PHARMACOLOGY

Only study guide for **BMI2605**

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LEARNING UNIT 0

Introduction

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Welcome to Pharmacology. We hope this course will broaden your understanding of drugs, and help you further your studies.

0.1 WELCOME NOTE

Welcome to Pharmacology (BMI2605). Pharmacology focuses on:

- the interaction between drugs and biological systems
- the properties of drugs and
- the reactions of the body to drugs.

Pharmacology incorporates knowledge and skills from various basic science disciplines, including biochemistry, physiology, cell biology, molecular biology and genetics. Pharmacologists use this knowledge to develop therapeutic agents that can be used to treat disease.

Pharmacology is important to medicine, veterinary medicine, pharmacy, nursing, dentistry and toxicology. Pharmacologists investigate the effects of chemical agents on cells and systems of the body. Not only do they consider chemicals that are used to prevent and treat disease, but they may also investigate the effects of toxins such as pesticides and herbicides on the body, or the effects of recreational drugs.

This module is a 12-credit course, which means that you will need to devote at least **120 study hours** to it. You will need to prepare a portfolio. The myUnisa website will be the main teaching medium for this module. Please visit this site frequently to interact with fellow students and to participate in discussions about certain topics that we will be covering. Try to be online at least once a week. I will say more about the structure of the course in the next sections.

I hope that you will find the module interesting and useful, and that you will be able to apply the knowledge you gain not only in your career, but also in developing a better understanding your own health and the drugs that can be used to enhance health.

0.2 COURSE INFORMATION

0.2.1 How this course is organised

Before you begin studying the first study unit, I would like to give you some details about the module as a whole. There are a number of concepts that are fundamental to pharmacology, such as pharmacokinetics, pharmacodynamics, drug safety, interactions and adverse effects. We will focus on these in the first four learning units.

We will then discuss the essentials of neurotransmission and study some examples of drugs that affect neurotransmission, their pharmacokinetic parameters, modes of action and physiologic effects, and a few disorders of the central nervous system. Following this, we will consider four different classes of drugs that are used to treat hypertension as examples of drugs that affect a different organ system. Finally we will introduce the pharmacology of drug abuse.

- Unit 1: What is pharmacology?
- Unit 2: Pharmacokinetics
- Unit 3: Pharmacodynamics
- Unit 4: Drug development, safety and interactions
- Unit 5: Neurotransmission and the peripheral nervous system
- Unit 6: The central nervous system
- Unit 7: Disorders of the CNS and their treatment
- Unit 8: Hypertension as an example of cardiovascular disease
- Unit 9: Drugs of abuse

0.2.2 Textbook

The prescribed textbook for BMI2605, which you will be using together with the online material, is:

Brenner, G. M. and Stevens, C. W. (2012). Pharmacology. 4th edition. Saunders Elsevier, Philadelphia. (ISBN: 978-1-4557-0282-4)

The textbook is a comprehensive guide to pharmacology. You do not have to study all of it: the online study material will guide you in terms of what you need to learn. You will need to study the chapters that are mentioned at the beginning of each learning unit and any recommended reading sections. If you find a topic particularly interesting, you are more than welcome to do further reading about it.

Note that if you purchase the latest edition of the textbook, you may find that the pages in the study guide do not directly correlate to the pages in this latest edition of the textbook. However, I am sure that you will find it easy to locate the relevant section, rather than the specific pages, in the newer textbook.

In the study guide I will refer to the textbook as Brenner and Stevens.

0.2.3 Purpose of this module

This introductory course deals with the fundamentals of pharmacology. My intention is to teach you about the action of pharmacologic agents, and we cover both the pharmacokinetic and pharmacodynamic principles. However, the module is not intended as a review of all pharmacotherapeutic agents, and we will be discussing only a limited number of drugs. Instead, our emphasis is on the **basic principles of physiology and biochemistry** in relation to the mechanisms of **drug action**, **bioabsorption**, **biodistribution**, **biotransformation** and **elimination**. We will be covering topics such as drug characteristics (preparations and delivery), pharmacodynamics (mechanisms of drug action), pharmacokinetics (drug absorption, distribution, metabolism and excretion), drug interactions and substance abuse. We will also review the pharmacokinetic and physiological effects of a number of selected agents.

0.2.4 Outcomes of the module

This module is designed to introduce you to some important concepts in pharmacology, and will cover a number of topics, including basic concepts of pharmacodynamics and pharmacokinetics, the pharmacology of drugs that act on the body systems (e. g. cardiovascular, autonomic and central nervous systems) and drugs of abuse.

After completion of this module you will be able to:

- explain what drugs are, the different types of drug preparations, and the different ways drugs can be administered
- discuss the pharmacokinetics of drugs and calculate a number of pharmacokinetic parameters
- discuss the pharmacodynamic properties of drugs
- describe neurotransmission in the peripheral and central nervous system and discuss examples of drugs that alter neurotransmission
- discuss the different classes of drugs that can be used in the treatment of hypertension as an example of drugs affecting the cardiovascular system
- discuss common drugs of abuse, their mechanisms of action and drug dependence

0.3 DISTANCE LEARNING

Distance learning is very different from learning in a contact situation. Once you have received your study material, please plan how you will approach and complete this module. Draw up a reasonable study schedule for the whole module. Remember to include the assignment due dates as given in Tutorial Letter 101.

0.3.1 Independent study

A crucial element in understanding and learning the basics of pharmacology is the ability to express your ideas both orally and in writing. Only when you have tried this for yourself will you understand the full value of this exercise.

Assessment measures an aspect of your success. For this module there is both formative (ongoing) and summative (final) assessment in the form of assignments and examinations. These are mainly in the form of written work. Your reflections on your learning are therefore also an important part of your studies. Since the focus in this module is on understanding and applying the concepts of pharmacology, assessment will focus on the competencies you need to display.

Work through your study guide, making use of the guidelines in the next section. Construct mind maps and make your own summaries of the objectives and content of chapters of the textbook. Restrict summaries to one page. Additional textbooks and articles give alternative views or provide more insight into issues under discussion, and are optional additional reading.

