam*** may alleviate the anxiety of anticipated chemotherapy-induced nausea and vomiting in a patient who has experienced these side-effects before.
- There are five major groups of anti-emetic drugs (drugs used to counteract nausea and vomiting). These groupings relate to their most prominent mechanisms of action.

## 12.1.2 Anti-emetic drugs

### The muscarinic and histamine receptor antagonists

Since the $M_1$ receptors are of particular importance in vomiting caused by afferent impulses from the vestibular apparatus, these drugs are highly beneficial in the pharmacotherapeutic management of motion sickness and Ménière's disease.

Also, it is of clinical significance to note that blocking of the $M_1$ and $H_1$ receptors in the vomiting centre implies that all afferent pathways into the centre have been effectively blocked out.

Specific drugs include:

- *Hyoscine*, applied as a skin patch behind the pinna of the ear (one of the thinnest skin areas of the body), is a competitive antagonist of ACh at muscarinic receptors. It exhibits excellent penetrative and absorptive qualities since it is lipid-soluble with a $pK_a$ of 7.8, and therefore causes less pronounced and cumbersome CNS side-effects with transdermal application.
- The older-type antihistamines act as **multipotent receptor blockers** (refer to chapter 1), including both muscarinic and $H_1$ receptors in the vomiting centre. *Cyclizine*, which does not cause pronounced drowsiness, is well tolerated by children and adults alike and is probably one of the best-known and widely used anti-emetics. It is available in a variety of dosage forms and medicinal formulations for oral, parenteral and rectal administration.
- *Cinnarizine* is especially useful in labyrinth-induced nausea and vomiting, being favoured by ocean travellers and sailors for the prevention of seasickness.

### The muscarinic, histamine and dopamine receptor antagonists

- ***Promethazine***, the phenothiazine that is famous for its antihistaminic action, also blocks muscarinic receptors (to a lesser extent) and dopamine receptors (the major phenothiazine effect).
- ***Promethazine*** is therefore effective in managing nausea and vomiting at the levels of the vomiting centre, the CTZ and the solitary tract nucleus. It causes pronounced drowsiness.

### The dopamine receptor antagonists

- These receptors are the most important drug targets in the CTZ. Dopamine antagonists such as *domperidone* and ***metoclopramide***, which block these receptors, are highly effective anti-emetic drugs. ***Metoclopramide*** also blocks 5-$HT_3$ receptors when larger dosages of this commonly used drug are administered.
- ***Metoclopramide*** is a $D_2$-receptor antagonist, a 5-$HT_3$-receptor antagonist and a 5-$HT_4$-receptor agonist, therefore acting as an anti-emetic at the level of the solitary tract nucleus, the CTZ and the vagal afferents (i.e. it possesses both central and peripheral anti-emetic activity). The agonism at 5-$HT_4$-receptors explains its prokinetic activity (refer to chapter 9). ***Metoclopramide*** does not usually cause pronounced sedation but it may elicit extra-pyramidal side-effects in a small percentage of patients, especially children.
- *Domperidone* does not cross the BBB to penetrate the CNS but is still effective in the management of central vomiting since the CTZ lies outside the BBB. Its anti-dopamine action is similar to that of ***metoclopramide***, without the extra-pyramidal side-effects.
- The **phenothiazines** (refer to chapter 5): Drugs belonging to the phenothiazine group are all multipotent receptor blockers. This includes dopamine receptor antagonism. ***Promethazine***, with its more pronounced antimuscarinic and antihistaminic action, has already been discussed. *Prochlorperazine* (to a greater extent) and ***chlorpromazine*** (to a lesser extent) are the *phenothiazines* of choice in the management of nausea and vomiting.

## The 5-hydroxytryptamine receptor (5-$HT_3$) antagonists

- The 5-$HT_3$-receptors are found both centrally (in the CTZ) and peripherally at the origins of vagal afferents in the gastrointestinal tract. Enterochromaffin cells in the gastric glands of the stomach release serotonin (or 5-HT), amongst other locally acting hormones and hormone-like substances. Cytotoxic drugs cause these cells to release serotonin, which in turn stimulates vagal afferents, and thus induces nausea and vomiting.
- *Ondansetron*, *granisetron*, and *tropisetron* are **selective antagonists of 5-$HT_3$-receptors**. Therefore, they block these receptors (1) at the origins of vagal afferents, (2) in the solitary tract nucleus, and (3) in the CTZ.
- These drugs are particularly useful in the management of nausea and vomiting caused by cytotoxic or oncostatic drugs. Other examples are *dolasetron* and *palonosetron*.

## The $NK_1$-receptor antagonists

- *Aprepitant* is a novel anti-emetic drug that acts by selectively inhibiting neurokinin-1 ($NK_1$) receptors in the brain.
- This drug is particularly effective in managing chemotherapy-induced nausea and vomiting (CINV) in combination with a corticosteroid and a 5-$HT_3$-receptor antagonist.

## Clinical application

- With the exception of the 5-$HT_3$-receptor antagonists and *domperidone*, all of the older anti-emetic drugs may cause drowsiness and impaired CNS functioning.
- All of the *phenothiazines* are capable of eliciting jaundice and should be used with caution in patients with pathology of the liver.
- A selective 5-$HT_3$-receptor antagonist (e.g. *ondansetron*), in combination with *dexamethasone*, will manage oncochemotherapy-induced nausea and vomiting most effectively. Larger dosages of ***metoclopramide*** or a phenothiazine such as *prochlorperazine* may be considered as a second choice. The antihistamines have proven to be less effective, even though they block muscarinic and histamine receptors in the vomiting centre. *Aprepitant* is especially effective as part of the abovementioned combination therapy, for both acute and delayed CINV.
- Post-anaesthesia nausea and vomiting will respond to any of the available anti-emetic drugs, since the major drug target will be the CTZ.
- Some opioid combination preparations contain *cyclizine* as the anti-emetic to counteract the effects of ***morphine*** and its derivatives on the CTZ. Examples include the combination of ***morphine*** and *cyclizine* in an ampoule for parenteral administration and a tablet that contains *dipipanone* together with *cyclizine* for oral administration.
- Severe pregnancy-induced nausea and vomiting may be controlled with *cyclizine*.

## 12.2 Ophthalmic drugs

**Suggested revision**

***Anatomy and physiology:***
- The structure and functioning of the eye
- The sense and accommodation of vision

***Pathology and pathophysiology:***
- Glaucoma

### 12.2.1 Aspects of the structure and functioning of the eye

Refer to figures 12.2A and B. A ring of smooth muscle, called the ciliary muscle, suspends the eye's lens from the fibres of a suspensory (or ciliary) ligament. The ring-like ciliary muscle contains smooth muscle fibres of two types, namely meridional fibres and circular fibres. Aqueous humour ('water-like fluid') fills the space between the lens (and suspensory ligament) and the cornea of the eye. The iris divides this space into an anterior and a posterior chamber.

The formation of aqueous humour is an ongoing process. Epithelial cells that are found on the ciliary processes (of the ciliary muscle) actively secrete the fluid, whilst reabsorption into the blood circulation takes places via the conjunctival veins. Following its secretion into the posterior chamber of the eye, the aqueous humour circulates through the pupil to reach the anterior chamber. From here the fluid enters the angle between the cornea and the lens (called the iridocorneal angle), from where the flow will enter the trabecular meshwork and finally pass through the canals of Schlemm to reach the conjunctival veins (referred to as the conventional route, or trabecular pathway).

The iris (containing the papillary opening at its centre) also contains two different smooth muscle layers. These are the sphincter pupillae (smooth muscle fibres that are arranged concentrically around the pupil) and the dilator pupillae fibres (which are arranged around the papillary opening in radial fashion).

Innervation of the smooth muscle layers of the eye is provided via the autonomic nervous system. The ciliary and the circular sphincter pupillae muscles contain muscarinic receptors (probably of the $M_3$-receptor subtype). The dilator pupillae muscle fibres receive sympathetic innervation and contain $\alpha_1$-receptors.

Sympathetic nervous system stimulation produces **mydriasis** (dilatation of the pupil) **through contraction of the dilator pupillae muscle** (the radial muscle).

Parasympathetic stimulation produces the following effects:

- **Contraction of the sphincter pupillae muscle:** This produces a consequent miosis (constriction of the pupil).
- **Contraction of the ciliary muscle:** This reduces tension on the fibres of the suspensory (ciliary) ligaments, and therefore on the lens. The lens then adopts a more spherical shape to accommodate the eye for **near vision**. The ciliary body is also moved in the direction of the **optical axis** (meaning that this ring-like muscle moves inward). This allows for the opening of the canals of Schlemm and the subsequent free flow of aqueous humour back to the venous circulation.

The **eyelids** contain both skeletal muscle fibres (mostly) and smooth muscle fibres (to a lesser extent). The latter receive sympathetic nervous system innervation. When the muscle fibres contract, the eyelids are retracted. Ptosis (drooping of the eyelids) follows muscle fibre paralysis (of either muscle type).

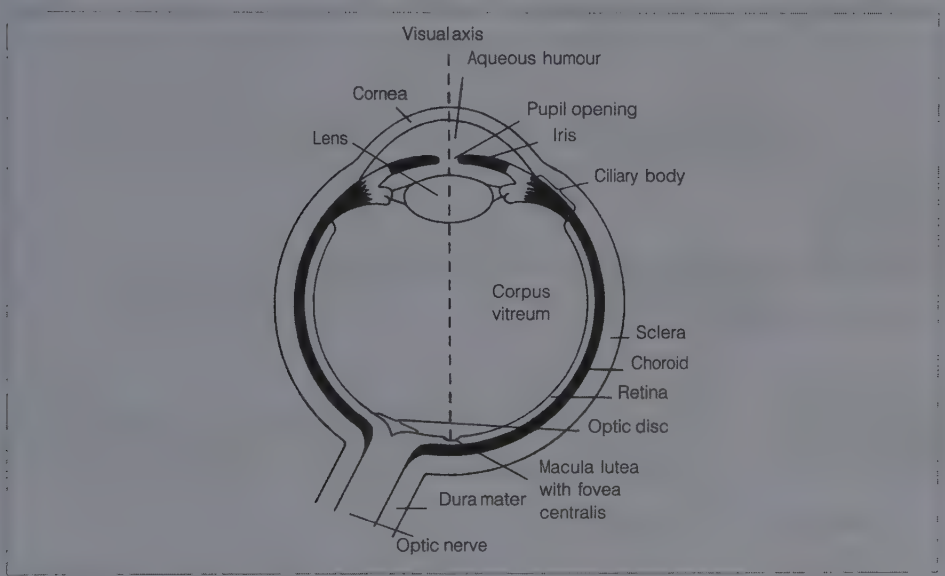



**Figure 12.2A Section through the right eye in the horizontal plane**

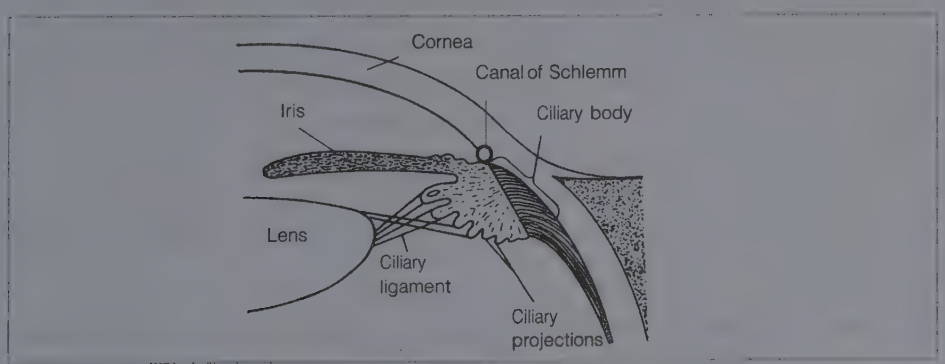



**Figure 12.2B Anatomic relationship between the ciliary body, ciliary ligament and the lens**

### 12.2.2 Drugs and the eye

The following are examples of drugs that may be instilled into the eye.

**Clinical application**

- ***Atropine***, the anti-cholinergic or anti-muscarinic agent, will produce mydriasis and cycloplegia (relaxation/paralysis of the ciliary muscle).
- ***Pilocarpine***, the cholinergic alkaloid, may be used as a miotic in the treatment of glaucoma (an increased intra-ocular pressure).
- β-blockers such as *timolol*, *betaxolol*, *levobunolol* and *metipranolol*. They reduce the formation of aqueous humour. $\alpha_2$-adrenergic receptor agonists also decrease intraocular pressure (IOP) by reducing the formation of aqueous humour, and include *apraclonidine* and *brimonidine*.
- Inhibitors of acetylcholinesterase and carbonic anhydrase. The latter include *dorzolamide* and *brinzolamide*.
- *Lantanoprost* (a prostaglandin $F_{2\alpha}$ analogue) that decreases IOP by increasing the outflow of aqueous humour through the uveoscleral pathway (i.e. the non-conventional route).
- A variety of other drugs, including examples such as *ketorolac*, *corticosteroids*, *sodium cromoglycate*, local anaesthetic agents, and many more.

## 12.3 The drug management of hypertension

**Suggested revision**

***Anatomy and physiology:***

- Blood-pressure control, including the role that the sympathetic nervous system and the RAAS have to play

***Pathology and pathophysiology:***

- Essential and secondary hypertension

Cardiac output (CO) is expressed as the function of stroke volume (SV) and heart rate (HR). In other words, CO = HR × SV. Blood pressure (BP), in comparison, may be expressed as the function of CO and peripheral (vascular) resistance (PR), i.e. BP = CO × PR. Both sympathetic tone and RAAS (renin-angiotensin-aldosterone system) activity (see figure 12.3) are determinants of the degree of peripheral resistance (amongst other factors). The major mechanisms of drug action that are utilised in the treatment of hypertension, i.e. in the lowering of the systemic blood pressure, are:

- Drugs that lower the peripheral resistance through their vasodilatory action (e.g. the inhibition of either the sympathetic vascular tone or the vascular effects of the RAAS)

- Drugs that decrease the cardiac preload through diuresis, the prevention or elimination of sodium and water retention (a definite RAAS-effect through the secondary effects of aldosterone), and through dilatation of the capacitance vessels (veins)
- Drugs that suppress sympathetic effects on cardiac functioning, both primarily and secondarily to the effects of the RAAS

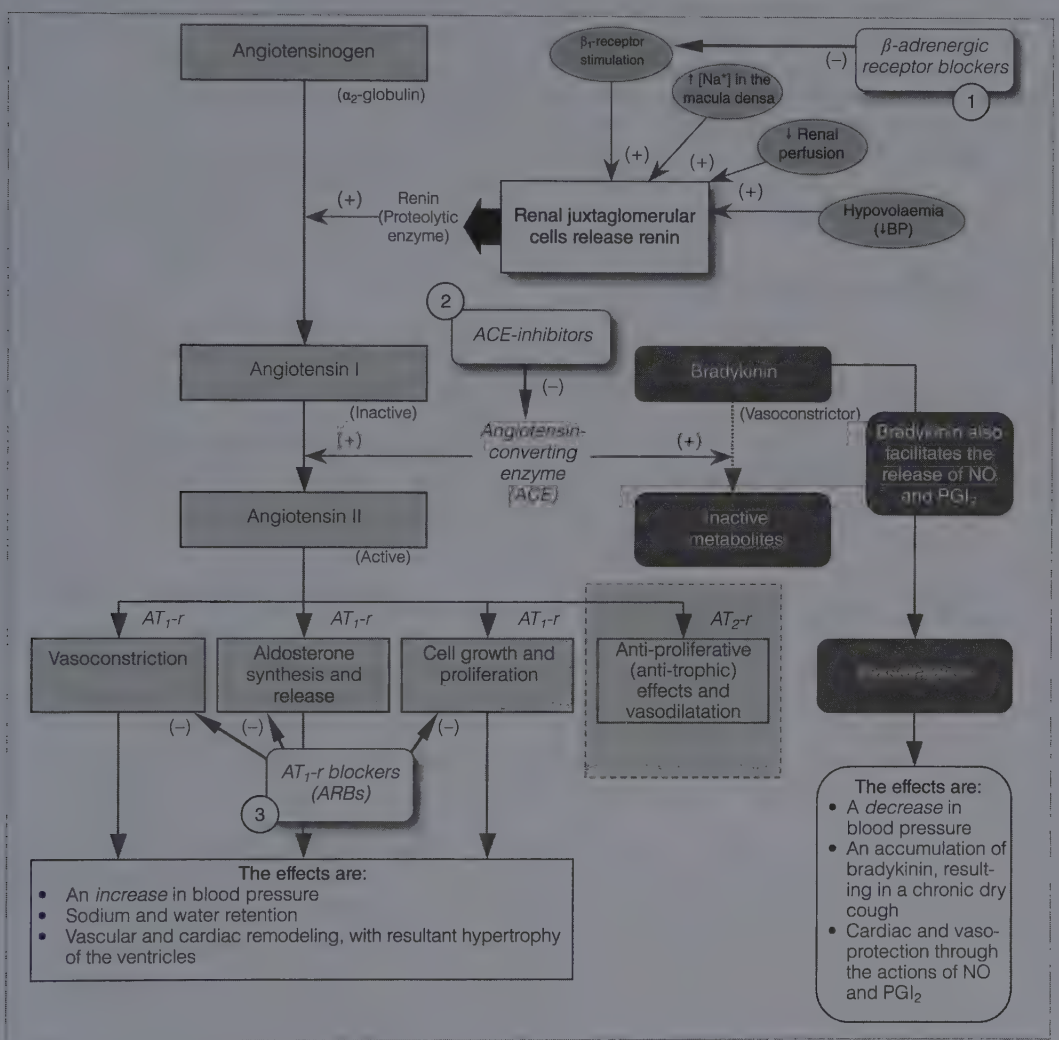



**Figure 12.3 Diagram of the mechanisms that control angiotensin production within the RAAS**

From the above, it is quite clear how important the RAAS is in the control of blood pressure in the body. It is most probably also the major pathophysiological mechanism in the pathogenesis of *essential* hypertension (which approximately nine out of every ten hypertensive patients suffer from). The major

antihypertensive drug groups are described below (also refer to the relevant sections of chapters 5, 6 and 10).