Be focused. Build up your own study and exam preparation **portfolio** (consisting of your assignments, activities, reflections, summaries, self-evaluations and notes) throughout your academic and/or experiential learning. **The lecturer will not assess this portfolio, but you will need to prepare it in order to be able to complete the assignments and ultimately pass the final examination**. It is also very important to use this portfolio, in combination with your assignments and subsequent feedback (tutorial letters), for your **exam preparation**. The advantage is that by doing this you take part actively in your learning, you set goals, you evaluate your own progress through reflective actions, and you evaluate your ability to realise the learning outcomes, thus becoming a more independent and self-directed learner.

What is a portfolio? A portfolio is a folder or file in which you gather and compile additional and/or summarised information during the year as you work through the study guide and textbook. This portfolio will help you to prepare for the examination by focusing on the most important facts and issues.

Your portfolio should comprise:

- answers to each activity in each study unit
- a mind map/summary of each study unit
- your marked assignments (or a copy you made prior to submitting your assignment)
- your reflections on each study unit
- extra reading material taken from the internet, additional books, and medical and/or scientific journals
- a new vocabulary of words or glossary of new terms defined in your own words

To help you, in the next sections I provide some study skills guidelines you may find helpful.

0.3.2 Improved study skills

It is critical that you think independently and learn to look beyond the study guide and textbook. I have included a number of additional references in this study guide, and I really encourage you to consult them. In addition, as a more advanced distance-education student, you need to learn how to search for research/scientific articles via the internet.

0.3.2.1 How to search for research/scientific articles

Google has created an additional search engine under "Advanced search", called Google Scholar. This has its own advanced search function. If you state your subject query in four to six words and press "Search enter", a variety of websites relating to the query will appear. This has the advantage of allowing you to access most of the journal references from any internet site in addition to myUnisa. Some journals, however, such as ScienceDirect, can be accessed only through a tertiary academic institution such as Unisa. To access this journal:

1. Go to Unisa online at http://www.unisa.ac.za/
2. Click on Library at the top of the page.
3. In the maroon area on the top of the page, click on "Search for information resources".

4. Follow the guidelines if you are a first-time user.
5. Click on the option "A–Z list of the names of all electronic resources" on the right-hand side of the page.
6. Various links for databases will now appear on your screen. Click on any database to do a search. For pharmacology I recommend Science-Direct, Nature or Springer Link.
7. Once you have entered one of these databases, you can search for scientific articles by typing keywords in the "Search" box. Use specific keywords. If you type in just a single, general word, you will usually get too much information, and it won't necessarily relate to the topic you are looking for.
8. You will need to do some independent searches yourself for your portfolio, assignments and exam preparation.

Contact the Unisa Library at +27 12 4293206 if you have any difficulties or if you need assistance, or consult the library website for the telephone number of your local branch library.

0.3.2.2 Skimming, scanning and study-reading strategy (SSS strategy)

The SSS strategy is one of a number of strategies you may find helpful. The three techniques in the SSS strategy are:

- **s**kimming,
- **s**canning and
- **s**tudy-reading.

Skimming

1. **Page through and explore**. First, read the section, chapter or unit quickly, forming a rough idea of the content. Concentrate on headings and subheadings, any words or phrases in bold or italics, text in boxes, tables and illustrations, and – in the case of a chapter or unit – introductions and summaries. The objectives set for a unit or chapter are important. (Think of how you would page through a magazine. When starting a new study unit, scan it and concentrate on the concepts that catch your eye.)
2. **Make a cursory survey**. As you read, ask yourself: What key terms occur in this section, unit or chapter? Stop when you identify a key term, read carefully what is said about it, and mark it so that you will be able to find it again easily later when you need to. Your key question at this point is: **Where**?

Scanning and reflecting

3. **Scan** the section, chapter or unit.
4. **Start a mind map** (either for the whole section, unit or chapter or for parts of it). You are looking for items and concepts while reading the information in the section, unit or chapter in a more evaluative way. Reflect on relationships between concepts. The question now is: **What**? What is the meaning and the purpose? Visualisation is important, and at this point you begin to write down key concepts.
5. **Deeper reflection**. As you work through the prescribed activities of the section, unit or chapter, keep returning to the mind map to fill in the detail. Reflect on the value and meaning of categories, concepts, motivations, variables and key terms.

Study-reading

6. **Study-read**. There is a close relationship between this stage and stages 2, 4 and 5. Read carefully, thoroughly and thoughtfully. During this stage you link the key terms

and concepts you have already identified, and this is where the mind map and summaries are important. (Remember to put your detailed mind map in your portfolio.) Pause while reading, consolidate what you remember and consider how new information fits in with what you already have.

7. **Activity-based approach**
   Whenever you get to an activity in your study guide, complete it in full on loose pages which you then insert in your portfolio, grouped together per section and study unit. Supplement this with your own notes. (You do not need to submit activities or the portfolio to the lecturer, but these are essential for exam preparation.)
8. **Understanding what you read**
   Take the time to note new vocabulary words. Consult a dictionary to understand the meaning of new words. You could compile a page for each study unit, and add it to your portfolio.

0.3.3 Managing your self-paced study time

If you are an average student, you need to devote at least **120** study hours to this module (however, this time may vary substantially). You should therefore plan to devote at least **8** study hours per week to the module, in which case you should complete it in **15** weeks. If you have registered for more than one module, you need to plan time for each module accordingly.

I advise you to keep a study schedule or diary, so that you have a clear idea of the time you have available for study. This will help you to manage your studies within the time you have available, and balance study with work and family life. In Tutorial Letter 101 you will find a list of due dates for the assignments, so enter these in your diary. Divide the large assignments into a series of smaller tasks to complete one step at a time.

In order to manage your workload, study frequently and regularly. Establish a routine in an environment with low noise and good lighting. Reward yourself after a productive session.

0.3.4 Academic specialist guidance

If you need help, please contact the staff of the Department of Life and Consumer Sciences who are responsible for this module.

0.4 PLAGIARISM

Never try to pass off other people's work (and that includes Unisa study material) as your own. If you want to quote other people's words and ideas or Unisa study material in your own answers, you must use quotation marks and acknowledge your source. (Use the Harvard method.) If you are unsure about the correct way of acknowledging sources, contact Unisa's Library Information Desk.

Students who fail to acknowledge quotations or who draw on lecture notes and other sources without acknowledgment or who copy someone else's answers may be refused permission to write the examination, or may be penalised in the assignment.

0.5 ASSESSMENT

A crucial element in understanding and learning the basics of pharmacology is the ability to express your ideas both orally and in writing. Only when you have tried this for yourself will you understand the full value of this exercise.