### The thiazides and related diuretics

- ***Hydrochlorothiazide*** is considered to be a first-line antihypertensive drug. Its diuretic effects, however, are not the only reason for its utilisation in the treatment of this condition, but also its effects on vascular smooth muscle cells.
- These drugs facilitate relaxation of arteriolar smooth muscle, resulting in vasodilatation and a subsequent decrease in peripheral resistance (the exact mechanism of which has not yet been fully elucidated).
- *Chlorthalidone* and *indapamide* are classified as being 'thiazide-like' diuretics. Refer to paragraph 10.1.

### The β-blockers

- These drugs reduce the cardiac output. They also inhibit renin secretion, which in turn inhibits the formation of angiotensin II, and also the secretion of aldosterone by the adrenal cortex. Refer to paragraph 5.2.2.
- These drugs also block the effects of the sympathetic nervous system (directly) and the RAAS (indirectly) in terms of cardiac remodelling and the resultant hypertrophy of the left ventricle (see figure 12.3).

### The ACE-inhibitors and blockers of the $AT_1$-receptors

- These drugs counteract or inhibit the effects of angiotensin II. Their lowering effects on the systemic blood pressure may be explained in terms of their inhibition of the vascular effects of the RAAS, which includes an accumulation of bradykinin. Bradykinin itself acts as a vasodilator, but also facilitates the release of nitric oxide (NO) and prostaglandin $I_2$ ($PGI_2$, or prostacyclin). (Also refer to chapter 7.)
- The accumulation of bradykinin is also responsible for the persistent dry cough, a cumbersome side-effect that may manifest itself in patients who receive ACE inhibitors. It is referred to as a 'class effect', meaning that all of the ACE inhibitors will elicit this side-effect. Patients suffering from this side-effect must be switched to another group of antihypertensive drugs.
- Well-known examples of ACE-inhibitors are *perindopril*, ***enalapril***, *lisinopril*, *cilazapril*, *quinapril*, *trandolapril*, *fosinopril* and *ramipril*.
- Stimulation of the $AT_1$-receptors in the adrenal gland by angiotensin II causes the secretion of aldosterone, while stimulation of these receptors in blood vessels will produce the pronounced vasopressor effects of angiotensin II (see figure 12.3). Examples of these receptor antagonists are *valsartan*, *telmisartan*, *irbesartan*, *candesartan*, *eprosartan* and *losartan*.

### The calcium channel blockers

- The calcium channel blockers (CCBs), as mentioned before, may be divided into two distinct groups, namely the '***nifedipine*** group', which elicits a reflex tachycardia, and the '*verapamil* group', which also inhibits the heart's pacemaker cells.
- These drugs block the L-type calcium channels in the membranes of arteriolar smooth muscle cells. The short-acting dihydropyridines (see paragraph 6.3) are not considered to be suitable antihypertensive drugs in situations other than the emergency management of severe hypertension. Reflex tachycardia may prove to be fatal in patients with ischaemic heart disease. When CCBs are to be used as part of the chronic management of hypertension, it is advisable to select a suitable agent with a sufficiently long half-life, or a sustained-release formulation.
- ***Amlodipine***, *felodipine* and *isradipine* belong to the '***nifedepine***' or dihydropyridine group.

### The $\alpha_1$-receptor blockers

- The selective $\alpha_1$-receptor blockers inhibit vasoconstriction, which is usually mediated by the sympathetic nervous system. These drugs do not block the presynaptic $\alpha_2$-receptors, thus leaving the normal negative-feedback mechanism unopposed. Therefore drugs such as *prazosin* and *doxazosin* do not elicit a reflex tachycardia. Refer to paragraph 5.2.2.

## 12.4 Diabetes mellitus

**Suggested revision**

***Anatomy and physiology:***

- The endocrine system
- Endocrine functioning of the pancreas
- The functions of insulin
- Carbohydrate metabolism

***Pathology and pathophysiology:***

- Diabetes mellitus, type 1 and type 2

The two major categories of diabetes mellitus are **type 1** (the previous insulin-dependent category) and **type 2** (the previous non-insulin-dependent category).

### 12.4.1 Type 1 diabetes mellitus

Typically these are the patients with diabetes mellitus who develop keto-acidosis and require ***insulin*** therapy. ***Insulin*** is a polypeptide hormone that has to be administered via parenteral injection since it would otherwise be destroyed inside the GIT when taken orally (note, however, that a human insulin inhalation powder has also been developed). ***Insulin*** may be divided into rapid-acting,

short-acting, intermediate-acting and long-acting preparations. Short-acting ***insulin*** preparations may be injected intravenously and are of great benefit in the management of diabetic ketoacidosis (DKA).

*Regular insulin* is soluble, short-acting and has not been modified. The rapid-acting ***insulins*** have each been slightly modified to produce three insulin analogues, namely *insulin aspart, insulin glulisine* and *insulin lispro.*

Intermediate- and long-acting ***insulin*** preparations cannot be administered intravenously. *Isophane insulin* is intermediate-acting; *insulin glargine* and *insulin detemir* are long-acting, basal insulins. Major complications of ***insulin*** therapy include the very real danger of hypoglycaemia and the possibility of allergic reactions (since ***insulin*** would constitute 'foreign protein' molecules that are introduced into the body). Patients who suffer from type 1 diabetes mellitus should not receive β-blocker therapy since it may mask the signs of a hypoglycaemic attack.

### 12.4.2 Type 2 diabetes mellitus

Patients who suffer from type 2 diabetes mellitus, as opposed to those suffering from type 1 diabetes, still have functional β-cells that produce insulin; however, they rather suffer from a relative lack of insulin (a combination of insulin resistance and the impaired secretion thereof). In many of these patients proper dietary management and exercise alone may prove sufficient in controlling their blood glucose levels. However, **oral anti-diabetic agents**, with the possible addition of ***insulin***, may be required. In the past there used to be two major groups of these drugs, namely the biguanides and the sulphonylureas. However, several new classes of oral anti-diabetic agents have now also been developed and research in this field is still ongoing. Some of the newer agents include:

- Thiazolidinediones, which include *pioglitazone* and *rosiglitazone*
- Meglitinides, including *nateglinide* and *repaglinide*
- The dipeptidyl peptidase-4 (DPP-4) inhibitors that include *sitagliptin* and *saxagliptin*

In addition to the oral anti-diabetic agents, the α-glucosidase inhibitor, *acarbose,* may be used to slow down the rate of carbohydrate digestion and absorption, resulting in a smaller rise in the postprandial (i.e. after a meal) blood-glucose concentration.

**The biguanides**

- Typically, biguanide therapy is indicated in the treatment of the type 2 diabetic patient who is overweight or obese.
- ***Metformin*** inhibits the uptake of glucose from the gastrointestinal tract and facilitates the utilisation of glucose in peripheral tissues.
- ***Metformin*** may also be combined with *insulin* therapy to facilitate more effective utilisation of the injected insulin in type 1 diabetes.

**The sulphonylureas**

- These drugs facilitate the release of insulin from still-functioning β-cells and are sulphonamide derivatives.
- Examples of the sulphonylureas are *glipizide*, ***glibenclamide*** (also known as *glyburide*), ***gliclazide*** and *glimepiride*.

## 12.5 Miscellaneous conditions and drug groups

### 12.5.1 Allergic reactions and anaphylaxis

Acute allergic reactions and anaphylaxis are mediated by histamine release from degranulated mast cells. Histamine, in combination with other vasoactive substances such as bradykinin, serotonin, prostaglandins and leukotrienes, causes glottis oedema, bronchospasm, increased capillary permeability and vasodilatation (with a subsequent drop in arterial blood pressure), skin signs such as blushing, pruritus and urticaria, as well as gastrointestinal symptoms such as cramping, nausea, vomiting and diarrhoea. The histamine receptor subtypes and the effects that they elicit were described in paragraph 4.10.

The treatment of severe allergic reactions and anaphylaxis is based on the principle of the so-called **four As of anaphylaxis**:

- **Adrenaline:** This is the mainstay of treatment, and is used to oppose the cardiovascular effects of histamine. ***Adrenaline*** is a potent sympathomimetic drug that produces vasoconstriction, with a subsequent rise in arterial blood pressure. It is the physiological, or functional, antagonist of histamine (see note 3.2).
- **Adrenocorticosteroids:** These drugs are used to counteract the inflammatory response and protect the patient against a relapse (refer to chapter 7).
- **Aminophylline:** This is the parenteral preparation of *theophylline* (theophylline ethylene diamine). ***Theophylline*** inhibits phosphodiesterase, and therefore increases the concentration of cAMP, with subsequent β-adrenergic effects. It may be used to relieve the severe bronchospasm of an acute allergic reaction or anaphylaxis.
- **Antihistamines:** The competitive antagonists of histamine are of little benefit in the management of anaphylactic shock (as was explained in note 3.1). They are, however, quite effective in the management of the skin and of gastrointestinal manifestations of allergic reactions, such as pruritus, hives, wheals and gastrointestinal upsets.

The antihistamines include the older, sedating, multi-potent blockers, including ***promethazine***, ***chlorpheniramine***, *dexchlorpheniramine* and *cyclizine*, and the newer, non-sedating, selective $H_1$-receptor blockers. Examples of these non-sedating antihistamines include ***cetirizine*** (and *levocetirizine*), *loratadine*, *ebastine*, *fexofenadine* and *mizolastine*.

## 12.5.2 Migraine headaches

**Clinical application**

Serotonin (5-HT) has been implicated in the pathogenesis of migraine headaches through the 5-$HT_1$-receptor subtype. During the typical aura phase, 5-HT is released from blood platelets to produce cerebral vasoconstriction and a temporary suppression of neurological functioning. Because 5-HT is rapidly metabolised in the bloodstream, vasodilatation subsequently results and produces a throbbing headache.

*Ergotamine* acts as a non-selective vasoconstrictor through its partial agonistic activity at 5-$HT_1$- and $\alpha_1$-receptors. *Sumatriptan, naratriptan, zolmitriptan, eletriptan* and *rizatriptan* are examples of 5-$HT_{1D}$-receptor agonists. This mechanism of action produces cerebral vasoconstriction. Drugs that may be used as prophylactic agents include the β-blockers, ***valproate***, ***amitriptyline***, *clonidine, pizotifen* and *methysergide.*

## 12.5.3 A few other drugs worth mentioning

- **The disease-modifying antirheumatic drugs (DMARDs):** The DMARDs are used in the treatment of rheumatoid arthritis (RA). The 'traditional' agents include *methotrexate,* the anti-malarial agents, *chloroquine* and *hydroxychloroquine, azathioprine, mycophenolate, sulphasalazine* and *leflunomide.* The 'biological response modifiers' (BRMs) are DMARDs that have been developed with the use of biotechnology (refer to paragraph 1.2). These biopharmaceuticals include *etanercept, adalimumab*, rituximab*, infliximab** (see note 12.2) and *abatacept.*
- **The biphosphonates:** These drugs are used in the treatment of osteoporosis. They effectively inhibit the activity of osteoclasts to decrease bone resorption. Examples include *alendronic acid (alendronate), clodronate, risedronate, zoledronic acid* and *pamidronate.*

**Note 12.2**

***Monoclonal antibodies:** These specific biopharmaceuticals are easily recognisable by the suffix '-mab' in their non-proprietary names. It is also interesting to note that the two letters directly preceding the 'mab'-suffix may be used to identify the origin of the monoclonal antibody in question. *Adalimumab*, for example, is a human antibody (the infix 'mu' precedes the suffix 'mab'); *infliximab* and *rituximab* are chimeric (i.e. 'mouse-human') antibodies and have the infix 'xi', while the 'zu'-infix identifies humanised antibodies (e.g. *bevacizumab*, which is used in the treatment of metastatic colorectal cancer).

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CHAPTER THIRTEEN

# *Nursing management of drug preparations and treatment*

Registered nurses must be able to administer prescribed medicines to patients in their care, monitor the effects of, and reactions to, such medicines, and provide effective patient advocacy relating to these therapeutic interventions, if necessary. To fulfil these obligations, nurses need to have:

- A sound, practical knowledge of applied pharmacology and pharmacotherapeutics
- The necessary knowledge and skills that are required to effectively manage drug preparations, to safely administer such preparations to their patients, and to identify, measure and report on the effects of such preparations
- The ability to search for, evaluate and interpret suitable drug information to assist them with the abovementioned requirements
- The necessary understanding of the legal framework, statutory requirements, and the expected attitudes and value system of practitioners involved in pharmacotherapy

## 13.1 The role of the registered nurse in the management of drug preparations and treatment

In the clinical practice setting, be it in a hospital or a primary care facility, nurses are faced with the challenging task of managing drug preparations and treatment on a daily basis. This entails a wide variety of activities, which include but are not limited to the following:

- Evaluating and interpreting prescriptions, liaising with the prescribing practitioners and other members of the multidisciplinary healthcare team, and implementing and coordinating their prescribed treatment regimens.
- Ordering, receiving, storing, issuing and reordering drug supplies (ward stock).
- Preparing and administering prescribed medication to patients in their care.
- Monitoring these patients for the effects of such medicines, as well as possible adverse reactions to the prescribed treatment.
- In settings where the prescribed treatment is not administered directly to the patient, there may be a need to monitor the patient for compliance (adherence) to the prescribed treatment regimen at regular intervals (see Annexure B).

It follows from the abovementioned activities that there is an important interaction between prescribers, dispensers and patients, and that nursing practitioners play an integral part in the success of this therapeutic interaction. Key aspects pertaining to this interaction are illustrated in figure 13.1, and these aspects will be discussed in more detail below.