Assessment measures an aspect of your success. For this module there is both formative (ongoing) and summative (final) assessment in the form of assignments and examinations. These are mainly in the form of written work. Your reflections on your learning are therefore also an important part of your studies. Since the focus in this module is on understanding and applying the concepts of pharmacology, assessment will focus on the competencies you need to display.

0.6 IN CONCLUSION

After reading this general introduction you should have a better understanding of what the module involves and how you should approach your studies in Pharmacology.

0.7 GETTING STARTED

To get to know your online environment and fellow students, I would like you to do an activity called an ice breaker.

This activity will help you to:

- understand the technologies that will be used in the course
- get to know and connect with your fellow students For this ice breaker, you need to create a blog entry.

Ice breaker: personal blog entry

Create your own blog entry and share your thoughts on the following: How do you think your life may have been affected if there were no pharmacotherapeutic agents (medicinal drugs)?

Go to the Blog tool by clicking on Blogs in the tool list on the left-hand side of your screen. You will find the instructions on how to use the blog in the FAQ section in the tool list on the left-hand side of your screen.

You can add links, bullets, lists and colour if you would like to, by using the editing buttons. You can also go back and edit your blogs. The next time I ask you to use the blog, you just click on "Add blog entry" again, and create a new blog, which will appear under your name.

LEARNING UNIT 1

What is pharmacology?

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1.1 INTRODUCTION

A drug is a **chemical substance** (natural or synthetic) which, when given to a living organism, produces a **biological effect**. Pharmacology is the science that deals with **drug action**. It includes the study of:

- the chemical properties of drugs
- the physiological and behavioural effects of drugs on living organisms
- mechanisms of action of drugs
- how drugs are biologically transformed in living systems
- the therapeutic and non-therapeutic uses of drugs

In this learning unit we will look at the history of pharmacology, the sources and preparation of drugs and the different ways they can be administered. To complete the study unit, you will need to refer to **chapter 1** in Brenner and Stevens.

1.2 LEARNING OUTCOMES

Upon completion of this learning unit you should be able to:

- explain what a drug is
- discuss the history of pharmacology
- describe the sources and preparation of drugs
- discuss the different routes of drug administration

1.3 HISTORY OF PHARMACOLOGY

Recommended reading: the section entitled "Pharmacology and related sciences" on pages 2–3 in chapter 1 of Brenner and Stevens

Pharmacology as a science was developed in the mid-19th century. Although people have been using natural products that have therapeutic value to treat various diseases for many centuries, the activity of these products was determined through trial and error, and no scientific principles were applied to understand why these products helped. Many of these early remedies contained herbs with active ingredients, but they also contained substances like dung, urine and worms, which had no therapeutic value. Only once the normal and abnormal functioning of the body was understood and the chemical properties of therapeutic agents could be analysed was it possible to understand the physiological and behavioural effects of specific drugs on living organisms.

In the beginning, pharmacology focused only on the effects of natural substances, mainly plant extracts. As synthetic organic chemistry developed, so did pharmacology. In 1804 morphine was isolated from opium, and after that many more drugs were extracted from plant sources. The use of these extracted compounds revealed that **chemicals**, rather than magic or vital forces, were responsible for the effects that plant extracts produced.

With advancements in chemistry new synthetic drugs, such as **local anaesthetics** and **antimicrobial agents**, were manufactured. At the same time, knowledge about physiology was increasing – this helped pharmacologists understand the interactions between chemical substances and living systems. Biochemistry developed as a distinct science, and the resulting knowledge about enzymes and biochemical pathways has helped us understand drug effects.

The result of this is that over the past 50 years there has been a boom in the number of drugs that have been developed; today drug development is driven by the pharmaceutical companies, and is a billion dollar industry.

The pharmacology of drugs is divided into a number of subdivisions, two important ones being:

- pharmacokinetics (what the body does to the drug), and
- pharmacodynamics (what the drug does to the body)

Refer to Figure 1-1 in Brenner and Stevens, which shows how pharmacokinetics and pharmacodynamics are related. I will be discussing pharmacokinetics and pharmacodynamics in greater detail in learning units 2 and 3, respectively.

1.3.1 Activity 1.1

Do the following activity and add it to your portfolio.

Remember, this could serve as part of your summary to use in preparing for the exam!

a) In your own words, describe what pharmacokinetics and pharmacodynamics are.
b) Briefly explain what the related disciplines toxicology, pharmacotherapeutics and pharmacy are.

1.4 DRUGS

Recommended reading: the section entitled "Drug sources and preparations" on pages 4–6 in chapter 1 of Brenner and Stevens

A drug is a chemical substance that, when given to a living organism, produces a biological change. Drugs are typically used to treat disease in humans or animals. People often think that drugs are addictive, narcotic or mind-altering substances, and all these negative connotations influence the way people feel about drugs for therapeutic purposes. Drugs

may be obtained from natural sources, or they can be synthetic chemicals or the products of genetic engineering.

Natural sources

Natural sources of drugs include substances that have been acquired from

- plants
- microorganisms
- animals
- fungi
- minerals

Morphine, cocaine, atropine and quinine are all alkaloids derived from plants. Antibiotics are typically isolated from bacteria or fungi, and hormones, for example heparin, are often obtained from animal tissue. Few minerals are useful therapeutically, although lithium is well known as a treatment for bipolar disorder.

Synthetically made

Many drugs are synthetically made or are products that have been modified from natural sources. Aspirin, barbiturates and local anaesthetics were the first drugs to be chemically synthesised.

Genetically engineered

Many genetically engineered drugs have been developed and approved for the treatment of a variety of diseases, and are produced using recombinant DNA technology. They include hormones, enzymes, growth factors, coagulation factors, antibodies and vaccines.

A **medicine** is a pharmaceutical preparation that contains **one or more drugs intended to generate a therapeutic effect**. Medicines usually contain other substances that make them more convenient to use.

1.4.1 Pharmaceutical preparations

Drug preparations may be in a variety of forms:

- crude extract,
- pure drug or
- pharmaceutical preparation

Refer to Figure 1-2 in Brenner and Stevens.