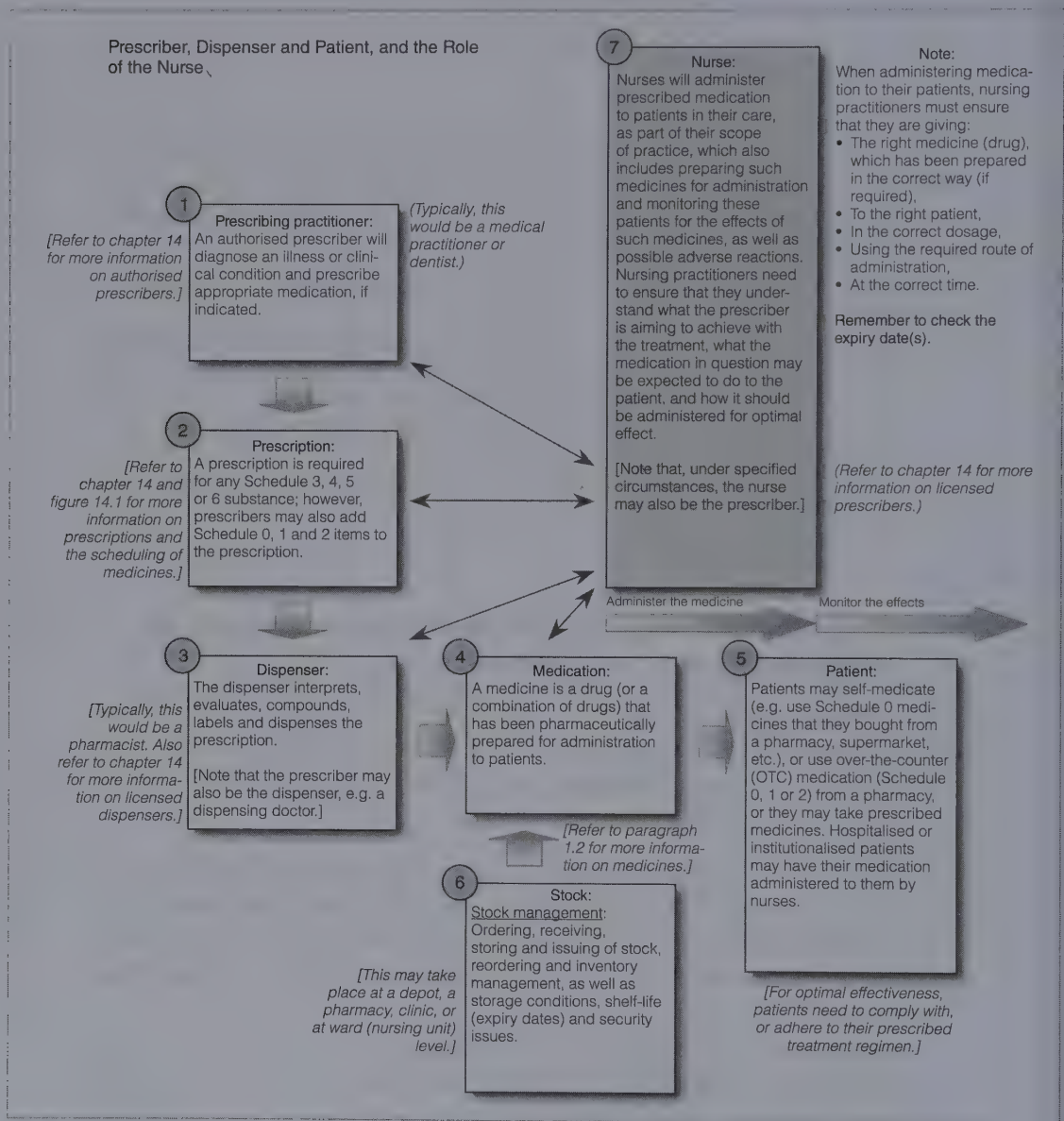


**Figure 13.1 The role of the nurse in the interaction between prescriber, dispenser and patient. Refer to the accompanying text for a discussion on the numbered labels, 1 to 7.**

1. **Prescribing practitioner:** An authorised prescriber will diagnose an illness or clinical condition, set attainable treatment goals, and prescribe appropriate medication, if indicated. Such a prescription may aim to relieve some, or all of the patient's symptoms, assist in diagnosing the full extent of the patient's condition, prevent further deterioration of the condition, address and modify the actual disease process, or aim to achieve a combination of these therapeutic goals. Typically, the prescriber would be a medical practitioner or a dentist. Under certain, specified circumstances, however, registered nurses may also act as prescribing practitioners (refer to chapter 14).
2. **Prescription:** As explained in chapter 14, a prescription is required for any Schedule 3, 4, 5 or 6 substance to be used as part of the patient's pharmacotherapy. Schedule 1 and 2 substances may be purchased as over-the-counter (OTC) medicines from a pharmacy, while Schedule 0 substances may be sold in an open shop (e.g. a supermarket or the front shop of a pharmacy). Refer to paragraph 14.2.1 and figure 14.1 for more information on the requirements for a prescription and the scheduling of medicines. A prescriber may, however, add Schedule 0, 1 and 2 items to the prescription as well. Note that without a prescription, nurses who are not authorised prescribers may not administer any medication, irrespective of the scheduling status thereof, to patients in their care (unless specific, legally acceptable provisions have been made in their scope of practice or otherwise).
3. **Dispenser:** The person who dispenses the prescribed medication (typically, a pharmacist) will interpret and evaluate the prescription, select, manipulate or compound the medicine, and label and supply the medicine in an appropriate container. Furthermore, instructions and information need to be given to the patient to ensure that the medicine will be used safely and effectively. In some situations, as is the case with a dispensing doctor, for example, the prescriber may also be the dispenser. Pharmacists are obliged by law to dispense interchangeable multi-source medicines (also referred to as generic substitution) in accordance with the stipulations of section 22F of the Medicines and Related Substances Act (No. 101 of 1965, as amended). In the case of a hospitalised patient, for example, the pharmacist will not dispense medication directly to the patient, but rather supply medicines that have been dispensed to individual patients and labelled accordingly, to the nursing unit or ward.
4. **Medication:** The difference between a 'drug' and a 'medication' was explained in paragraph 1.2. It is important to note that a certain medication may contain more than one drug as an active ingredient. The other important aspect pertaining to the medication is adequate information on its correct, safe and effective use in clinical practice. The importance

of referring to the approved package insert cannot be overstated. The pharmacist also plays a vital role as a member of the multidisciplinary team and will be able to provide information on the classification and mechanisms of action of medicines, their required storage conditions, indications, preparation for, and routes of administration, safe and effective dosages, possible drug interactions, expected adverse effects, therapeutic drug monitoring (TDM) and other relevant aspects. In addition, a variety of other resources may be consulted (refer to paragraph 1.9). With regard to the interchangeable multi-source medicines (IMSMs), these are medicines that contain the same active ingredients (i.e. the same drugs), in the same dosage form, strength or concentration, and are meant to be administered via the same route (e.g. oral or parenteral). Registered IMSMs are considered to be therapeutically equivalent to the original product.

5. **Patient:** Patients may self-medicate (e.g. use Schedule 0 medicines that they bought from a pharmacy, supermarket, etc.), or use over-the-counter (OTC) medication (Schedule 0, 1 or 2) from a pharmacy, or they may take prescribed medicines. Hospitalised or institutionalised patients may have their medication administered to them by nurses. For optimal effectiveness, patients need to comply with, or adhere to their prescribed treatment regimen (see Annexure B).
6. **Stock:** The management of pharmaceutical stock entails activities such as the ordering, receiving, storing and issuing of stock, reordering and inventory management, as well as storage conditions, shelf-life (expiry dates) and security issues. This may take place at various levels, including a depot, pharmacy, clinic, or at ward (nursing unit) level. Refer to paragraph 13.2 for more information.
7. **Nurse:** Nurses will administer prescribed medication to patients in their care, as part of their scope of practice, which also includes preparing such medicines for administration and monitoring these patients for the effects of such medicines, as well as possible adverse reactions. Nursing practitioners need to ensure that they understand what the prescriber is aiming to achieve with the treatment, what the medication in question may be expected to do to the patient, and how it should be administered for optimal effect. Note that, under specified circumstances, the nurse may also be the prescriber (refer to chapter 14).

**Note 13.1**

When administering medication to their patients, nursing practitioners must ensure that they are giving:

- The right medicine (drug), which has been prepared in the correct way (if required)
- To the right patient
- In the correct dosage
- Using the required route of administration
- At the correct time.

Refer to paragraph 13.3 for more information.

## 13.2 Managing pharmaceutical stock in the healthcare unit

Stock management involves various different levels and aspects, including the ordering of stock, receiving the stock in the healthcare unit (i.e. ward, department, operating theatre or clinic), issuing of the stock, and the reordering thereof, according to the specific levels used for inventory management. If this is managed inadequately it could lead to wastage of essential drugs and financial resources, as well as a decrease in the quality of care rendered to the patient.

Proper stock management and drug control are vital to the successful management of a nursing unit, as well as the healthcare facility as a whole. The following is a proposed checklist for effective stock management:

- Find a structured system for the management of stock in the unit, with regularly-updated minimum and maximum stock levels (or reorder levels), and a system for proper stock control. This will better manage (and prevent) stock losses (i.e. expired stock, damage or theft).
- Assign a dedicated registered nurse in the unit to manage the stock and ensure that there are open lines of communication between the nursing staff and the pharmacist.
- Identify fast-moving items (i.e. medicines that are in high demand) and add them to the list of ward stock (if available and not already done); the ordering interval for ward stock and the ward stock levels should be adequate enough to ensure a sufficient supply of these items.
- Upon receipt of ward stock, assign a specific method for unpacking (or rotating) stock, either using the 'FIFO' (i.e. the 'first in, first out' principle), or 'FEFO' (i.e. the 'first expired, first out' principle). The former principle may, for instance, be applied when more than one consignment of a particular item (from the same batch, and therefore with the same expiry date) are received on two or more consecutive occasions. Since all of these

items have the same expiry date, the 'FIFO' principle determines that the stock units that were received first, be used first, followed by the second consignment, the third consignment, and so forth. On the other hand, the 'FEFO' principle is applied when different consignments of the same stock item come from different batches and therefore (probably) carry different expiry dates. In the latter scenario it makes obvious sense to first use the items that are closest to their expiry date.

- Identify stock that is about to expire and that is not used very often, and return these items to the pharmacy in a timely manner.
- Assign regular (fixed) intervals for checking ward stock and to update the minimum and maximum stock levels, if necessary.
- Appropriate operating procedures or guidelines should be in place, but even more important than having these policy documents in place, is ensuring that all of the staff members are familiar with the stock and drug management policies and procedures. This will ensure uniformity on the part of the ward staff and lessen the likelihood of unnecessary mistakes.
- Check storage conditions, including temperature readings, on a regular basis (and, whenever indicated or required, ensure that a proper **cold chain** is maintained). Good Pharmacy Practice, or GPP (2008: 30–40) requires that a dispensary or medicine room be air-conditioned so as to maintain an ambient temperature of below 25 °C. Furthermore, a dedicated refrigerator is required for thermo-labile (i.e. temperature-sensitive) medicines. Both the air conditioner and the refrigerator should be kept in good working order and cleaned regularly. The temperature inside the refrigerator should be maintained between 2 °C and 8 °C and a suitable thermometer should be used to verify this. Access to the medicine room and pharmaceutical stock should be controlled.
- The storage of drugs and preparations for internal use must be clearly marked and separated from products for external use to prevent any mistakes. Inflammable agents should also be separated from the other stock.

When not in use, keep drug cabinets or medication trolleys locked to prevent unauthorised access and possible stock losses.

Proper procedures need to be in place for the control of Schedule 6 medicines at ward level, including storage conditions, stock management, access to these drugs, and the keeping of the required register of Schedule 6 substances that clearly reflects the balance of each one of these items that remain in stock.

Practitioners who have been licensed to dispense medication in terms of the Medicines and Related Substances Act, No. 101 of 1965, as amended (see chapter 14) are required by law to have a **designated** medicine room for use as a storage facility. The specifications that such a medicine room needs to comply with, including storage areas within the medicine room, dispensing equipment and

reference materials, are determined by the standards for GPP in South Africa (2008: 37–40) and are enforced by the South African Pharmacy Council (SAPC).

## 13.3 Administering medication to patients

When administering medication to their patients, nursing practitioners must ensure that they are giving:

- The right medicine (drug), which has been prepared in the correct way (if required)
- To the right patient
- In the correct dosage
- Using the required route of administration
- At the correct time.

Also remember to check the expiry date(s). Never use expired medication.

### 13.3.1 The right medicine (drug), which has been prepared in the correct way (if required)

While it is the responsibility of the doctor to prescribe drugs, the nurse who administers the medication must have adequate knowledge and a good understanding of the drugs being given to a patient. Both doctor and nurse are accountable for the drugs being administered but, if the nurse administers the incorrect dosage or drug, she or he will be held accountable even if the drug was incorrectly prescribed.

Nurses must evaluate and interpret the prescription to ensure the effective preparation and administration of the prescribed medication. The following points need to be considered:

- The reason(s) why the medication is being prescribed and the effects that it is expected to have. This will guide the nursing staff in the observations that need to be made to evaluate whether the drug treatment is effective or not.
- Is the prescribed dosage within the recommended range for the patient's age and condition and, if not, is it justified?
- Is the patient allergic to anything?
- Can this drug interact with other drugs, herbal or nutritional supplements, or foodstuffs that the patient is taking? Also check the patient history for other drugs that may have been used recently so as to prevent possible interactions.
- Are there any special instructions for the preparation or administration of the medication?

- Is the safest and most effective route of administration being used, and how often should the medication be administered?

**Clinical application**

Should the prescription not be clear or legible, or the prescribed medication, its dosage and dosage intervals be outside the usual recommended range, or if an unusual route of administration or instructions for the preparation of the medication have been given, check and verify the prescription with the prescribing practitioner.

Nurses need to follow the instructions of the manufacturer for any medicine that needs to be prepared for administration and consult the pharmacist if in any doubt as to the correct diluents or method of reconstitution to be used.

'Triple-check' every item prior to administering it to the patient, once when selecting the medicine from the stock room, cupboard or trolley, a second time while preparing the medicine for administration, and a third time when replacing the container back into the medication room, cupboard or trolley, or when discarding the used or empty container into the medical waste receptacle.

### 13.3.2 To the right patient

Identify the patient, the prescription chart and the medication, and be absolutely sure that the right medication is being administered to the right patient.

### 13.3.3 In the correct dosage

Once the prescription has been evaluated, interpreted and verified (if necessary), the correct dosage needs to be administered to the patient. This may be as simple as counting out the required number of tablets or capsules from a medicine bottle, or as complicated as having to accurately calculate and measure the correct volume of medication to be administered. Consider the following examples:

**Clinical application**

**Example 1:**
Patient ABC needs to take 500 mg of *amoxicillin* eight-hourly. The only *amoxicillin* capsules that are currently in stock are 250 mg in strength. Therefore, Patient ABC will simply need to be given two 250 mg-capsules every eight hours.

**Clinical application**

**Example 2:**

Baby XYZ is two days old and weighs 2 000 grams. The following prescription for an antibacterial agent was received for this patient:
Rx: *Amikacin* 15 mg/kg/day IV in two divided dosages.
The neonatal intensive care unit has *amikacin* vials in stock that contain 100 mg in 2 ml.

***Dosage of the medicine to be administered:***
[15 mg × 2 kg (i.e. from the 2 000 grams)] ÷ 2 (i.e. the two divided dosages, which will be administered 12-hourly):
∴ [15 mg × 2 kg] ÷ 2
∴ [15 × 2] ÷ 2
∴ 30 ÷ 2 = 15 mg per dosage, every 12 hours

***Volume of the medicine to be administered:***
The following formula may be used:

$$\text{Volume to be administered}^{**} = \frac{\text{Dosage required (any unit)}^{*}}{\text{Dosage in stock (same unit)}^{*}} \times \frac{\text{Volume (ml)}}{1}$$

[**Note:** *The units of measurement must be the same, e.g. mg, mEq, IU, etc.
**The answer will always be in ml, i.e. millilitres required, or the volume to be administered.]

***Calculation:***

$$\text{Volume to be administered}^{**} = \frac{15\ \text{mg}^{*}}{100\ \text{mg}^{*}} \times \frac{2\ \text{ml}^{***}}{1}$$

[**Note:** *The units of measurement are both given in milligrams.
** The answer will always be in ml, i.e. millilitres required, or the volume to be administered.
*** The unit has 2 ml-vials in stock that contain 100 mg of *amikacin* each.]
∴ [15 mg ÷ 100 mg] × [2 ml ÷ 1]
∴ 0.15 × 2 = 0.3 ml of *amikacin* to be withdrawn from the 100 mg/2 ml vial

## 13.3.4 Using the required route of administration

Where at all possible, a non-invasive route of administration is preferred. A detailed discussion of the various routes of drug administration, as well as the pharmaceutical dosage forms most often encountered in clinical practice, may be found in paragraph 2.1, note 1.1 and note 2.1. In addition, the following guidelines should be taken into consideration:

- **Oral route:** This route usually necessitates the patient's ability to swallow oral drug formulations (unless a feeding tube is being used), with solid forms (such as tablets and capsules) presenting a bigger challenge than liquid forms (such as syrups, suspensions and elixirs). In general, only scored and double-scored tablets may be broken or crushed. Sugar-coated, film-coated and enteric-coated tablets should not be broken, and capsules should not be opened. Consult the pharmacist or the drug manufacturer, when patients cannot swallow oral preparations that cannot be broken, crushed or opened. The taste of an oral drug formulation may also pose some problems, especially when children need to take 'bad-tasting' medication. Again, the pharmacist or the manufacturer should be consulted when wanting to mask the taste of such a preparation with honey, sugar or another 'taste enhancer'. Medicine measuring cups or spoons, droppers, or disposable syringes should be used to accurately measure out the correct dosage of a liquid formulation.
- **Parenteral injection:** Intravenous drug administration should not take place through the same intravenous line as one that is used for the administration of total parenteral nutrition (TPN), blood, or blood products. Always ensure that the correct diluents are used during the preparation of the medication for injection. Sterile liquids for parenteral injection should not be contaminated during the preparation and administration thereof.

### 13.3.5 At the correct time

The prescription will indicate the time(s), or dosage intervals that should be used. Consider the following examples:

- ***Stat*:** give at once, or immediately
- ***Ad lib*:** give as desired, or as much as is required
- ***Mane*:** every morning
- ***Nocte*:** every night
- ***Pro re nata (prn)*:** as needed, or when required
- **For specific dosage intervals:** daily (*qd* or *od*), twice daily (*bd* or *bid*), three times daily (*tds* or *tid*), four times daily (*qds* or *qid*), every four hours (*q4h*), every six hours (*q6h*), and so forth.

Other aspects to considers in terms of the timing of drug administration include interactions with food (i.e. should the medicine be taken on an empty stomach, or after a meal), or a possible interaction with another drug when the two are administered simultaneously (e.g. tetracyclines should not be administered together with antacids). In such instances the timing of the drug administration would need careful consideration, so as to ensure that all of the prescribed medicines are administered, not only at the right time of day, but also at the right time in relation to one another.

## 13.4 Pharmaceutical waste management and the destruction of medicines

Proper medical waste (including pharmaceutical waste) management is crucial to prevent injuries or exposure of patients, caregivers and healthcare workers to diseases such as viral hepatitis or HIV infection, as well as the inadvertent and possibly toxic exposure to drugs. Pharmaceutical waste comprises a diverse group of chemical and biological products, as well as used and empty containers, and includes unwanted and expired over-the-counter medicines, prescription medicines, diagnostic agents, nutritional supplements and so on. In addition, medical waste such as needles, syringes, intravenous infusion sets, catheters and other equipment used in the administration of such medicines and supplements will also need to be managed. The following guidelines should be applied:

- Suitable policies and operating procedures need to be in place for the management of pharmaceutical, as well as other medical waste at every level within the healthcare facility.
- Do not allow waste to accumulate in the nursing unit or the pharmacy. Collect waste in suitable containers for removal to the appropriate collection points. Used medication bottles, blister packs, vials, broken ampoules and other containers that contained medication, also need to be managed as medical waste, because these vessels are tainted with drugs that are capable of contaminating the environment.
- Do not dispose of any pharmaceutical substances or waste down surface water drains (such as storm water drains) or in the municipal sewerage system.
- Do not dispose of any medical waste in the municipal waste removal system. Products and equipment that were used during home care need to be returned in a suitable container to the pharmacy, healthcare practitioner or institution where these items had been issued (and where suitable waste removal systems should be in place).
- Unwanted, unused or expired medication needs to be returned to the pharmacy, from where suitable destruction will be effected.

CHAPTER FOURTEEN

# The legal framework for the prescribing and dispensing of medicine by nurses in South Africa

New trends, new legislation and new issues of practice necessitate a thorough knowledge and understanding of the following aspects of the legal framework in terms of which nurses in South Africa may prescribe and dispense medicine:

- The sections of the legislation relating to the various healthcare professions which pertain to the prescribing and dispensing of medicines by nurses and midwives
- An analysis of the context, nature and extent of the legal framework within which the nurse and midwife may prescribe and dispense medication
- The sections of the Nursing Act (No. 33 of 2005) which pertain to the prescribing and dispensing practices of medicines by nurses and midwives
- The sections of the Medicines and Related Substances Act (No. 101 of 1965, as amended) in terms of which nurses and midwives may acquire, keep, use, prescribe, supply or dispense medication

The need to amend legislation to enable South African healthcare practitioners to provide a comprehensive health service arose during the 1970s, owing to the establishment of the 'independent' and self-governing 'homelands'. There were too few medical practitioners in these areas to provide proper and adequate health services. A special arrangement had to be made to allow registered nurses to provide these services. Furthermore, in the aftermath of the Soweto uprising, all white medical practitioners were withdrawn from the 'homelands', leaving only the registered nurses behind to run the health services.

These developments necessitated an amendment to the legislation to enable the nurses to deliver a more comprehensive health service at clinic level. Accordingly, in 1981, the Nursing Act (then, No. 50 of 1978) was amended through the promulgation of section 38A as part of the Nursing Amendment Act (No. 71 of 1981).

Since the transition to a democratic government in 1994, developments in healthcare policy, and the decision that nurses would be the frontline healthcare practitioners in the field, have required further amendments to the legislation.

## 14.1 Supreme law and subordinate law

The Constitution of the Republic of South Africa (Act No. 108 of 1996, as amended) is the supreme law, and Parliament is the supreme legislature with regard to certain matters. Parliament makes law, which has to accord with the Constitution. The laws (or Acts) provide the framework for the drafting of *subordinate legislation* (i.e. regulations that detail the actual implementation of the parent legislation, procedures to be followed, and behaviour to be observed by persons to whom the parent legislation applies). Any subordinate legislation that is in conflict with an Act of Parliament is invalid. Therefore, if the Nursing Act did not indicate that a nurse might make diagnoses and prescribe medication, the Director-General of Health could also not issue a regulation that authorises nurses to do so.

### 14.1.1 The South African Constitution

Section 22 of the Constitution of the Republic of South Africa (Act No. 108 of 1996, as amended) determines that all citizens have the right to choose their occupations or professions freely, but that some professions or occupations may be regulated by additional laws.

### 14.1.2 The general rule

The general rule regarding medicines is based on the Medicines and Related Substances Act (No. 101 of 1965, as amended) and the Acts governing the various health professions. These Acts inform us of the general rule, namely that medical practitioners, dentists, veterinary surgeons and some allied health practitioners may prescribe medication; that pharmacists and some of the allied health practitioners may prepare and dispense a prescribed medication; that nurses may administer the medication; and that all of these health practitioners should evaluate the effectiveness of such medication.

### 14.1.3 Provision for special circumstances

Taken together, the fundamental purpose of the Pharmacy Act (No. 53 of 1974) and the Medicines and Related Substances Act is to:

- Regulate the manner in which scheduled substances are made available to the public (refer to figure 14.1);
- Control the quality and supply of medicines in general;
- Provide measures that are designed to:
  - Ensure proper standards and quality;
  - Control and maintain these standards; and
  - Protect honest health professionals and society at large.
- Regulate the establishment, maintenance and safeguarding of standards in the myriad of healthcare undertakings in the country.

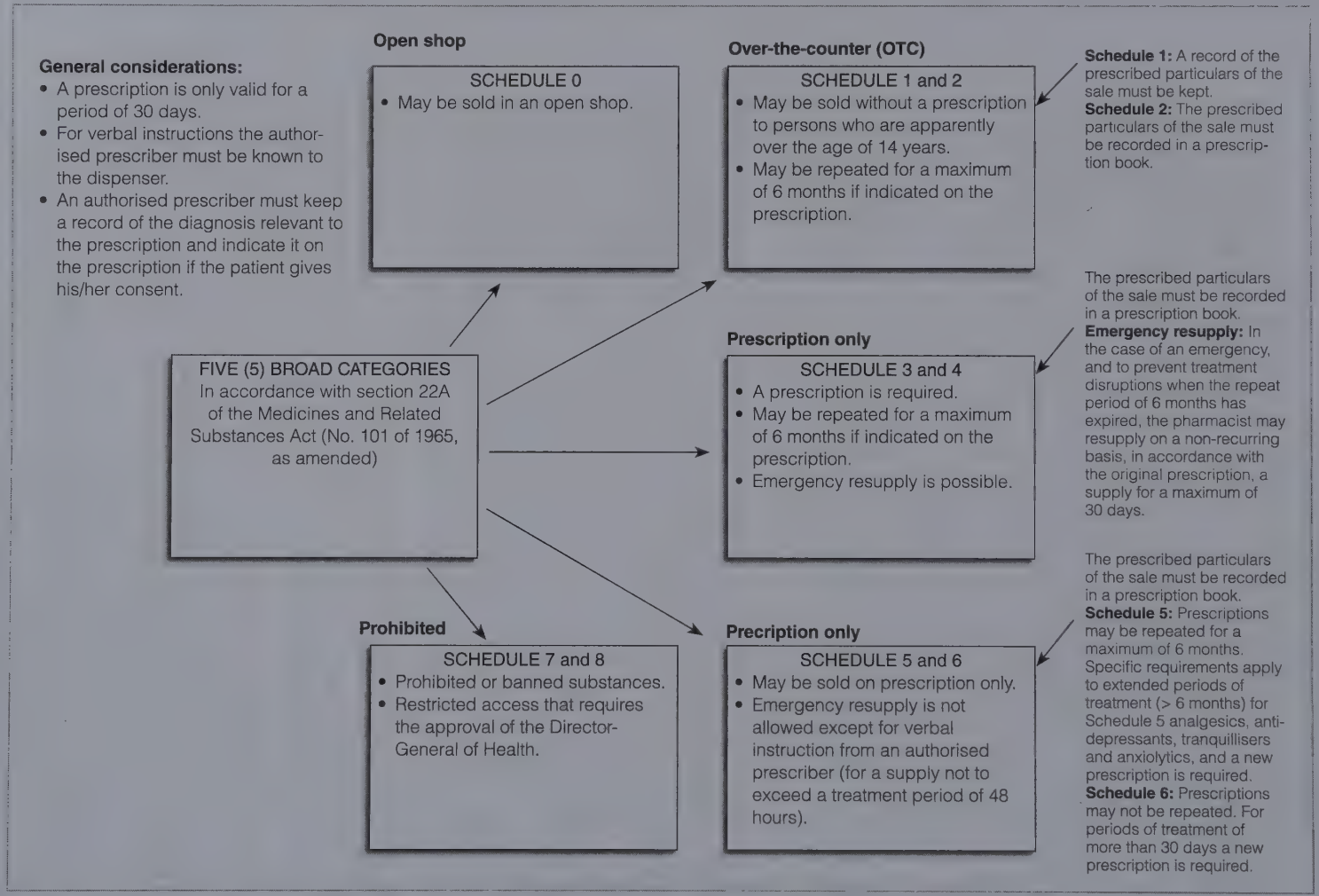


**Figure 14.1 Regulating how scheduled substances are made available to the public**

There are many circumstances where nurses are the only healthcare practitioners available at a particular service point, and are responsible for all activities that take place there, including diagnosing, prescribing and dispensing. As discussed in the previous section, wherever there are exceptions to the general rule, new laws or regulations have to be made in order to meet the needs of the situation.

To accommodate such special circumstances (which are the exception to the rule), section 22A (15) of the Medicines and Related Substances Act (in terms of the Amendment Act No. 90 of 1997) makes provision for a concession in terms of which persons or institutions can apply for a permit to acquire, possess, use and supply medication. In addition, Regulation 47 of the General Regulations (R.510 of 10 April 2003), made in terms of the Medicines and Related Substances Act (No. 101 of 1965, as amended), makes provision for the special circumstances of midwives who do home deliveries. This regulation allows the midwife to carry certain drugs with her to enable her to perform this type of service.

A 'permit system' has been in place, for use by non-pharmacists (persons) and institutions other than hospitals and pharmacies, to acquire, possess, use and supply medication. In terms of section 22A (15) of the abovementioned Amendment Act (No. 90 of 1997), the Director-General of Health may issue a permit to a person or institution performing a health service to acquire, possess, use or supply specified Schedule 1 through 5 substances. The conditions for issuing permits are determined by the Director-General of Health. Permits are issued after consultation with the South African Pharmacy Council (SAPC). This stipulation does not prohibit nurses from possessing substances to administer them in accordance with their scope of practice.

Section 22A (15) does not authorise nurses to prescribe medicines – this is provided for in section 56 of the Nursing Act (No. 33 of 2005). This section makes provision for the registration of professional nurses, midwives or staff nurses (i.e. persons who are registered in terms of section 31 (1) (a), (b) and (c) of the Nursing Act) by the South African Nursing Council (SANC) to assess, diagnose and prescribe treatment, and to keep and supply medication for prescribed illnesses and health-related conditions. In addition, section 56 (6) allows for the Director-General of Health or the head of a health service, including designated services, to authorise nurses to diagnose and prescribe medication for physical disorders.

## 14.2 Legislation pertaining to health professionals

The legislation pertaining to the practice of the various health professions sets out the rights and obligations of the practitioners involved (the Health Professions Act, No. 56 of 1974; the Pharmacy Act, No. 53 of 1974; the Nursing Act, No.

33 of 2005; and the Chiropractors, Homeopaths and Allied Health Professions Act, No. 63 of 1982). None of these Acts provides guidelines for the handling of medicine; this is done by the Medicines and Related Substances Act (No. 101 of 1965, as amended), which also provides for the Medicines Control Council (MCC), which oversees the production, registration and handling of medicines.

These Acts set out certain rules of conduct for the various healthcare professionals. There are certain overlaps in the scopes of practice of the different professional groups. Sometimes a nurse's duties fall into these 'grey areas' of overlap with those of medical doctors, physiotherapists, dieticians or pharmacists. If other members of the multi-professional team are not available, the nurse must have the skills and discretionary ability either to do what needs to be done or to refer the patient. This requires not only knowledge, skills and expertise but also enabling legislation and regulations.

### 14.2.1 The Nursing Act (No. 33 of 2005)

The Nursing Act stipulates that any person who is not registered as a professional nurse, midwife, staff nurse, or auxiliary nurse, and performs any act pertaining to the profession of nursing for gain, is guilty of an offence. The Act provides for quality assurance in the training and education of nurses, and for the monitoring of professional conduct through peer review. The Minister of Health may, on the recommendation of the SANC, create additional nursing categories and make regulations relating to various issues, including the scope of practice of all categories of nurses.

#### *The authorisation to prescribe*

Certain nurses may be registered with the South African Nursing Council to assess, diagnose, prescribe treatment, and keep and supply medication for prescribed illnesses and health-related conditions, in terms of section 56 (1) of the Nursing Act (No. 33 of 2005). Such registration is dependent upon the provision of proof of having completed a prescribed qualification and training, paying the prescribed fee and complying with the stipulations contained in section 56 (6) of the Act. This provision therefore only applies to professional nurses, staff nurses or midwives employed by the National Department of Health, a Provincial Department of Health, a Local Authority (or municipality) or an organisation that performs any health service designated by the Director-General of Health.

Section 56 (6) also creates an alternative system to authorise nurses to assess, diagnose, prescribe treatment, and keep and supply medication. The nurse is given the necessary authorisation, in terms of this section, by the Director-General of Health or the head of a provincial department of health, the medical

officer of health of a municipality, or the medical practitioner in charge of a designated organisation.

Health services may be designated in terms of section 56 (6) of the Nursing Act (No. 33 of 2005). Occupational health services that mainly operate in the private sector, community-based organisations and other private healthcare institutions fall into this category. In addition, the Occupational Health and Safety Act (No. 85 of 1993, as amended) makes it compulsory for employers with 20 or more employees who work in one place to provide for their occupational health and safety.

As is the case with any other health service, there are not enough medical practitioners available to perform these services. Thus the services are rendered by nurses. The Department of Health has designated some occupational health services in companies as health services in terms of section 56 (6) (d) of the Nursing Act. This enables the medical practitioner employed by such a service to authorise nurses to assess, diagnose, prescribe treatment, and keep and supply medication for prescribed illnesses and health-related conditions.

A nurse who is duly authorised in terms of this section may, in the course of duty, physically examine a person, keep prescribed medicines, prescribe, supply, and administer medicines under specified conditions. This may only be done when the services of a medical practitioner or pharmacist are not available, as the circumstances may require. Prescribing medication without the required authorisation is a criminal offence, and nurses who make themselves guilty of such an offence can be reported to the South African Nursing Council or the Department of Health.

### *The limitations of section 56 (6)*

A nurse in private practice cannot obtain the required legal authorisation to prescribe medication unless there is some kind of employment relationship with a designated organisation. For example, a nurse in private practice who has a contract with a local authority or provincial department of health to deliver services (usually childhood immunisation services) on behalf of the authority or department is in such an employment relationship. The authority or department provides the nurse with the required medication free of charge on condition that the nurse does not charge the patient for the medication, and provides the authority or department with a record of the services delivered. The local authority or provincial health service provides the authorisation to prescribe the medication as it would for any of its other employees. The authority or health service then allows the nurse to charge a consultation fee for professional services rendered and any consumables used during the consultation. It is strongly recommended that a nurse in such a situation obtain a written agreement from the particular authority or service.

- Nurses in the South African National Defence Force, the mining industry and the Department of Correctional Services are excluded as they are governed by other laws and are therefore not supervised by the Director-General of Health.
- Provision is made for physical diagnosis and assessment only, thus excluding the diagnosis and assessment of mental disorders.
- Authorisation can only be granted in the absence of a medical doctor or pharmacist. This is in contradiction to the Government's health policy, where it is not physically possible for one medical practitioner to assess hundreds of patients that may be attending the clinic. To ensure that an effective service is rendered, nurses need to be legally authorised to provide a comprehensive service.

The person who has been delegated the task of authorising the nurses in the relevant services to diagnose and prescribe medication will at least have to consider the following aspects before issuing the authorisation:

- The nurse must meet all the legal requirements of section 56 of the Nursing Act (No. 33 of 2005), namely that he or she must be working for one of the Department of Health's primary healthcare services, a municipality or an organisation designated to perform such a health service, and be registered as a nurse with the South African Nursing Council (SANC).
- The nurse must have successfully completed a prescribed course accredited by the SANC that gives her or him:
  - A qualification in the assessment, diagnosis, and prescribing of treatment, the keeping and supplying of medication for prescribed illnesses and related conditions.
  - The ability to recognise the symptoms of the most prevalent diseases in the country.
  - Assessment and diagnosing skills, prescribing skills and the ability to respond to the demands of the Essential Drugs Programme by supporting other healthcare professionals and receiving support from them.

This requires a knowledge of the relevant aspects of pharmacology and pharmacokinetics, including drug interactions, the drug–patient relationship, drug supply management, drug procurement, storage, supply, control and maintenance. It also requires communication skills and a knowledge of all relevant legislation, as well as the limitations of the nursing profession.