Pharmaceutical preparations are drug products that are suitable to administer to a patient. Drugs that are taken orally are typically in **tablet** or **capsule** form, although they may also be in **solution** or **suspension**, especially if they are to be taken by children who cannot swallow tablets. Tablets and capsules can be formulated either:

- to release drug directly after ingestion or
- to release the drug over a period of time, in which case they are called sustained-release products.

Tablets normally contain other inert substances:

Their function	What they are called
Provide bulk	Fillers
Make manufacture easier	Lubricants
Increase stability	Adhesives
Aid in drug solubilisation	Disintegrants

Solutions and **suspensions** are the most common liquid pharmaceutical preparations. They can be either taken orally or administered parenterally (as an injection or infusion). Skin patches can also be used to administer drugs, in which case the drug is absorbed through the skin.

Aerosols, ointments, creams, lotions and suppositories are other types of pharmaceutical preparations that can be used to deliver drugs.

1.4.2 Activity1.2

Do the following activity and add it to your portfolio.

a) What is the difference between a crude drug preparation, a pure drug compound and a pharmaceutical preparation?
b) Briefly describe the different coatings of tablets and capsules and the substances they contain that modify the release of drug.
c) Discuss some advantages and disadvantages of drug solutions and suspensions.
d) Discuss skin patches and aerosol pharmaceutical preparations. When may these be used?

1.4.3 Feedback on activity1.2

The different types of drug preparations are illustrated in Figure 1-2 in Brenner and Stevens. When describing the different preparations, did you mention that quantifying and identifying the pharmacologic effects of crude drug preparations is complicated, as they often contain multiple ingredients, and the concentrations of active ingredients may vary from batch to batch?

When discussing the coatings of tablets, did you mention enteric coatings, and when describing sustained-release products, did you discuss controlled diffusion and controlled dissolution?

Figure 1-3 in Brenner and Stevens illustrates the use of osmotic pressure to achieve the sustained release of drug.

1.5 HOW ARE DRUGS ADMINISTERED

Recommended reading: the section entitled "Routes of drug administration" on pages 6–7 in chapter 1 of Brenner and Stevens.

The routes of drug administration include:

- enteral administration
- parenteral administration
- transdermal administration
- inhalational administration

- topical administration

Enteral administration includes all methods where the drug is absorbed from the **gastrointestinal tract**. This incorporates sublingual, buccal, oral and rectal means.

Parenteral administration includes all methods of drug administration that require a **needle and syringe** or **intravenous infusion pump**. The most frequently used parenteral routes are intravenous, intramuscular and subcutaneous.

Transdermal administration involves placing either a **skin patch** or **ointment** on the skin. The drugs are then absorbed into circulation through the skin.

Inhalational administration involves **breathing in a drug**. Inhaled medications are typically absorbed quickly, and can act both locally and systemically, depending on the drugs involved. Smoking cigarettes is a common inhalational method of delivery of nicotine (I will say more about drugs of abuse in learning unit 9).

Have a look at Table 1-2 in Brenner and Stevens to see the advantages and disadvantages of the four most common methods of drug delivery.

1.5.1 Activity 1.3

Do the following activity and add it to your portfolio.

a) Define sublingual, buccal, oral and rectal means of drug delivery.
b) Discuss intravenous, intramuscular and subcutaneous administration of drugs. Include the advantages and disadvantages of each method.
c) Where are drugs injected if they are administered intrathecally or by epidural?
d) Discuss inhalational and topical routes of drug administration.
e) Read the section on drug names on page 7 in Brenner and Stevens. What is the difference between the chemical name, non-proprietary name and proprietary name of a drug?

LEARNING UNIT 2

Pharmacokinetics

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2.1 INTRODUCTION

Pharmacokinetics is the study of the **movement of drugs within the body**, and focuses on the **change in drug concentration** in the body over time. It involves examining the time course of drug absorption, distribution, metabolism, and excretion, as these factors all affect the concentration of drug in the body.

A drug's **therapeutic effect** is typically related to its concentration at the location where it acts. As it is not generally possible or practical to measure the concentration at the site of

action, the concentration of drug in the blood or plasma and other easily sampled body fluids (e. g. saliva, urine) can be measured instead. Changes in the drug plasma concentration will be proportional to changes in drug concentrations at their sites of action. When the concentration of drug in the blood plasma increases, the concentration of drug in most tissues will also increase. Similarly, as the concentration of drug in the blood plasma decreases, the concentration of drug in the tissues will decrease.

In this learning unit we discuss **absorption**, **distribution**, **metabolism**, and **excretion** of drugs, and how these processes result in changes in the blood plasma concentration of the drug. To complete the study unit, you will need to refer to **chapter 2** in Brenner and Stevens.

2.2 LEARNING OUTCOMES

Upon completion of this learning unit you should be able to:

- explain what pharmacokinetics is
- discuss the absorption of drugs by the body
- identify factors that affect drug distribution in the body
- describe the different ways that drugs are metabolised
- describe how drugs are excreted
- discuss the use of drug plasma concentration in understanding the pharmacokinetics of drugs
- describe a number of different pharmacokinetic parameters, including bioavailability, volume of distribution, clearance and elimination half-life

2.3 DRUG DISPOSITION IN THE BODY

Drugs move around the body in two ways:

- either via bulk flow in the bloodstream, lymphatics or cerebrospinal fluid or
- through diffusion over short distances.

All drugs tend to move equally well via bulk flow. Diffusion, however, is highly dependent on the chemical nature of the drug. A drug's ability to cross cell membranes is determined mainly by its **lipid solubility**, and the rate of its aqueous diffusion depends on its **size** (the diffusion coefficient for small molecules is inversely proportional to the square root of molecular weight). Therefore, larger molecules tend to diffuse more slowly than smaller ones in aqueous solutions.

Drug disposition in the body is determined by four processes:

- absorption
- distribution
- metabolism
- excretion

I will say more about these in the sections that follow.

2.4 DRUG ABSORPTION

Recommended reading: the section entitled "Drug absorption" on page 9 in chapter 2 of Brenner and Stevens

By absorption of drugs we mean the **movement of drug molecules from the site of administration into the bloodstream**. During drug absorption, drugs typically need to cross one or more layers of cells and cell membranes. The method of administration of

the drug influences how easily it is absorbed; drugs administered parenterally are absorbed more easily than drugs that are administered orally, because drugs administered orally must first pass through the layer of closely packed epithelial cells lining the gut. During intravenous administration the drug enters circulation immediately and does not need to be absorbed.

The majority of drugs are absorbed by passive diffusion across or between cells. The rate of diffusion of a drug across a cell membrane depends on its chemistry and is proportional to the drug concentration gradient across the membrane and the surface area available for absorption. Passive diffusion through cells can occur by lipid diffusion or aqueous diffusion through aqueous pores.

Molecules can also cross cell membranes by combining with membrane transporter proteins.

Lipid diffusion - Lipid solubility is very important in influencing whether a molecule will diffuse through a lipid bilayer. Small non-polar molecules are able to dissolve in the membrane lipids, and in this way diffuse into the cell. Molecules that are **more** soluble in lipids will diffuse **more easily** across a cell membrane than molecules that are less soluble in lipids. Many drugs are mildly acidic or basic, and therefore may be ionised depending on the pH of the environment (refer to Box 2-1 on page 10 in Brenner and Stevens). Ionised molecules have low lipid solubility and therefore need to utilise specific transport mechanisms to cross cell membranes.

Aqueous diffusion - Aqueous diffusion occurs through aqueous pores formed by transmembrane proteins (aquaporins) in the cell membrane. Only small molecules can pass through the pores. Many drugs are too large to pass through these pores, and therefore need to utilise other methods to cross cell membranes.

Membrane transporter - There are two main types of membrane transporters: the **solute carrier (SLC)** transporters and the **ATP-binding cassette** transporters. The SLC transporters mediate facilitated diffusion of molecules down their concentration gradient, whereas the ATP-binding cassette transporters actively transport molecules across the membrane and can pump molecules against their concentration gradient. They require ATP for energy.

Typically these transport systems require a carrier molecule (transmembrane protein) that binds one or more molecules. A conformational change then occurs, and the molecules are released on the other side of the membrane.

2.4.1 Activity 2.1

Do the following activity and add it to your portfolio.

Remember, these activities serve as part of your summary to use in preparing for the exam!

a) Why are drugs that are administered parenterally more easily absorbed than drugs that are administered orally?
b) Discuss the effect of pH on the absorption of weak acids and bases.
c) Would you expect weak acids or weak bases to be more easily absorbed from the stomach? Explain your answer.
d) The two main methods by which drugs cross lipid membranes are passive diffusion and carrier- mediated transfer. Discuss these two processes.

2.4.2 Feedback on activity 2.1

The effect of pH on the absorption of weak acids and bases is described on page 9 in Brenner and Stevens. Did you discuss the pKa value of the drug and how a pH lower or higher than the pKa value will alter the ratio of protonated species to unprotonated species? Whether the drug is weakly acidic or basic will determine whether the protonated species is ionised or nonionised. The drug in the nonionised form is more easily absorbed, and so acidic and basic drugs will be more readily absorbed at pH values lower and higher than their pKa values, respectively.

2.5 DRUG DISTRIBUTION

Recommended reading: the section entitled "Drug distribution" on pages 9– 11 in chapter 2 of Brenner and Stevens

Drug distribution refers to the process where the drug **leaves the bloodstream and enters the organs and tissues**. Drugs are distributed around the body to various organs by the circulatory system, where they then diffuse into the interstitial fluid and cells. Drugs are not always distributed evenly throughout the body, and may be found in differing concentrations in the extracellular fluid and plasma compartments.

Drugs may become concentrated within cells through **ion trapping** if there is a difference in pH across a cell membrane. Depending on the pKa of a drug and the pH of the surrounding solution a drug may be either **charged** or **uncharged** (see Box 2-1 in Brenner and Stevens). The cell membrane is more permeable to non-ionised (uncharged) molecules than ionised (charged) molecules, so if the pH difference is such that a larger fraction of the drug is uncharged outside the cell and a larger fraction is charged within the cell, the drug will move into the cell and be less likely to move out of it again.

The pH within cells is typically lower than the pH outside the cell (except for the cells lining the gut). As a result, basic drugs will be less ionised in the extracellular matrix than they will be in the intracellular fluid. If the basic drug then diffuses into the cell, a larger fraction of drug will be ionised in the cell; it will be unable to cross back, and so it will be trapped. **The overall concentration of drug inside the cell increases compared with the concentration outside the cell**, although the uncharged molecules of the drug remain in equal concentration on either side of the cell membrane.

Transport proteins can also influence the distribution of drug in cells. Certain drugs may be actively transported **into** cells against the concentration gradient and therefore accumulate in the cells, or else they may be transported **out** of the cells, reducing their concentration in the cells.

A number of additional factors affect the distribution of drugs in the body. These include:

- organ blood flow
- plasma protein binding
- molecular size
- lipid solubility

2.5.1 Activity 2.2

Do the following activity and add it to your portfolio.

a) In your own words, describe ion trapping.
b) Discuss how organ blood flow, plasma protein binding, molecular size and lipid solubility affect the distribution of drugs within the body.

2.6 DRUG BIOTRANSFORMATION (DRUG METABOLISM)

Recommended reading: the section entitled "Drug biotransformation" on pages 11–15 in chapter 2 of Brenner and Stevens

Biotransformation, or drug metabolism, is the **conversion of drugs to other metabolites by enzymes within biological systems**. Animals have evolved a number of metabolising enzymes that work to inactivate and detoxify drugs and other foreign compounds that may cause harm in the body. Although drugs can be metabolised in many different tissues, most biotransformation occurs in the **liver**. Typically, during drug metabolism drugs become more **hydrophilic**, which aids in their elimination from the body. Lipophilic drugs are not efficiently excreted in the urine, but if the drugs are metabolised to more hydrophilic molecules, then they can be eliminated by the kidneys.

Metabolites may be made more or less active than the parent drug after biotransformation. In some cases a drug becomes active only after it has been metabolised in the body. These drugs are called **prodrugs**. An example is dipivefrin, which is metabolised into its active metabolite, epinephrine, by enzymes in the body.

2.6.1 Phases of biotransformation

As I have already said, the liver is the main organ involved in drug biotransformation, although other tissues such as the gut, kidneys, brain, lungs and skin also play a role in drug metabolism.

Biotransformation can occur by two types of reactions, called phase I and phase II reactions. These often, although not always, occur sequentially. Some drugs are never metabolised by phase I reactions before being metabolised by phase II reactions.