### *Regulatory requirements for a prescription*

Regulation 28 of the General Regulations (R.510) made in terms of the Medicines and Related Substances Act (1965, as amended) clearly states the requirements for a legal order or a prescription for medicine. The order or prescription should be

written in legible and indelible print, or be typewritten or computer-generated, and be signed by the medical practitioner, dentist, veterinarian, or authorised prescribing practitioner (e.g. the nurse); or the person who has been duly authorised to place an order. It should at least state the following:

- The name, qualifications, practice number and address of the prescribing practitioner[1]
- The name and address of the patient (for a prescription)
- The date of issue of the order or prescription
- The approved generic name or the proprietary name of the medicine
- The dosage form
- The strength of the active ingredient(s) contained in the dosage form, as necessary, and the **quantity** of the medicine to be supplied
- The instructions for the administration of the specified dosage form and the frequency of the administration (for a prescription)

And for prescriptions:

- The age and sex of the patient (especially important in the case of children and the elderly). Also note that the patient's body weight and/or body mass index (BMI) may be desirable for accurate dosage calculations to be made.
- The number of times that the prescription may be repeated (if applicable and allowed).

Furthermore, take note of the following:

- The signature of the prescribing practitioner **must** be handwritten.
- In the case of substances with a high potential for abuse and where the likelihood exists that prescriptions may be altered to exaggerate the quantities or dosage strengths to be supplied (e.g. Schedule 5 and 6 substances), the quantities should preferably be written in both symbols and words.

When a prescription is sent by fax, email, telephone or electronic transmission, the dispenser has to verify its authenticity. A permanent record must be made of the prescription. The original prescription must follow within seven working days. In the case of a verbal instruction (i.e. a telephonic prescription) the treatment period may not exceed seven days. However, in the case of a Schedule 5 or Schedule 6 substance, the verbal instruction may only be given for a maximum treatment period of 48 hours and must be signed by the prescribing practitioner within 72 hours.

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1 In the case of an order, the particulars of the person who has been duly authorised to place such an order.

The General Regulations do not provide any specific guidelines for receiving telephonic orders. Therefore, it is recommended that the following guideline be followed in the clinical practice setting:

> A telephonic order must be written down upon receipt and then read back to the prescribing practitioner and signed by the person taking down the prescription. A second person should preferably be available to verify the process and co-sign the prescription. Healthcare institutions may also have specific guidelines or policy documents on the exact procedure to be followed.

### *Education and training*

The education and training of practitioners to diagnose and to prescribe medication, and, in some cases, to dispense the medication, is crucial. Nurses or midwives will always remain accountable for all their own acts and omissions, and must have the competency required to deliver the health services for which they are responsible. Support systems and adequate facilities must be put in place to enable nurses and midwives to deliver a comprehensive service of consistently high quality. Nurses and midwives are required to do a course in health assessment, treatment and care, as well as a dispensing course accredited by the SAPC in case they are ever required to dispense medication. However, the mere successful completion of any of these courses does not entitle the nurse or midwife to be registered as a prescriber or a dispenser.

### *The Scope of Practice regulations*

In terms of these regulations (R.2598 of 30 November 1984, as amended), the following acts or procedures relating to diagnosing and prescribing fall within a professional nurse's scope of practice:

- Diagnosing health needs and prescribing, providing for and executing nursing regimens to meet patients' needs or, where necessary, referring the case to a registered person;
- Executing programmes of treatment or medication prescribed by a registered person;
- Treating patients, caring for them, administering medicine, and monitoring patients' vital signs and their reaction to disease conditions, trauma, stress, anxiety, medication and treatment; and
- Preventing disease and promoting health and family planning by teaching and counselling individuals and groups.

The exact definition of the term 'nursing and midwifery regimen' is the greatest limiting factor in the legal authorisation of nurses and midwives to diagnose

and to prescribe medication. The scope of practice is currently being revised to accommodate the changed healthcare needs of the country.

### 14.2.2 The Pharmacy Act (No. 53 of 1974, as amended)

The Pharmacy Act stipulates that any person who is not registered as a pharmacist and who performs any act for gain that specifically pertains to the profession of a pharmacist is guilty of an offence. Only a pharmacist may sell or supply medicine that a medical practitioner has prescribed.

An exception provided for is that hospitals and other institutions for the treatment of sick persons may keep medicines and supply them to patients. In such situations, a registered nurse may supply medication to a patient under the direction of a medical practitioner and in accordance with the provisions of the Pharmacy Act (No. 53 of 1974, as amended), section 29. This section also gives nurses in the armed forces the legal authority to handle medication and supply it to members of the forces. In terms of this section, a person can further be granted the authority to perform a service specifically falling within a pharmacist's scope of practice, under conditions determined by the Minister of Health.

### 14.2.3 The Health Professions Act (No. 56 of 1974, as amended)

This Act stipulates that only persons registered under it may diagnose and prescribe for gain, unless another Act makes provisions to the contrary. Therefore the Act does not preclude nurses from performing the services they are entitled to perform by virtue of their professional status. This includes diagnosing and prescribing medicine, as the Nursing Act makes provision for such activities as a special concession.

### 14.2.4 The Medicines and Related Substances Act (No. 101 of 1965, as amended)

The Medicines and Related Substances Act establishes the legal framework in terms of which all healthcare practitioners may handle or dispense medicines and related substances. Section 22A (17) (a) includes nurses among the 'authorised prescribing practitioner(s)'.

#### *Permits to acquire, keep, use and supply drugs*

Section 22A (15) of the Medicines and Related Substances Act (No. 101 of 1965, as amended) states that the Director-General may issue a permit:

- To any person or organisation performing a health service;
- Authorising such a person to acquire, possess, use and supply medication, keeping in mind the obligation of section 22C;
- For specified Schedule 1 to Schedule 5 substances;

- In consultation with the South African Pharmacy Council; and
- Subject to such conditions as the Director-General may determine.

To obtain a permit, the practitioner must complete an application form and submit it to the National Department of Health. The premises where the medication will be stored will be inspected before the permit is considered for approval. Permits will be issued only when the Director-General has established that it is needed. A section 22A (15) permit does not allow the practitioner:

- To *sell* medicine, but only to *supply* medicines;
- To access all medicines, but only certain Schedule 1 to Schedule 5 drugs included in the Government's Essential Drugs List (EDL); nor
- To prescribe medication. Provision to prescribe medication will be made in the Acts governing the relevant health professions. Section 56 of the Nursing Act only provides for *nurses* to diagnose and prescribe, and not for any other practitioner.

### *Licensing to compound and dispense*

The Amendment Act of 1997 distinguishes between the skills of prescribing and dispensing. Section 22C (1) states that the Director-General of Health may issue a licence to compound and dispense medication to a medical practitioner, a dentist, a practitioner, a nurse or any other person registered under the Health Professions Act (No. 56 of 1974).

Applicants have to complete a dispensing course before their applications will be considered. The outcomes of this course must include the following abilities:

- Identifying and applying ethical, legal and therapeutic standards in all aspects of dispensing;
- Evaluating prescriptions and assessing patient profiles;
- Dispensing prescriptions;
- Managing the procurement and storage of medicines; and
- Advising patients to ensure the quality use of medicine and to improve their health status.

Applicants for the licence have to apply on the prescribed form and pay the prescribed fee. They must have completed a supplementary course accredited by the SA Pharmacy Council in consultation with the SA Nursing Council, the Health Professions Council of SA, and the Allied Health Professions Council of SA. The application form asks for information on the applicant, the location of the business, the accessibility of the applicant's service and the distance of the business from hospitals, pharmacies and other health services in its vicinity. The applicant must also provide information on the geographical area and the population to be served, including the specific population's disease patterns and health status. An applicant must show that the service is needed, and the application must be

accompanied by proof that a notice has been published in a relevant newspaper circulating in the area in which the applicant plans to conduct business.

If the Director-General approves the application, the licensee has to pay a licensing fee. The licence is valid for three years from the date of issue. Should the application be turned down, the Director-General must give the applicant a reason for not awarding the licence. The applicant may appeal against such a decision.

A nurse or midwife who has been granted a licence to compound and dispense will be able to sell drugs in accordance with the policy of the institution where he or she works. Another important point that must be kept in mind is that the legislation **obliges** dispensers to consider dispensing interchangeable multi-source medicines (i.e. generic equivalents) if the prescribing practitioner has not forbidden such a substitution.

## Summary

The Medicines and Related Substances Act (No. 101 of 1965, as amended) and the different Acts governing the various health professions inform us of the **general** rule. This rule states that medical practitioners, dentists, veterinary surgeons and some allied health practitioners may prescribe medication; that pharmacists and some of the allied health practitioners may prepare and dispense prescribed medication; that nurses may administer the medication; and that all of these health practitioners should evaluate the effectiveness thereof.

The Medicines and Related Substances Act (No. 101 of 1965, as amended) recognises practitioners registered with the South African Nursing Council in terms of section 31 (1) (a), (b) and (c) of the Nursing Act (No. 33 of 2005) as prescribers of medication provided that they are also recognised and registered by the Nursing Council to do so.

The authorisation of nurses and midwives to assess, diagnose, prescribe treatment, keep and supply medication is a special **concession** awarded in terms of the Nursing Act (No. 33 of 2005): In terms of section 56 (1), persons registered in terms of section 31 (1) (a), (b) and (c) may be registered with the SA Nursing Council to assess, diagnose, prescribe treatment, keep and supply medication for prescribed illnesses and health conditions provided that they:

- Provide proof of having successfully completed a prescribed training programme;
- Pay the prescribed fee; and
- Work in a public health service or designated private health service.

Such registered practitioners must comply with the provisions of the Medicines and Related Substances Act (No. 101 of 1965, as amended) which includes provisions for:

- A section 22A (15) **permit** to acquire, possess, use and supply certain drugs;

- A section 22C **licence** to compound and dispense medication where appropriate.

Notwithstanding these provisions, the Director-General of Health, or the head of the relevant health service, can authorise nurses in terms of section 56 (6) of the Nursing Act (No. 33 of 2005) to physically examine, diagnose a physical condition or illness, prescribe treatment or keep and supply medication where the situation may require them to do so.

A diagrammatic summary of the legal framework for prescribing and dispensing by nurses in South Africa is provided in figure 14.2.

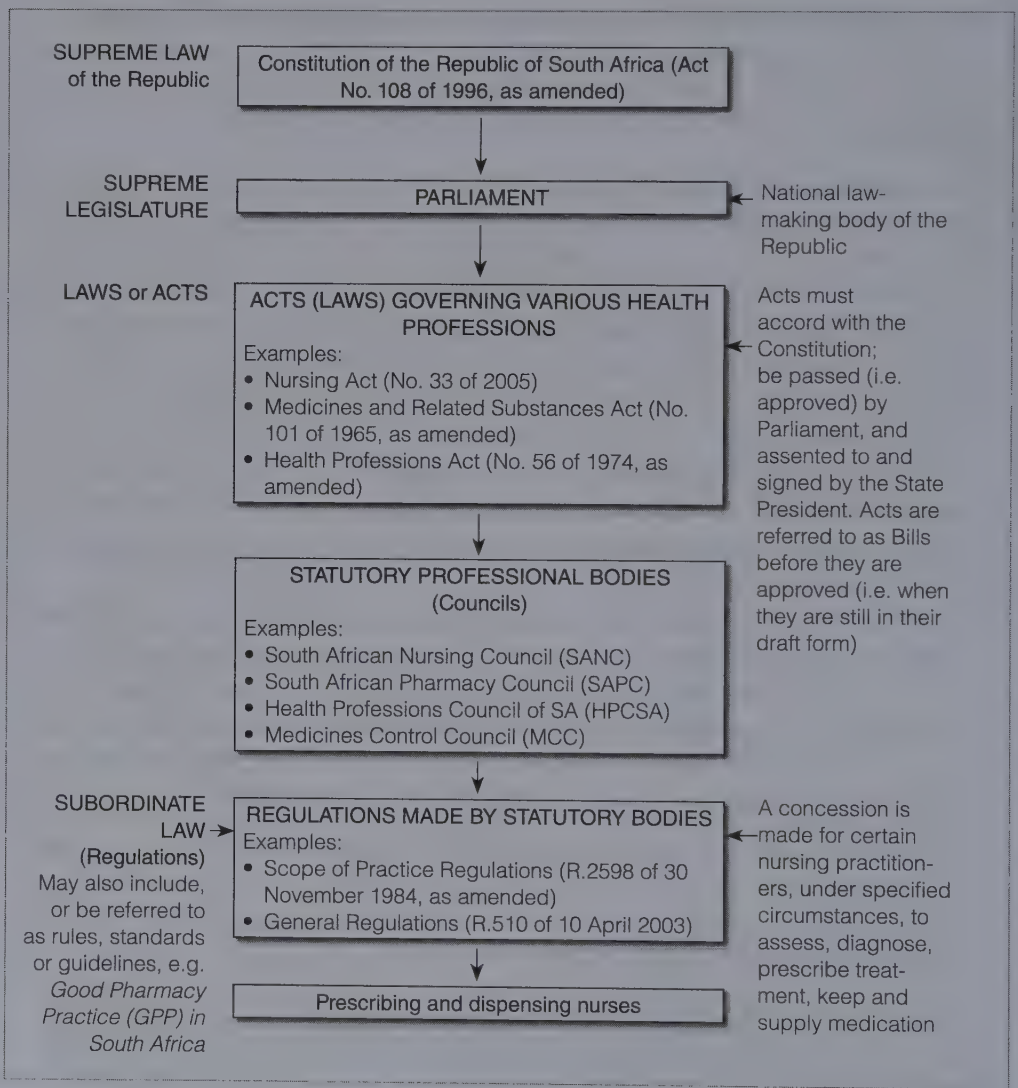


**Figure 14.2 The legal framework for prescribing and dispensing by nurses in South Africa**

# Annexure A

## List of essential medicines or drugs at primary healthcare level in South Africa

The list below has been adapted from the Standard Treatment Guidelines and Essential Medicines List for South Africa: Primary Health Care Level, 2008 edition. It is important to note that this list has been edited for ease of reference.

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| **A:** | |
| ACE-inhibitor (e.g. enalapril) | ➲ ACE-inhibitors (such as enalapril and perindopril) are used as part of a step-wise approach to the management of CCF and HT in adult patients, combined with diuretics and other suitable agents. ACE-inhibitors are contraindicated during pregnancy, and in aortic valve stenosis, bilateral renal artery stenosis and patients with a history of angioedema.<br>➲ They may also be used for proteinuria associated with chronic kidney disease (by blocking the effects of angiotensin II on the efferent arterioles, glomerular hypertension may be addressed → this decreases proteinuria and helps to stabilise renal function).<br>➲ Also refer to chapter 6 and paragraph 12.3. |
| Acetazolamide | ➲ This is a carbonic anhydrase (CA) inhibitor. Acetazolamide and other CA-inhibitors reduce the production of aqueous humour in the eye (and therefore ↓ IOP) through their inhibition of an isoform of CA that is found in the ciliary body. They are used in the systemic treatment of acute glaucoma.<br>➲ Also refer to paragraphs 10.1 and 12.2.2. |
| Acetic acid/alcohol | ➲ A combination topical antimicrobial and disinfectant for diffuse otitis externa, instilled into the ear canal. A solution of acetic acid 2% in alcohol is used.<br>➲ Diffuse otitis media (as opposed to the furuncular form) does not usually require the use of an antibacterial agent. |
| Acyclovir (aciclovir) | ➲ Acyclovir (aciclovir) is a nucleoside analogue used in the treatment of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections.<br>➲ It is only converted to its active form within virus-infected cells. |
| Activated charcoal | ➲ Activated charcoal is used in the management of poisoning with ingested substances or drug overdose, where it acts as an adsorptive substance.<br>➲ Activated charcoal should not be used in cases of poisoning with volatile hydrocarbons (e.g. paraffin), strong acids or alkali, alcohols, lithium or other metals. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| Adrenaline | ➲ Adrenaline is a sympathomimetic agent, a non-selective α- and β-adrenergic receptor agonist.<br>➲ During resuscitation adrenaline may also be administered via an endotracheal tube (when intravenous access is not achievable). Adrenaline has a short half-life and dosages may therefore need to be repeated.<br>➲ Always dilute adrenaline for nebulisation in accordance with the relevant guidelines.<br>➲ Also refer to paragraph 5.2.1 and note 5.2. |
| Albendazole | ➲ Broad-spectrum anthelmintic agent for tapeworm infections, as well as sandworm (cutaneous larva migrans).<br>➲ Also refer to paragraph 11.5.3. |
| Allopurinol | ➲ Xanthine oxidase (XO) inhibitor for the treatment of chronic gout.<br>➲ Also refer to paragraph 10.2 and figure 3.2. |
| Alpha-1 and non-selective beta-blocker | ➲ See carvedilol. |
| Aluminium hydroxide/ magnesium trisilicate | ➲ This antacid combination may be used for dyspepsia, heartburn and indigestion.<br>➲ Antacids may interfere with the absorption of some orally-administered medicines.<br>➲ Also refer to paragraph 9.2.1. |
| Amitriptyline | ➲ Amitriptyline is a tricyclic antidepressant drug (see paragraph 5.1.3) and therefore a multipotent blocker (see paragraph 3.5), which explains why the tricyclic antidepressants are contraindicated in glaucoma and benign prostatic hyperplasia (BPH) and they are unsuitable for use in cardiac patients. They may cause a dry mouth, blurred visions and urinary retention, and they are cardiotoxic (and potentially lethal) in overdose.<br>➲ Amitriptyline may also be used in the management of post-herpetic neuralgia, or if the pain associated with the shingles does not respond to a combination of paracetamol and tramadol, and as adjuvant (add-on) therapy in adult patients with chronic pain. |
| Amlodipine | ➲ Amlodipine is a long-acting calcium-channel blocker (CCB), belonging to the dihydropyridine group of CCBs.<br>➲ Also refer to paragraphs 6.3 and 12.3. |
| Amoxicillin | ➲ Amoxicillin is an aminopenicillin (i.e. a β-lactam antibacterial).<br>➲ Also refer to paragraph 11.3.1. |
| Amoxicillin/clavulanic acid | ➲ Also referred to as co-amoxiclav, this is a combination of amoxicillin and the β-lactamase inhibitor, clavulanic acid (see paragraph 11.3.1). For the primary healthcare sector the following formulations are listed:<br>● Adults: tablets that contain 250 mg of amoxicillin and 125 mg of clavulanic acid (i.e. 375 mg of co-amoxiclav), or 500 mg of amoxicillin and 125 mg of clavulanic acid (i.e. 625 mg of co-amoxiclav). If higher dosages of amoxicillin are required, then amoxicillin capsules of the required strength should be added, up to a maximum of 750 mg of amoxicillin every eight hours. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| | ● Children: suspensions containing either 125 mg of amoxicillin and 31.25 mg of clavulanic acid per 5 ml, or 250 mg of amoxicillin and 62.5 mg of clavulanic acid per 5 ml. These suspensions are dosed according to the amoxicillin component (on a milligram-per-kilogram basis). |
| Amphotericin B | ➲ This is a polyene antifungal agent.<br>➲ Lozenges (troches) are used for the treatment of oral candidiasis (thrush) in adult patients.<br>➲ Also refer to paragraph 11.4.3. |
| Antazoline/tetrahydrozoline HCl | ➲ Antazoline is an antihistamine that has been combined with the sympathomimetic agent, tetrahydrozoline (or tetryzoline), which acts as an $\alpha_1$-receptor agonist and therefore as a conjuctival decongestant.<br>➲ Also refer to paragraph 5.2.1. |
| Anti-D immunoglobulin | ➲ Immunosuppressive antibodies used in the prophylaxis in Rh(D)-negative, non-sensitised women (mothers) following a miscarriage or childbirth.<br>➲ Anti-D immunoglobulin is used to prevent haemolytic disease of the newborn (a condition in which antibodies from an Rh(D)-negative mother cross the placental barrier and causes damage to the red blood cells of an Rh(D)-positive foetus) by preventing Rh(D)-negative mothers from becoming sensitised to the D-antigen. |
| Antifungal lozenge (troche) | ➲ See amphotericin B. |
| Aqueous cream (UEA) | ➲ UEA is an emollient. Emollients soften and soothe the skin.<br>➲ UEA is a semisolid emulsion, whereas UE (emulsifying ointment) is a semisolid, greasy preparation. |
| Artemether/lumefantrine | ➲ Antimalarial combination for the treatment of malaria.<br>➲ **Always consult the latest guidelines for the treatment of malaria.** |
| Aspirin | ➲ Non-steroidal anti-inflammatory drug (NSAID), a non-selective COX-inhibitor.<br>➲ In low daily dosages (i.e. in the range of 75 to 150 mg per day) aspirin will selectively inhibit COX-1 (and therefore also platelet aggregation).<br>➲ These treatment guidelines recommend dosages of 150 mg per day.<br>➲ Also see paragraph 7.3 and figure 7.1B. |
| Atenolol | ➲ Beta-adrenergic receptor blocker, water-soluble and cardioselective.<br>➲ Atenolol and other β-blockers are absolutely contraindicated in asthma and COPD, and relatively contraindicated in insulin-dependent diabetes mellitus and peripheral vascular disease, as well as bradycardia. It should also not be used in patients with congestive cardiac failure (where carvedilol is better suited).<br>➲ Also see paragraph 5.2.2. |
| Atropine | ➲ Parasympatholytic agent, anti-cholinergic (anti-muscarinic).<br>➲ Also see paragraph 5.2.4. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| **B:** | |
| Bacillus Calmette-Guérin (BCG) vaccine | ➲ Refer to the relevant guidelines on cold chain management, storage and handling of vaccines.<br>➲ **Always consult the latest vaccination guidelines and childhood immunisation schedule (as needed).** |
| Beclomethasone | ➲ Glucocorticosteroid.<br>➲ Refer to paragraph 7.2 and table 7.1. |
| Benzathine benzylpenicillin (benzathine penicillin G) | ➲ β-lactam antibacterial agent, penicillin.<br>➲ This is an intramuscular depot formulation (to extend the plasma half-life of penicillin G).<br>➲ Also refer to paragraph 11.3.1. |
| Benzoyl peroxide | ➲ Topically applied preparation used to treat acne vulgaris. |
| Benzyl benzoate | ➲ Ectoparasiticide used for scabies and pediculosis.<br>➲ Also refer to paragraph 11.5.4. |
| Benzylpenicillin (penicillin G) | ➲ β-lactam antibacterial agent, penicillin.<br>➲ Also refer to paragraph 11.3.1. |
| Beta-agonist | ➲ See salbutamol. |
| Beta-blocker | ➲ See atenolol. |
| Betamethasone | ➲ Glucocorticosteroid.<br>➲ Refer to paragraph 7.2 and table 7.1. |
| Biguanide | ➲ See metformin. |
| Biperiden | ➲ Anti-muscarinic (anti-cholinergic) agent for the management of extrapyramidal side-effects and acute dystonic reactions in patients on antipsychotic medication.<br>➲ Also refer to paragraph 5.1.4. |
| Bismuth subgallate compound | ➲ Symptomatic treatment of anal fissures and painful haemorrhoids. |
| Budesonide | ➲ Glucocorticosteroid.<br>➲ Refer to paragraph 7.2 and table 7.1. |
| **C:** | |
| Calamine | ➲ Applied to the skin as an anti-pruritic agent (i.e. to provide symptomatic relief of itching). |
| Calcium | ➲ Mineral supplement.<br>➲ Calcium gluconate 10% is also given intravenously to counteract the effects of magnesium toxicity. |
| Calcium-channel blocker (CCB), long-acting | ➲ See amlodipine and nifedipine. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| Carbamazepine | ➲ Anti-epileptic agent.<br>➲ Also refer to paragraph 5.1.6. |
| Carvedilol | ➲ $\alpha_1$ and non-selective β-blocker.<br>➲ Also refer to paragraphs 5.2.2 and 6.2. |
| Cefixime | ➲ Cephalosporin (i.e. a β-lactam antibacterial agent), 3rd generation.<br>➲ Also refer to paragraph 11.3.2. |
| Ceftriaxone | ➲ Cephalosporin (i.e. a β-lactam antibacterial agent), 3rd generation.<br>➲ Ceftriaxone is not compatible with calcium-containing solutions.<br>➲ Also refer to paragraph 11.3.2. |
| Cetirizine | ➲ A selective $H_1$-receptor blocker (i.e. a non-sedating antihistamine).<br>➲ Also refer to paragraph 12.5.1. |
| Chloramphenicol | ➲ A broad-spectrum antimicrobial agent.<br>➲ Also refer to paragraph 11.3.7. |
| Chlorhexidine | ➲ Antiseptic agent. |
| Chlorpheniramine | ➲ This is an older-type, sedating antihistamine with multi-potent blocking properties.<br>➲ Also refer to paragraph 12.5.1. |
| Chlorpromazine | ➲ Typical (first-generation) antipsychotic agent (a phenothiazine, belonging to the aliphatic group).<br>➲ Also refer to paragraph 5.1.5. |
| Choline salicylate/ cetalkonium chloride | ➲ This is an oral gel formulation that contains choline salicylate, which is used as a local analgesic agent, combined with cetalkonium chloride, which is an antiseptic agent. |
| Cimetidine | ➲ Selective $H_2$-receptor blocker.<br>➲ Also refer to paragraph 9.2.2. |
| Ciprofloxacin | ➲ Fluoroquinolone antibacterial agent.<br>➲ Also refer to paragraph 11.3.12. |
| Clotrimazole | ➲ An azole antifungal agent, belonging to the imidazole group.<br>➲ Also refer to paragraph 11.4.5. |
| Codeine | ➲ Opioid analgesic.<br>➲ Refer to paragraph 5.1.1. |
| Corticosteroids | ➲ See the various glucocorticosteroids (e.g. beclomethasone and betamethasone). |
| Co-trimoxazole (trimethoprim-sulphamethoxazole, or TMP-SMX) | ➲ Combination antimicrobial agent (trimethoprim, or TMP, combined with sulphamethoxazole, or SMX).<br>➲ The combination is synergistic and an example of the sequential blocking of a metabolic process that is essential to micro-organisms.<br>➲ Also refer to paragraph 11.3.13. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| **D:** | |
| Dextrose 10% | ➲ Solution for oral or intravenous administration.<br>➲ Dextrose is the naturally-occurring or biologically active D-form of glucose (D-glucose, or dextrose) and is used to treat carbohydrate (and fluid) depletion. |
| Dextrose 5% | ➲ Solution for intravenous administration, crystalloid.<br>➲ The 5% concentration is iso-osmotic with blood.<br>➲ Dextrose is the naturally-occurring or biologically active D-form of glucose (D-glucose, or dextrose) and is used to treat carbohydrate (and fluid) depletion. |
| Dextrose 5%/sodium chloride 0.9% | ➲ Solution for intravenous administration, crystalloid.<br>➲ Dextrose is the naturally-occurring or biologically active D-form of glucose (D-glucose, or dextrose) and is used to treat carbohydrate (and fluid) depletion. |
| Dextrose 50% | ➲ Solution for intravenous administration.<br>➲ Solutions containing more than 10% dextrose should preferably not be administered through a peripheral vein.<br>➲ Dextrose is the naturally-occurring or biologically active D-form of glucose (D-glucose, or dextrose) and is used to treat carbohydrate (and fluid) depletion. |
| Diazepam | ➲ Benzodiazepine, long-acting.<br>➲ Also refer to paragraph 5.1.2. |
| Didanosine (ddI) | ➲ Antiretroviral (ARV) agent, nucleoside reverse transcriptase inhibitor (NRTI).<br>➲ Use as part of a suitable HAART-regimen. **Always consult the latest treatment guidelines.**<br>➲ Refer to paragraph 11.6. |
| Digoxin | ➲ Digoxin is a cardiac glycoside.<br>➲ Also refer to paragraph 6.1. |
| Diphtheria/tetanus/ pertussis vaccine (DTP) | ➲ Refer to the relevant guidelines on cold chain management, storage and handling of vaccines.<br>➲ **Always consult the latest vaccination guidelines and childhood immunisation schedule (as needed).** |
| Doxycycline | ➲ Tetracycline antimicrobial agent.<br>➲ Also refer to paragraph 11.3.8. |
| **E:** | |
| Efavirenz (EFV) | ➲ Antiretroviral (ARV) agent, non-nucleoside reverse transcriptase inhibitor (NNRTI).<br>➲ Use as part of a suitable HAART-regimen. **Always consult the latest treatment guidelines.**<br>➲ Refer to paragraph 11.6. |
| Emulsifying ointment (UE) | ➲ Emulsifying ointment is an emollient. Emollients soften and soothe the skin.<br>➲ UEA is a semisolid emulsion, whereas UE (emulsifying ointment) is a semisolid, greasy preparation. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| Enalapril | ➲ See ACE-inhibitor. |
| Ergometrine | ➲ This is an ergot alkaloid and is used to control bleeding from the uterus following delivery, abortion or curettage.<br>➲ Ergometrine produces intense contraction of the uterine smooth muscle, which is more prolonged than the rhythmic contractions that are induced by oxytocin. |
| Erythromycin | ➲ Macrolide antibacterial agent.<br>➲ Also refer to paragraph 11.3.4. |
| Ethambutol | ➲ Antimycobacterial agent, first-line.<br>➲ Also refer to paragraph 11.3.14. |
| **F:** | |
| Ferrous gluconate | ➲ Iron supplement. |
| Ferrous lactate | ➲ Iron supplement. |
| Ferrous sulphate compound (BPC) | ➲ Iron supplement. |
| Flucloxacillin | ➲ β-lactam antibacterial agent, penicillinase-resistant penicillin (PRP).<br>➲ Also refer to paragraph 11.3.1. |
| Fluconazole | ➲ An azole antifungal agent, belonging to the triazole group.<br>➲ Also refer to paragraph 11.4.5. |
| Fluoxetine | ➲ Selective serotonin re-uptake inhibitor (SSRI).<br>➲ Also refer to paragraph 5.1.3. |
| Flupenthixol decanoate | ➲ Typical (first-generation) antipsychotic agent (a thioxanthene).<br>➲ This is a depot formulation.<br>➲ Also refer to paragraph 5.1.5. |
| Fluphenazine decanoate | ➲ Typical (first-generation) antipsychotic agent (a phenothiazine, belonging to the piperazine group).<br>➲ This is a depot formulation.<br>➲ Also refer to paragraph 5.1.5. |
| Folic acid | ➲ Vitamin supplement. |
| Furosemide | ➲ Loop diuretic.<br>➲ Also refer to paragraphs 6.2 and 10.1. |
| **G:** | |
| Gentian violet | ➲ Also known as crystal violet or methylrosanilinium chloride, gentian violet may be used as a topical antifungal preparation (especially in the case of yeast infections such as oral thrush). |
| Glibenclamide | ➲ Oral anti-diabetic agent (a sulphonylurea).<br>➲ Refer to paragraph 12.4.2. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| Gliclazide | ➲ Oral anti-diabetic agent (a sulphonylurea).<br>➲ Refer to paragraph 12.4.2. |
| **H:** | |
| *Haemophilus influenzae* type b vaccine (Hib) | ➲ Refer to the relevant guidelines on cold chain management, storage and handling of vaccines.<br>➲ **Always consult the latest vaccination guidelines and childhood immunisation schedule (as needed).** |
| Haloperidol | ➲ Typical (first-generation) antipsychotic agent (a butyrophenone).<br>➲ Also refer to paragraph 5.1.5. |
| Hepatitis B vaccine (Hep B) | ➲ Refer to the relevant guidelines on cold chain management, storage and handling of vaccines.<br>➲ **Always consult the latest vaccination guidelines and childhood immunisation schedule (as needed).** |
| HMG-CoA-reductase inhibitors ('statins') (e.g. simvastatin) | ➲ See simvastatin. |
| Hydrochlorothiazide | ➲ As the name implies, this is a thiazide diuretic.<br>➲ Also refer to paragraphs 6.2, 10.1 and 12.3. |
| Hydrocortisone | ➲ Glucocorticosteroid.<br>➲ Refer to paragraph 7.2 and table 7.1. |
| Hyoscine butylbromide | ➲ Parasympatholytic agent, anti-muscarinic.<br>➲ This drug is also referred to as N-butylhyoscine or hyoscine N-butylbromide and does not cross the BBB.<br>➲ Also refer to paragraphs 5.2.4 and 9.2.3. |
| **I:** | |
| Ibuprofen | ➲ Non-steroidal anti-inflammatory drug (NSAID), a non-selective COX-inhibitor.<br>➲ Also see paragraph 7.3 and figure 7.1B. |
| Imidazole | ➲ See clotrimazole. |
| Influenza vaccine | ➲ Refer to the relevant guidelines on cold chain management, storage and handling of vaccines.<br>➲ **Always consult the latest vaccination guidelines and childhood immunisation schedule.** |
| Insulin, biphasic | ➲ Biphasic insulin is a combination of intermediate-acting and short-acting insulin (i.e. a premixed or ready-mixed insulin preparation).<br>➲ Refer to paragraph 12.4.1. |
| Insulin, intermediate-acting | ➲ Refer to paragraph 12.4.1. |
| Insulin, soluble short-acting | ➲ Refer to paragraph 12.4.1. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| Iodine tincture BP | ➲ Antiseptic agent. |
| Ipratropium bromide | ➲ Parasympatholytic agent, anti-muscarinic.<br>➲ This drug does not cause thickening of bronchial secretions.<br>➲ Also refer to paragraphs 5.2.4 and 8.1. |
| Iron | ➲ Iron supplement. |
| Isoniazid | ➲ Antimycobacterial agent, first-line.<br>➲ Also refer to paragraph 11.3.14. |
| Isosorbide dinitrate | ➲ Organic nitrate.<br>➲ Also refer to paragraph 6.3. |
| Isosorbide mononitrate | ➲ Organic nitrate.<br>➲ This is the active metabolite of isosorbide dinitrate.<br>➲ Also refer to paragraph 6.3. |
| **L:** | |
| Lactulose | ➲ Osmotic laxative.<br>➲ Also refer to paragraph 9.2.4. |
| Lamivudine (3TC) | ➲ Antiretroviral (ARV) agent, nucleoside reverse transcriptase inhibitor (NRTI).<br>➲ Use as part of a suitable HAART-regimen. **Always consult the latest treatment guidelines.**<br>➲ Refer to paragraph 11.6. |
| Lamotrigine | ➲ Anti-epileptic agent.<br>➲ Also refer to paragraph 5.1.6. |
| Levonorgestrel | ➲ Hormonal contraceptive agent, progestogen (progestin).<br>➲ Also refer to paragraph 10.3.1. |
| Levonorgestrel/ethinyl oestradiol | ➲ Combination oral contraceptive agent (hormonal).<br>➲ Also refer to paragraph 10.3.1. |
| Lignocaine | ➲ Also referred to as lidocaine, this is an amide-type local anaesthetic agent.<br>➲ Also refer to paragraph 5.2.6. |
| Loperamide | ➲ Non-analgesic opioid derivative.<br>➲ This drug is used to manage diarrhoea in adult patients (it is generally not recommended for paediatric use).<br>➲ Also refer to paragraph 9.2.3. |
| Lopinavir/ritonavir (LPV/rtv) | ➲ Antiretroviral (ARV) agent, combination of protease inhibitors (PIs); rtv is used to 'boost' the trough serum concentration of LPV.<br>➲ Use as part of a suitable HAART-regimen. **Always consult the latest treatment guidelines.**<br>➲ Refer to paragraph 11.6. |
| Lorazepam | ➲ Benzodiazepine, intermediate-acting.<br>➲ Also refer to paragraph 5.1.2. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| **M:** | |
| Magnesium sulphate | ➲ Mineral supplement.<br>➲ Intravenous magnesium sulphate is also used as part of the drug management of eclampsia (during pregnancy). |
| Measles vaccine | ➲ Refer to the relevant guidelines on cold chain management, storage and handling of vaccines.<br>➲ **Always consult the latest vaccination guidelines and childhood immunisation schedule (as needed).** |
| Mebendazole | ➲ Broad-spectrum anthelmintic agent for roundworm, pinworm, hookworm and whipworm infections.<br>➲ Also refer to paragraph 11.5.3. |
| Medroxyprogesterone | ➲ Hormonal contraceptive agent, progestogen (progestin) and hormone replacement therapy (HRT).<br>➲ Long-acting injectable formulation.<br>➲ Also refer to paragraph 10.3.1. |
| Metformin | ➲ Oral anti-diabetic agent (a biguanide).<br>➲ Refer to paragraph 12.4.2. |
| Methyl salicylate | ➲ Topical anti-inflammatory preparation for painful muscles, ligaments and joints. |
| Methyldopa | ➲ This is an $\alpha_2$-receptor agonist; a centrally-acting antihypertensive agent.<br>➲ Also refer to figure 4.4 and paragraph 5.2.2. |
| Metoclopramide | ➲ Metoclopramide acts as an antagonist at $D_2$- and 5-$HT_3$-receptors, and as an agonist at 5-$HT_4$-receptors.<br>➲ Also refer to paragraphs 9.2.1 and 12.1. |
| Metronidazole | ➲ A nitroimidazole antimicrobial agent.<br>➲ Also refer to paragraph 11.3.15. |
| Misoprostol | ➲ Synthetic prostaglandin $E_1$ ($PGE_1$) analogue.<br>➲ Also refer to paragraph 7.1. |
| Morphine | ➲ Opioid analgesic.<br>➲ Refer to paragraph 5.1.1. |
| Multivitamin | ➲ Vitamin supplement. |
| **N:** | |
| Naloxone | ➲ Naloxone is an opioid-receptor antagonist.<br>➲ Also refer to paragraph 5.1.1. |
| Nevirapine (NVP) | ➲ Antiretroviral (ARV) agent, non-nucleoside reverse transcriptase inhibitor (NNRTI).<br>➲ Use as part of a suitable HAART-regimen. **Always consult the latest treatment guidelines.**<br>➲ Refer to paragraph 11.6. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| Nicotinamide | ➲ Vitamin supplement. |
| Nifedipine, short-acting | ➲ This is a short-acting calcium-channel blocker (CCB), belonging to the dihydropyridine group of CCBs.<br>➲ Also refer to paragraphs 6.3 and 12.3. |
| Nifedipine, slow-release | ➲ This is a long-acting calcium-channel blocker (CCB), belonging to the dihydropyridine group of CCBs.<br>➲ However, the slow-release formulation prolongs its duration of activity.<br>➲ Also refer to paragraphs 6.3 and 12.3. |
| Nitrous oxide ($N_2O$) | ➲ An inhalant anaesthetic agent.<br>➲ Also refer to paragraph 5.1.7. |
| Norethisterone enanthate (enantate) | ➲ Hormonal contraceptive agent, progestogen (progestin).<br>➲ Long-acting injectable formulation.<br>➲ Also refer to paragraph 10.3.1. |
| Norgestrel/ethinyl oestradiol | ➲ Combination oral contraceptive agent (hormonal).<br>➲ Also refer to paragraph 10.3.1. |
| NSAID | ➲ See ibuprofen and aspirin. |
| Nystatin | ➲ This is a polyene antifungal agent.<br>➲ Nystatin cannot be used for systemic treatment.<br>➲ Also refer to paragraph 11.4.3. |
| **O:** | |
| Oestradiol | ➲ Hormone replacement therapy (HRT).<br>➲ Also refer to paragraph 10.3.1. |
| Oestrogen, conjugated | ➲ Hormone replacement therapy (HRT).<br>➲ Also refer to paragraph 10.3.1. |
| Oral polio vaccine (OPV) | ➲ Refer to the relevant guidelines on cold chain management, storage and handling of vaccines.<br>➲ **Always consult the latest vaccination guidelines and childhood immunisation schedule (as needed).** |
| Oral rehydration solution (ORS) | ➲ A solution containing glucose and electrolytes for rehydration. |
| Orphenadrine | ➲ Anti-muscarinic (anti-cholinergic) agent for the management of extrapyramidal side-effects in patients on antipsychotic medication.<br>➲ Also refer to paragraph 5.1.4. |
| Oxygen | ➲ Medical gas. |
| Oxymetazoline | ➲ Sympathomimetic agent, which specifically acts as an $\alpha_1$-receptor agonist and therefore as a vasoconstrictor and decongestant.<br>➲ Nasal drops may be used to relieve the blocked nose that is associated with acute bacterial sinusitis, and the eye drops may be used as a conjunctival decongestant in cases of allergic and viral conjunctivitis.<br>➲ Also refer to paragraph 5.2.1. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| Oxytocin | ➲ Oxytocin may be used to induce or augment labour, and to control bleeding from the uterus following delivery or abortion.<br>➲ Ergometrine produces intense contraction of the uterine smooth muscle, which is more prolonged than the rhythmic contractions that are induced by oxytocin. |
| **P:** | |
| Paracetamol | ➲ Paracetamol is also called acetaminophen and has antipyretic and analgesic (for mild to moderate pain) properties.<br>➲ Paracetamol is not effective as an anti-inflammatory agent.<br>➲ Also refer to paragraph 7.4. |
| Permethrin | ➲ Ectoparasiticide used for scabies and pediculosis.<br>➲ Also refer to paragraph 11.5.4. |
| Pethidine | ➲ Opioid analgesic.<br>➲ Refer to paragraph 5.1.1. |
| Petroleum jelly | ➲ Petroleum jelly may be used to protect the skin that surrounds warts when treating the latter with suitable topical agents, or to smother lice on the eyelid margins and eyebrows.<br>➲ It may also be used on dry, cracked (chaffed) lips, or to cover the lesions caused by the herpes simplex virus on the lips. |
| Phenobarbitone | ➲ Anti-epileptic agent (a barbiturate).<br>➲ Also refer to paragraph 5.1.6. |
| Phenoxymethylpenicillin (penicillin V) | ➲ β-lactam antibacterial agent, penicillin.<br>➲ Also refer to paragraph 11.3.1. |
| Phenytoin | ➲ Anti-epileptic agent.<br>➲ Also refer to paragraph 5.1.6. |
| Pilocarpine | ➲ Parasympathomimetic agent, a cholinergic alkaloid.<br>➲ This drug is used topically as a miotic in the management of acute glaucoma.<br>➲ Also refer to paragraphs 5.2.3 and 12.2. |
| Pneumococcal vaccine | ➲ Refer to the relevant guidelines on cold chain management, storage and handling of vaccines.<br>➲ **Always consult the latest vaccination guidelines and childhood immunisation schedule (as needed).** |
| Podophyllin solution | ➲ Podophyllin is synonymous with podophyllum.<br>➲ A tincture of podophyllin solution 20% is used in the management of genital warts.<br>➲ Protect the skin that surrounds the warts with petroleum jelly. |
| Podophyllum resin/ salicylic acid | ➲ This keratolytic combination is used in the management of plantar and common warts.<br>➲ Protect the skin that surrounds the warts with petroleum jelly. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| Polyvalent antivenom (snake) | ➲ An antiserum against the venom of certain snakes.<br>➲ The antivenom should only be used if and when indicated and the treatment guidelines need to be followed very carefully.<br>➲ Snake antivenom may elicit anaphylactic reactions and suitable precautionary measures need to be taken. |
| Povidone iodine | ➲ Antiseptic agent. |
| Praziquantel | ➲ This is the drug of choice in the management of bilharziasis (schistosomiasis).<br>➲ Also refer to paragraph 11.5.2. |
| Prednisone | ➲ Glucocorticosteroid.<br>➲ Refer to paragraph 7.2 and table 7.1. |
| Procaine penicillin G | ➲ β-lactam antibacterial agent, penicillin.<br>➲ This is an intramuscular depot formulation (to extend the plasma half-life of penicillin G).<br>➲ Also refer to paragraph 11.3.1. |
| Promethazine | ➲ Typical (first-generation) antipsychotic agent (a phenothiazine, belonging to the aliphatic group).<br>➲ Also refer to paragraph 5.1.5. |
| Pyrazinamide | ➲ Antimycobacterial agent, first-line.<br>➲ Also refer to paragraph 11.3.14. |
| Pyridoxine | ➲ Vitamin supplement (vitamin $B_6$). |
| **Q:** | |
| Quinine dihydrochloride | ➲ Used in the drug treatment of severe falciparum malaria.<br>➲ Also refer to paragraph 11.5.1.<br>➲ **Always consult the latest guidelines for the treatment of malaria.** |
| **R:** | |
| Rabies immunoglobulin | ➲ This immunoglobulin provides passive immunity against the rabies virus, as part of post-exposure prophylaxis, combined with the rabies vaccine. |
| Rabies vaccine | ➲ Refer to the relevant guidelines on cold chain management, storage and handling of vaccines.<br>➲ **Always consult the latest vaccination guidelines and childhood immunisation schedule (as needed).** |
| Rifampicin | ➲ Antimycobacterial agent, first-line.<br>➲ Also refer to paragraph 11.3.14. |
| Rifampicin/isoniazid combination | ➲ Combination of antimycobacterial agents, first-line.<br>➲ Also refer to paragraph 11.3.14. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| Rifampicin/ isoniazid/pyrazinamide combination | ➲ Combination of antimycobacterial agents, first-line.<br>➲ Also refer to paragraph 11.3.14. |
| Rifampicin/isoniazid/ pyrazinamide/ ethambutol combination | ➲ Combination of antimycobacterial agents, first-line.<br>➲ Also refer to paragraph 11.3.14. |
| Ringer's lactate | ➲ Solution for intravenous administration, crystalloid. |
| **S:** | |
| Salbutamol | ➲ Sympathomimetic, selective $\beta_2$-receptor agonist used as an inhalant bronchodilator.<br>➲ Salbutamol may also be used as an intravenous tocolytic agent (i.e. an agent that suppresses uterine contractions). See paragraph 4.6.2.<br>➲ Also refer to paragraph 8.1. |
| Selenium sulphide | ➲ A topical antifungal that may be used as a treatment for an itching, scaling scalp with dandruff, or tinea versicolor. |
| Sennosides A and B (senna) | ➲ Irritant or contact laxative.<br>➲ Also refer to paragraph 9.2.4. |
| Simple linctus | ➲ Cough preparation for children under the age of six years.<br>➲ Also refer to note 8.1. |
| Simvastatin | ➲ Simvastatin inhibits the enzyme HMG-CoA-reductase to effectively decrease total serum cholesterol levels, LDL-levels, as well as the VLDL-levels. It also increased HDL-levels to some extent.<br>➲ Also refer to paragraph 6.4. |
| Sodium chloride (normal saline) | ➲ Intravenous fluid, crystalloid (0.9 % NaCl). |
| Spironolactone | ➲ Aldosterone antagonist (diuretic agent, potassium-sparing).<br>➲ Also refer to paragraphs 6.2 and 10.1. |
| Stavudine (d4T) | ➲ Antiretroviral (ARV) agent, nucleoside reverse transcriptase inhibitor (NRTI).<br>➲ Use as part of a suitable HAART-regimen. **Always consult the latest treatment guidelines.**<br>➲ Refer to paragraph 11.6. |
| Streptokinase | ➲ Fibrinolytic agent.<br>➲ Also refer to paragraph 6.6.2. |
| Streptomycin | ➲ Antimycobacterial agent, first-line.<br>➲ Also refer to paragraph 11.3.14. |
| Sulphonylurea | ➲ See glibenclamide and gliclazide. |
| Sulphur | ➲ Sulphur 5% ointment is used to treat scabies in children less than six years of age, or when benzyl benzoate has failed to eradicate the scabies mite. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| **T:** | |
| Tenofovir (TDF) | ➲ Antiretroviral (ARV) agent, nucleotide reverse transcriptase inhibitor (NtRTI).<br>➲ Use as part of a suitable HAART-regimen. **Always consult the latest treatment guidelines.**<br>➲ Refer to paragraph 11.6. |
| Tetanus toxoid vaccine (TT) | ➲ Refer to the relevant guidelines on cold chain management, storage and handling of vaccines.<br>➲ **Always consult the latest vaccination guidelines and childhood immunisation schedule (as needed).** |
| Tetanus/diphtheria vaccine (Td) | ➲ Refer to the relevant guidelines on cold chain management, storage and handling of vaccines.<br>➲ **Always consult the latest vaccination guidelines and childhood immunisation schedule (as needed).** |
| Tetracaine | ➲ Also referred to as amethocaine, this is an ester-type local anaesthetic agent.<br>➲ Also refer to paragraph 5.2.6. |
| Theophylline | ➲ This is a non-selective phosphodiesterase (PDE) inhibitor (see figure 4.5).<br>➲ Also refer to paragraph 6.1.<br>➲ Aminophylline is the parenteral preparation of theophylline (namely theophylline ethylene diamine). |
| Thiamine | ➲ Vitamin supplement (vitamin $B_1$). |
| Tramadol | ➲ Opioid analgesic, low-affinity μ-agonist.<br>➲ Refer to paragraph 5.1.1. |
| Tussi infans | ➲ Cough preparation for children under the age of six years.<br>➲ Also refer to note 8.1. |
| **V:** | |
| Vaccines that have been added to the childhood immunisation schedule since the publication of the 2008 Essential Medicines List:<br>➲ Rotavirus vaccine<br>➲ Diphtheria, tetanus, acellular pertussis, inactivated polio vaccine and *Haemophilus influenzae* type b combination vaccine<br>➲ Pneumococcal conjugated vaccine | |
| Valproate | ➲ Anti-epileptic agent.<br>➲ Also refer to paragraph 5.1.6. |
| Vitamin A (retinol) | ➲ Vitamin supplement. |
| Vitamin B complex | ➲ Vitamin supplement. |
| Vitamin K | ➲ Vitamin supplement. |