- During **phase I biotransformation** drugs are transformed into more **polar metabolites**, either through the **unmasking** of functional groups or through the **addition** of functional groups. The metabolites may or may not be active, and may even be more toxic than the parent drug. Phase I biotransformation involves **oxidative**, **hydrolytic** and **reductive** reactions (refer to Figure 2-3 in Brenner and Stevens). Oxidative reactions are catalysed by enzymes embedded in the smooth endoplasmic reticulum. The cytochrome P450 monooxygenase system (CYP) is important in the oxidative biotransformation of drugs (refer to Figure 2-4 in Brenner and Stevens) and is able to catalyse the biotransformation of a variety of drugs with different chemical structures. A few CYP enzymes can carry out hydrolytic reactions, and some are also involved in certain reductive reactions.
- In **phase II biotransformation** reactions drugs are made more **hydrophilic** by **conjugation with endogenous compounds** (attachment of a substituent group). Acetyl, methyl sulphate and glucuronyl groups are the groups most often conjugated, and conjugation generally results in the drug becoming inactive (refer to Figure 2-5 in Brenner and Stevens). Most conjugation reactions occur in the liver, but the lungs and kidneys may also be involved.

2.6.2 First-pass metabolism

Some drugs are metabolised very efficiently by the liver and the gut wall, so that the amount of drug that is available in systemic circulation is far less than the amount that is absorbed. Drugs that are administered orally enter the liver before entering circulation, and if they are metabolised efficiently to an inactive form they will have low bioavailability because of this (refer to Figure 2-2 in Brenner and Stevens). This is called the **first-pass effect** or **first-pass metabolism**. Drugs administered by other methods of administration

(e. g. parenterally) may not undergo first-pass metabolism. This needs to be taken into account when determining dosage for different methods of administration.

2.6.3 Activity 2.3

Do the following activity and add it to your portfolio.

a) Discuss oxidative, hydrolytic and reductive reactions involved in the biotransformation of drugs.
b) Some drugs may either inhibit or induce cytochrome P450 monooxygenase systems (CYP) if taken concurrently with other drugs that are metabolised by the same CYP enzymes. How may these drugs affect the metabolism of the other drugs?
c) Read the section, "Pharmacogenomics" on page 15 in Brenner and Stevens and discuss how polymorphisms in the genes that encode for the following enzymes can influence the metabolism of certain drugs:
    - variations in acetyltransferase activity
    - variations in CYP2D6 and CYP2C19
d) Describe first-pass metabolism.

2.6.4 Feedback on activity 2.3

The oxidative, hydrolytic and reductive reactions involved in biotransformation of drugs are described on pages 12–14 in Brenner and Stevens. Did you refer to the cytochrome P450 monooxygenase system (CYP)?

Imagine that drug A induces CYP enzymes. If an additional drug, drug B, which is metabolised by the same CYP enzymes, is taken, then the bioavailability of drug B will be lower in the presence of drug A than in its absence, because the induction of the CYP enzymes will increase the metabolism of drug B.

2.7 DRUG AND METABOLITE EXCRETION

Recommended reading: the section entitled "Drug excretion" on pages 15– 17 in chapter 2 of Brenner and Stevens

Drug elimination is the **loss of drug from the body**, and can occur through metabolism and excretion of the drug. Drugs are excreted mainly in the urine, but they may be excreted to a limited degree in saliva, sweat, bile, faeces, tears, breast milk and exhaled air. Drugs may be excreted either unchanged or as metabolites.

Renal drug excretion

Drugs vary greatly in the rate at which they are excreted in the urine by the kidneys. Drugs that are excreted in the urine may be in their original form, or may be drug metabolites. Refer to Box 2-2 in Brenner and Stevens, which describes the renal excretion and clearance of penicillin G.

Many drugs, especially larger drugs with molecular masses higher than 300, are excreted in the bile. Conjugation of drugs by phase II reactions enhances bile excretion. Bile empties into the intestine, and sometimes these drugs are reabsorbed by the intestine. This is called **enterohepatic recycling** (refer to Figure 2-6 in Brenner and Stevens). Before reabsorption, the excreted drugs may be hydrolysed back to the parent drug by intestinal bacteria. This process reduces the elimination of drug from the body.

2.7.1 Activity 2.4

Do the following activity and add it to your portfolio.

a) Describe renal drug excretion. Be sure to mention glomerular filtration, active tubular secretion and passive tubular reabsorption.
b) Determine the renal clearance if the excretion rate is 1500 μg/min and the plasma drug concentration is 5 μg/ml.
c) The pH of the urine can be manipulated to increase the excretion of a drug; this may be used to enhance the excretion of poisons and drugs if excess drug has been taken. Explain how this process works.
d) Describe enterohepatic cycling.

2.7.2 Feedback on activity 2.4

The renal clearance for question b) is 300 ml/min.

Urine acidification and alkalinisation in the treatment of drug overdose is described in Box 2-3 in Brenner and Stevens.

2.8 QUANTITATIVE PHARMACOKINETICS

Recommended reading: the section entitled "Quantitative pharmacokinetics" on pages 17–23 in chapter 2 of Brenner and Stevens

Quantitative pharmacokinetics involves formulating models that can relate the **plasma concentration** of drugs to the rate of drug **absorption**, **distribution**, **metabolism** and **elimination**. The way the body deals with drugs can be very complex, and so simpler models that describe the behaviour of drugs in the body mathematically are formulated. The basic type of model used in pharmacokinetics is the **compartment model**.

Two compartment models are typically used:

- the one-compartment model and
- the two-compartment model (refer to Figure 2-7 in Brenner and Stevens).

The **one-compartment** model is simpler, and the drug concentration at a specific time is the amount of drug in the body at the time divided by the volume of the compartment.

In terms of the **two-compartment** model the drug is absorbed into the blood (central compartment) and is then distributed into the tissues. The concentration of drug in the blood and the tissues may differ, and is dependent on the distribution of the drug to the tissues.

These models are used to predict how the concentration of drug changes in the body over time, and therefore how the effect of the drug changes.

2.8.1 Drug plasma concentration curve

The concentration of drug in the **blood** is usually determined as a way of assessing the drug concentration in the body. A drug plasma concentration curve is a **graph** showing the **change in plasma drug concentration over time after administration of the drug**. Figure 2-8A in Brenner and Stevens shows a typical drug plasma concentration curve after the oral administration of a single dose of drug.