| Essential drug or medicine, supplement, intravenous solution, or other product | Drug description and comments |
|---|---|
| **X:** | |
| ➲ Two entries have been deleted because of the incorrect use of a registered trade name. The two listed agents are local anaesthetics for dental use, one combined with, and one without adrenaline (as a vasoconstrictor).<br>➲ Also refer to paragraph 5.2.6. | |
| **Z:** | |
| Zidovudine (AZT) | ➲ Antiretroviral (ARV) agent, nucleoside reverse transcriptase inhibitor (NRTI).<br>➲ Use as part of a suitable HAART-regimen. **Always consult the latest treatment guidelines.**<br>➲ Refer to paragraph 11.6. |
| Zinc and castor oil | ➲ An ointment used to treat nappy (or diaper) rash. |
| Zinc | ➲ Mineral supplement. |
| Zuclopenthixol acetate | ➲ Typical (first-generation) antipsychotic agent (a thioxanthene).<br>➲ Also refer to paragraph 5.1.5. |
| Zuclopenthixol decanoate | ➲ Typical (first-generation) antipsychotic agent (a thioxanthene).<br>➲ This is a depot formulation.<br>➲ Also refer to paragraph 5.1.5. |

[Adapted from: The National Department of Health. 2008. Standard Treatment Guidelines and Essential Medicines List for South Africa: Primary Health Care Level. 2008 edition. Pretoria: The National Department of Health.]

# Annexure B

## Notes on patient adherence, or compliance with prescribed drug therapy

**Consider the following example:**

Patient PQR is a 42-year-old man who suffers from hypothyroidism and hypertension. On 4 January 2010 he received a prescription for *enalapril* 20 mg daily (as antihypertensive treatment), as well as 100 mcg of *thyroxine* daily (as thyroid hormone replacement therapy). He was given a 4-week supply of each drug, instructed to take the first dosage of each immediately, and requested to return to the clinic on the 1st of February 2010.

At his follow-up visit the prescribing practitioner decided to check his compliance (adherence) to the prescription and asked him about his treatment and whether he was taking his medication regularly and as prescribed. He was very positive about his treatment and claimed that he felt a lot better. However, he also mentioned that he still had two of his 'blood pressure pills' and five of his 'thyroid pills' left over, after he had taken one of each that morning. He stated that he found it difficult remembering to take his medication every single day.

**Calculating his compliance with the prescribed treatment:**

- Patient PQR received 28 tables of each drug (i.e. a 4-week supply of each, since he only needed to take one tablet of each drug daily).
- He started taking his medication of 4 January 2010. Therefore he should have taken the 28th tablet of each drug on the 31st of January 2010 (requiring a re-supply on the 1st of February 2010).
- However, he had some tablets left over at home, and took one of each on the morning of 1 February 2010.
- Therefore, he did not take all of his medication as prescribed. From the 4th to the 31st of January 2010 (i.e. 28 days), he only took 25 tablets of *enalapril* (since he took one on the 1st of February and had two left at home), and 22 tablets of *thyroxine* (since he took one on the 1st of February and had five left at home).
- Thus, his compliance for the *enalapril* was [(25/28) × 100] = 89%, and for the *thyroxine* it was [(22/28) × 100] = 79%.

There are numerous factors that may influence the degree of compliance (adherence) that patients will have with their prescribed treatment, including (but not limited to) the following:

- The ease of taking the medication, the ability to swallow the tablets or capsules, or to be injected, for example.
- The taste of oral formulations, or other unpleasant or bothersome obstacles, such as topical preparations that stain the skin or clothing, or medication that discolours bodily secretions.

- Adverse effects that make it difficult to tolerate the medication, such as nausea, headache, dizziness, drowsiness and other side-effects that make patients feel 'bad', cause discomfort or interfere with their activities of daily living.
- Socio-cultural and religious influences, and possible stigmatisation.
- Restrictions on dietary intake, smoking or the use of alcohol.
- Complexities such as having to specially prepare or self-inject medication.
- Complicated dosing regimens that make if difficult to comply, for example, if a patient in full-time employment had to take tablets every four hours.
- How well the patient has been educated and informed about the treatment regimen, and what the prescribing practitioner hopes to achieve with the treatment, as well as what the realistic expectations are. Also the patient's ability to understand the instructions and to remember to adhere to the treatment regimen. Various tools or aids may be used to assist patients in this regard.
- The (perceived) benefits that patients may obtain from their treatment.

These are examples of factors to evaluate and consider whenever patients are found not to be complying or adhering to their prescribed treatment. These factors determine how well patients will tolerate their treatment, and the better they are able to tolerate the treatment, the more likely they will be to comply or adhere thereto.

# Glossary

**Analogues:** These are substances that have similar chemical structures, which only differ in respect of a specific component. A drug is an analogue if it resembles the structure of another chemical substance, enzyme or compound. Two related terms that are often encountered in pharmacology textbooks are derivative and congener.

**Beta-lactams:** A 'family' of antimicrobials (a few are true antibiotics) that have a β-lactam ring structure in common. The ring structure allows them to form covalent bonds with so-called penicillin-binding proteins (PBPs) that act as catalytic enzymes. These covalent bonds inhibit the activity of these enzymes in the bacteria in question. There are different types of PBP, which differ from one organism to the next. The various β-lactams bind to different types of PBP. Therefore, the susceptibility of certain organisms will vary from one β-lactam to the next.

**Biotransformation:** This term is used when referring to the metabolism of substances, such as drugs, that are foreign to the body.

**Chelating agents:** These agents can remove multivalent metal ions such as $Ca^{2+}$ and $Mg^{2+}$ from a solution, e.g. *dimercaprol* chelates mercury ($Hg^{2+}$) during mercury poisoning.

**Circulating blood cells:** The cellular component of blood comprises three main cell types, namely red blood cells (erythrocytes), white blood cells (leukocytes) and platelets (thrombocytes). The leukocytes are divided into two main groups, namely granulocytes (neutrophils, basophils and eosinophils) and agranulocytes (lymphocytes and monocytes). Mast cells are the tissue equivalent of circulating basophils.

**Congener:** Drugs are said to be congeners when they share similarities in their chemical structure (i.e. they are chemically related to one another). Such drugs would most likely have been derived from the same source.

**Conjugation reactions:** In the liver, drugs and certain toxins are combined with glucuronic or sulphuric acid for example, or acetylated, to terminate their biological activity and prepare them for renal excretion.

**Cytochrome P450 enzymes:** In pharmacological terms the cytochrome P450 (CYP) enzymes constitute the biggest and most significant family of drug metabolising liver enzymes and are responsible for the majority of Phase I biotransformation reactions. There are several important isoforms including CYP3A4, CYP2C9 and CYP2D6.

**Cytokines:** A diverse group of small signalling proteins primarily produced by the cells of the immune system, which modulate numerous homeostatic,

immune system and haematopoietic functions through their binding to specific target receptors. Examples include colony-stimulating factors, various growth factors, interleukins, interferons, tumour necrosis factor and chemokines. The cytokines constitute one of four major classes of signalling molecules for cellular communication; the other three being neurotransmitters, hormones and autacoids.

**Daltons:** The dalton is the unit of measurement used to express molecular mass (indicative of the size of a molecule). The symbol is Da and 1 000 daltons equal 1 kDa (kilo-dalton).

**Derivative(s):** When a new drug has been produced by chemically altering the structure of an existing compound or drug it is referred to as a derivative of the former (i.e. the source of its chemical composition was another compound or drug).

**Drug-receptor complex:** see ligand-receptor complex.

**Enterobacteriaceae:** This is a family of gram-negative enterobacteria (including* *Klebsiella, E. coli, Enterobacter, Proteus* and *Serratia* species). Many of them are normal, non-pathogenic organisms that reside in the gastrointestinal tract but turn into harmful pathogens when introduced into other areas, cavities or compartments of the body, or when they produce enterotoxins that act on the intestinal tract. Gram-negative organisms are notoriously more difficult to kill than gram-positive organisms. (*Note that there are several other members of this large and diverse family of bacteria, including *Salmonella, Shigella, Citrobacter, Hafnia, Yersinia, Morganella* and *Providencia*.)

**Excipients:** The inactive substances that are used to make up dosage forms are known as excipients. Excipients may be used as preservatives, flavourings, colorants, antioxidants, thickeners, emulsifiers, etc. Preparing a dosage form to contain one or more active pharmaceutical ingredient(s) (i.e. drugs), therefore, requires the addition of one or more excipients.

**Exfoliative dermatitis and toxic epidermal necrolysis:** These are severe dermatological conditions that may occur as a result of drug allergies. Exfoliative dermatitis is a generalised inflammatory reaction of the skin with severe erythema (redness) and scaling, as well as possible pruritus and hair loss. Toxic epidermal necrolysis (TEN) and the closely related Stevens-Johnson syndrome (SJS) are characterised by involvement of the mucous membranes with blister formation, skin rash and widespread peeling of the epidermis, which resembles scalding of the skin. SJS may also be associated with systemic signs of inflammation. Both TEN and SJS can be life-threatening.

**Gustatory pathway:** The afferent nerve pathway involved in the sense of taste.

**Hydrolysis:** The drug molecule is cleaved (a bond or bonds are broken) and combined with the $H^+$ and $OH^-$ parts of water ($H_2O$). This reaction takes place during phase I biotransformation.

**Inter-individual variation:** The rate of biotransformation of certain drugs differs amongst individuals due to genetic differences between them. This could significantly influence efficacy or drug toxicity from one person to the next.

**International Conference on Harmonisation (ICH):** The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use provide the pharmaceutical industry with harmonised *tripartite* (i.e. a three-party agreement) guidelines, agreed upon by the *three major drug development regions of the world*, namely the United States, Europe and Japan. The ICH Secretariat is based in Geneva, Switzerland. Amongst their various sets of guidelines, the Guideline for Good Clinical Practice (E6) is of particular importance to the conduct of clinical trials and is commonly referred to as ICH-GCP.

**Ligands:** Ligands are molecules that bind to receptor sites to transmit chemical signals. Ligands may be endogenous substances or drug molecules.

**Ligand-receptor or drug-receptor complexes:** Ligand-receptor or drug-receptor complexes occur once a stable but reversible chemical bond has formed between the two molecules in question (i.e. between the macromolecule that provides the receptor site and the drug or endogenous ligand).

**Lipocortin:** Also known as lipocortin-1 or annexin-1, lipocortin is a protein that is newly synthesised in response to glucocorticosteroid-induced gene transcription. Lipocortin inhibits phospholipase $A_2$ ($PLA_2$) and, therefore, prevents the activation of the arachidonic acid cascade (membrane $PLA_2$ is responsible for the release of arachidonic acid).

**Marketing authorisation:** Terminology used by different regulatory authorities may range from *registration* or *certification* to *licensing* or *marketing authorisation*. Local regulations and other regulatory guidance need to be followed by applicants when seeking authorisation to bring a new drug or medicine to market. In generic terms a marketing authorisation, therefore, implies that the regulatory authority has satisfied itself that the product is safe, effective, useful, of good quality and suitable for human consumption. Permission is then granted for such a product to be manufactured, packaged, labelled, marketed and sold in accordance with the applicable legislation, rules, regulations and guidelines that govern the licence, marketing authorisation, registration or certification.

**Medicines:** Drugs are made into formulated preparations or medicines (in one or more dosage forms) to allow them to be delivered to the human body. This

process usually involves the addition of inactive substances that are required to make up a dosage form, such as a tablet, capsule, mixture or emulsion.

**Medicines Control Council (MCC):** The MCC is the South African drug regulatory authority (refer to paragraphs 1.9 and 1.10). However, current draft legislation aims to change certain aspects pertaining to the regulatory oversight of medicines, certain foodstuffs, cosmetics and medical devices in South Africa, to abolish the MCC and to establish a new regulatory body, namely the South African Health Products Regulatory Authority.

**Ménière's disease:** A disorder of the labyrinth, caused by dilatation of the cochlear lymphatic ducts, with a resultant accumulation of inner ear fluid within the endolymphatic sac. The condition may cause severe nausea and vomiting, accompanied by other labyrinth symptoms such as tinnitus, vertigo and a progressive loss of hearing.

**Modalities:** The employment or application of therapeutic agents or regimens during the treatment of disease.

**Motilin:** Motilin is a gastrointestinal tract hormone that increases motor activity such as gastric emptying.

**Motor endplates:** Some authors use the terms neuromuscular junction (NMJ) and motor endplate interchangeably. However, others are of the opinion that the latter term should rather be used to describe the highly specialised areas of the postsynaptic membrane of the NMJ, i.e. those areas that contain the post-synaptic nicotinic receptors (also refer to paragraph 4.7.2).

**Optical axis:** The axis that connects the anterior and posterior poles of the eye (not to be confused with the visual axis, which diverges from it slightly).

**Over-the-counter (OTC) drugs/medicines:** These are drugs that may be obtained from a pharmacy without a prescription.

**Oxidation:** The drug molecule loses hydrogen and gains oxygen. This reaction takes place during phase I biotransformation.

**PCP:** PCP, or *Pneumocystis (carinii)* pneumonia, is a defining infection of AIDS. The organism, previously regarded as a protozoan, has been re-classified as a fungus and consequently renamed *P. jirovecii*.

**Penicillinase or β-lactamase:** Enzymes produced by certain strains of bacteria, both gram-positive and gram-negative. Collectively referred to as the β-lactamase enzymes, these hydrolytic enzymes open up the β-lactam ring and therefore destroy the antimicrobial activity of these drugs. Penicillinase produces bacterial resistance against the penicillins, while cephalosporinase produces resistance against the cephalosporins. Some cephalosporins are resistant to penicillinase but not to cephalosporinase.

**Peptide:** A peptide is formed when two or more amino acids are linked together by peptide bonds. Arbitrarily, polypeptides are chains of approximately 20 to 50 linked amino acids and proteins are chains of polypeptides containing

more than 50 amino acids in total. A dipeptide is made up of only two linked amino acids.

**Physicochemical characteristics:** The physical properties or characteristics of chemical substances and their molecules.

**Placebo:** This is a pharmacologically inactive substance that is administered as a harmless substitute for drugs during clinical trials or to manage carefully selected clinical problems.

**Plant alkaloid:** The plant alkaloids are base substances, organic in nature, which are found in, and extracted from, plant material. The alkaloids usually exhibit potent physiological activity and include the opioid alkaloids (***morphine*** and ***codeine***), the cholinergic alkaloids (muscarine and ***pilocarpine***), *reserpine* (a Rauwolfia alkaloid), the ergot alkaloids, ***quinine***, *caffeine*, nicotine and *cocaine*.

**Polar:** The molecule in question is electrically neutral but has an unequal charge distribution within it. This will result in the molecule having two oppositely charged (negative and positive) ends (or poles). $H_2O$ is a good example of a polar molecule.

**Polymorphonuclear (PMN) leukocytes:** This term may be used as a synonym for granulocytes because the latter have multi-lobed nuclei that may take on a variety of morphological shapes. Neutrophils, however, are the most abundant of the granulocytes and can take on the greatest variety of shapes (i.e. they are polymorphic) of their multi-lobed nuclei. Therefore, the term is also used synonymously with neutrophils.

**Porphyria:** A group of disorders that involve the biosynthesis of haem and cause an excessive renal excretion of porphyrins, or their precursors.

**Portacaval anastomosis:** An anatomical anastomosis between veins that feed into the inferior vena cava directly and those reaching it via the hepatic portal vein. The anastomosis allows a percentage of the venous blood to directly enter the vena cava, thus bypassing the liver. The anastomosis between the three rectal veins is a good example.

**Receptors:** These are proteins or protein-containing macromolecules (i.e. large molecules) that are found on the surfaces of cells, or within their cytoplasm or nuclei, which serve as binding sites for chemical signal transmitters.

**Reduction:** The opposite of oxidation: oxygen is lost and hydrogen gained. This reaction takes place during phase I biotransformation.

**Selective permeability:** The plasma membrane is relatively freely permeable to solvents such as water, but rather impermeable to solutes. The nature of the membrane, therefore, determines which molecules, and how many of them, actually cross it.

**Spasmogens:** These are agents capable of causing muscle spasms. In this context, these are the agents responsible for causing spasms of the bronchial smooth

muscle, resulting in bronchoconstriction and bronchospasm. Examples include the cysteinyl-leukotrienes (i.e. $LTC_4$, $LTD_4$ and $LTE_4$), histamine, platelet-activating factor (PAF), and prostaglandin $D_2$ ($PGD_2$) and $F_{2\alpha}$ ($PGF_{2\alpha}$). (Also see chapter 7.)

**Substrates:** Chemical compounds that are catalysed by enzymes. Compounds are chemical substances that are made up of two or more elements. Organic compounds contain carbon atoms; inorganic compounds do not.

**Superinfections:** These are new infections that occur 'on top' of the infection(s) already present. These infections are often due to antimicrobial therapy that does not include the organism(s) responsible for the superinfection in the given spectrum of activity.

**Titration:** Sequentially administering carefully measured amounts or dosages of a drug until the desired effect is achieved.

**Toxic epidermal necrolysis:** See exfoliative dermatitis.

**Urinary tract antiseptics:** These are oral antimicrobial agents that do not significantly influence the normal intestinal flora and do not exhibit any systemic antibacterial effects, but will exert these effects in the urine. In other words, these agents can only be used in the management of LUTI (lower urinary tract infection).

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2nd edition

# Pharmacology in Clinical Practice

## Application Made Easy for Nurses and Allied Health Professionals

The second edition of *Pharmacology in Clinical Practice* (formerly known as *Pharmacology in Clinical Nursing Practice*) has been extensively revised and updated.

The authors are specialists in the fields of clinical research, health sciences education, clinical pharmacy and applied pharmacology. They have endeavoured once again to provide a simplified approach to this complex subject. By illustrating how pharmacological principles apply to clinical practice, they successfully present nurses and allied health professionals with the fundamentals of drug science as well as the basics of pharmacodynamics and pharmacokinetics.

The authors have, where applicable, included suitable cross-references to the latest edition of the Standard Treatment Guidelines and Essential Medicines List (EML) for South Africa: Primary Health Care Level, 2008 edition.

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- A glossary to explain problematic terminology.

The principal author and editor, Gustav Schellack, is a clinical research associate in the pharmaceutical industry and specialises in applied pharmacology. Formerly, he lectured in the Department of Nursing Science at the University of Pretoria.



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