The important features to take note of are:

- C_{max},

- T_{max},
- minimum effective concentration (MEC),
- duration of action and
- area under the curve (AUC).

This type of curve can be useful when comparing the bioavailability of different pharmaceutical formulations or drugs administered by different routes.

2.8.2 Bioavailability, volume of distribution and drug clearance

The fraction of administered drug that enters systemic circulation in active form is its **bioavailability.** The calculation of the bioavailability of an orally administered drug is shown in Figure 2-8B. The bioavailability of orally administered drugs can change depending on a number of pharmaceutical and biological factors, which include:

- the extent of tablet disintegration
- gastric pH, which may inactivate the drug
- variations in enzyme activity in the gut wall and liver of individuals, which may inactivate a greater or lesser portion of the drug
- the effect of food on drug absorption

The bioavailability of a specific drug preparation cannot be defined, as it will vary from individual to individual and each time it is administered.

Another important parameter is the **volume of distribution** (V_d). The volume of distribution is the **volume of fluid required to dissolve the total amount of drug that is in the body, such that it has the same concentration as it has in the plasma**. It is an important indicator of how well the drug is distributed into the body fluids and tissues. The calculation of the volume of distribution of drug is shown in Figure 2-9 in Brenner and Stevens. Because the V_d is a measure of the extent of distribution of a drug, it will depend on how much drug enters each compartment.

- If a drug is found evenly distributed in the extracellular and intracellular fluid (distributed extensively in tissues and body fluids), then the V_d value will be equivalent to the total body water.
- If, however, the drug is found mostly in the plasma and at lower concentrations in the tissues, then the V_d value will be lower.
- If the V_d value is much greater than the volume of body fluid, this indicates that the drug is concentrated in the tissues rather than being in the plasma.

Although the V_d value indicates the extent of distribution of a drug in the body, it does not give any information as to which tissues the drug can be found in. Two different drugs may have the same V_d value, but one may be found predominantly in the muscle tissue, whereas the other may be found predominantly in the adipose tissue.

Drug **clearance** (Cl) is a measure of the **rate of elimination of drug from the body**. It is defined as the volume of body fluid from which a drug is removed per unit time, and is calculated in Box 2-2 in Brenner and Stevens.

2.8.3 Single dose pharmacokinetics

Most drugs exhibit first order kinetics.

- In **first order kinetics** the rate of drug elimination is **proportional** to the plasma drug concentration.

- In **zero order kinetics** the rate of elimination is **constant** and **independent** of the plasma drug concentration (refer to Figure 2-10, which shows the difference between first and zero order kinetics).

If a drug shows first order kinetics, then the drug plasma concentration at any time can be determined from the dose of drug and its rate of clearance. For a drug displaying first order kinetics the rate of elimination is equal to the plasma drug concentration multiplied by the drug clearance. The rate of clearance should remain constant if the renal and hepatic function remains the same. If there is progressive liver or kidney disease, the rate of clearance may change over time.

The **elimination half-life** ($t_{1/2}$) is the time that is needed to reduce the concentration of drug by half. It is usually determined from the plasma drug concentration curve (refer to Figure 2-11 in Brenner and Stevens). A number of physiological differences can change the volume of distribution or drug clearance, which will affect the elimination half-life.

In zero-order kinetics the rate of drug elimination is constant (refer to Figure 2-10B in Brenner and Stevens). In most cases drug elimination follows zero-order kinetics because the elimination process becomes saturated.

2.8.4 Continuous and multiple dose kinetics

Most drugs are not given as a single dose, but instead in multiple doses or continuously (intravenous administration). If a drug shows first order kinetics and is given to a patient continuously or in multiple doses, the drug concentration will increase until it reaches a steady state concentration. Refer to Figure 2-12 in Brenner and Stevens. At steady-state equilibrium the rate of drug elimination equals the rate of drug administration. The time taken to reach steady-state depends on the elimination half-life of the drug. For first-order processes, the time taken to reach the steady-state drug concentration is about five half-lives. The steady-state drug concentration will depend on the half-life of the drug and the drug dose administered per unit time. Refer to Figure 2-13 in Brenner and Stevens, which shows the change in plasma drug concentration after continuous or intermittent drug administration.

2.8.5 Dosage calculations

The **loading dose** is the dose of drug that is required to raise the plasma drug concentration to a therapeutic level quickly. The loading dose is typically administered as a single dose, although it may be split up into several doses to be given over a number of hours if the drug is particularly toxic.

The **maintenance dose** is the dose that is required to maintain the chosen drug plasma concentration. It is dependent on the rate of elimination of the drug. When drugs are administered orally, then the bioavailability of the drug also needs to be taken into account.

The method for calculating the loading dose and maintenance dose is described in Box 2-4 in Brenner and Stevens.

2.8.6 Activity 2.5

Do the following activity and add it to your portfolio.

a) Define C_{max}, T_{max}, minimum effective concentration, duration of action and area under the curve. Can you find these values on a drug plasma concentration curve?
b) Explain how Vd values can be interpreted.
c) Discuss drug clearance, specifically renal clearance and hepatic clearance.

d) A drug has a Vd value of 17 l. The desired plasma concentration is 10 mg/l. Calculate the loading dose.
e) Answer the review questions at the end of chapter 2 on page 27 of the textbook.

2.8.7 Feedback on activity 2.5

Drug clearance is discussed on page 20 in Brenner and Stevens. A renal drug clearance rate greater than 100 ml/min indicates that the drug undergoes tubular secretion. Do you understand what this means? If not, go back to the section in the textbook on tubular secretion. Did you explain what a renal drug clearance rate of less than 100 ml/min indicates?

Refer to the equation in Box 2-4 to help you calculate the loading dose of a drug.

LEARNING UNIT 3

Pharmacodynamics

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3.1 INTRODUCTION

Pharmacodynamics is the study of the **mechanisms of action by which drugs produce their effect**. The pharmacologic response of drugs is brought about through the **chemical interaction of drugs** with **one or more constituents of cells**. The sites where drugs bind are referred to as **drug targets**. After a drug binds a target the receptor often activates a **signal transduction pathway**, and secondary messengers then bring about a change within the cell. The mechanism by which a drug molecule binds that leads to a physiological response is an important part of pharmacologic research.

In this learning unit I will describe some drug targets and the mechanisms by which they exert an effect. To complete the study unit, you will need to refer to **chapter 3** in Brenner and Stevens.

3.2 LEARNING OUTCOMES

Upon completion of this learning unit you should be able to:

- define pharmacodynamics and relate it to pharmacokinetics
- describe the different types of drug receptors
- explain signal transduction
- explain how drugs bind to receptors

- describe the difference between a graded dose-response and quantal dose-response relationship, and explain when each is used

3.3 TYPES OF DRUG RECEPTORS

Recommended reading: the sections entitled "Nature of drug receptors" and "Drug receptor interactions" on pages 26–30 in chapter 3 of Brenner and Stevens

The term "receptor" is generally used to describe the target molecules by means of which physiological mediators such as hormones and neurotransmitters produce their effects. The term "receptor" may also be used to refer to any target molecule that a drug molecule can interact with to elicit a specific effect. In this instance, enzymes and other molecules may also be referred to as receptors (refer to Table 3-1 in Brenner and Stevens, which lists a number of important drug receptors).

Drugs generally produce their effects by interacting with various proteins. There are four main types of regulatory protein molecules that are common primary drug targets. They are:

- receptors
- enzymes
- membrane transport proteins
- ion channels

Drugs that affect enzymes do so by binding and inhibiting the function of the enzyme by either **competitive** or **noncompetitive** inhibition. Membrane transport proteins, for example neurotransmitter transporter proteins, may be bound by re-uptake inhibitors, which changes their activity. In the case of ligand-gated ion channels the drugs may either bind to the same site as the endogenous ligand or they may bind at an allosteric site, and in that way influence the flow of ions through the ion channel.

A few drugs do not interact with proteins, but instead interact directly with **DNA**. Many antimicrobial agents and antitumour drugs belong in this category. Other drugs interact directly with **lipids** and **phospholipids** in the cell membrane to elicit a response.

We will now look at four different types of drug receptors in greater detail.

3.3.1 G protein-coupled receptors

The biggest family of drug receptors for pharmaceutical agents is the G protein-coupled receptors (GPCRs). Refer to Figure 3-1 in Brenner and Stevens, which shows the typical structure of a GPCR. GPCRs are the receptors for many endogenous ligands and drugs such as acetylcholine, epinephrine, opioids and serotonin. Signal transduction in these receptors is well understood, and involves the following steps:

1. Ligand binding
2. Conformational change in receptor
3. Receptor interaction with effector molecule
4. Interaction of effector molecule with secondary messengers
5. Physiological effect

Refer to Figure 3-4 and the associated text in Brenner and Stevens discussing signal transduction in GPCRs.

3.3.2 Ligand-gated ion channels

Ligand-gated ion channels are **tetrameric** or **pentameric membrane proteins**. When drugs or ligands bind to ligand-gated ion channels, the movement of ions through the channels changes. These types of channels are especially important in the nervous system, and we will discuss them in greater detail in later learning units.

3.3.3 Kinase and related receptors

There are many membrane-bound enzymes that serve as receptors for drugs and transmit signals across the cell membrane. Structurally they have an extracellular ligand binding domain linked to an intracellular domain by a membrane spanning region. The function of the receptor depends on the enzyme activity of the intracellular domain.

3.3.4 Nuclear receptors

Receptors for some steroid hormones, such as oestrogen, are present in the cytoplasm of cells and are translocated into the nucleus when bound to their steroid ligand. This type of receptor is known as a **nuclear receptor**. The nuclear receptors are **ligand-activated transcription factors that modify gene transcription by binding to specific DNA sequences upstream of specific genes, which influences transcription of those genes**. Refer to Figure 3-2, which illustrates the binding of a steroid hormone to a nuclear receptor. Nuclear receptors are important drug targets, and are accountable for the physiological effects of approximately 10% of prescription drugs.

The nuclear receptor family consists of two main classes of receptors: the **type I** receptors and the **type II** receptors. The two types of receptors have similar structures.

- Type I nuclear receptors include the receptors for a number of steroid hormones, including glucocorticoid receptors, mineralocorticoid receptors as well as the receptors for oestrogen, progesterone and androgen. They become activated when steroids diffuse through the cell membrane and bind to them.
- Type II nuclear receptors are generally present in the nucleus. These receptors include receptors for nonsteroid ligands such as thyroid hormone, vitamin A and vitamin D. Both types of receptors, when activated, bind specific DNA sequences influencing transcription.

3.3.5 Activity 3.1

Do the following activity and add it to your portfolio.

Remember, these activities serve as part of your summary to use in preparing for the exam!

a) What is the difference between a competitive and noncompetitive inhibitor?
b) What are stereoisomers?
c) Explain what G protein-coupled receptors are, and discuss signal transduction in G protein- coupled receptors.
d) Explain what tyrosine kinase receptors are. What types of ligands activate these receptors, and how do they change the activity of specific enzyme cascades?
e) Describe how type I nuclear receptors are activated.

3.4 DRUG RECEPTOR INTERACTIONS

Recommended reading: the section entitled "Drug receptor interactions" on pages 26–30 in chapter 3 of Brenner and Stevens

Drugs generally bind to receptors by forming hydrogen, ionic or hydrophobic bonds with a specific site on a specific receptor molecule (refer to Figure 3-3 in Brenner and Stevens). Drugs are often **stereospecific**, in that only **one** of their stereoisomers will bind to a receptor. Because the binding is reversible, the amount of drug bound will be determined by the concentration of the drug in the surrounding area and the drug– receptor association and dissociation rate constants. Refer to the equation in Brenner, in the section entitled "Receptor binding and affinity" on page 27. The affinity of a drug is a measure of the strength of the drug–receptor interaction. If the association and disassociation rate constants for drug–receptor binding are k1 and k2 respectively, then the ratio of k2 to k1 is the KD. The lower the KD, the greater the affinity of the drug for the receptor.

Binding of a drug molecule to a receptor may or may not result in activation of the receptor. Activation of a receptor occurs if the receptor is affected by the bound molecule such that it elicits a response in the tissue.

- If a drug binds and activates a receptor, then it is classified as an **agonist**.
- If a drug binds to a receptor and does not cause activation, but does stop the binding of the agonist, then it is called a **receptor antagonist**.

The propensity of a drug to bind to a receptor is its **affinity**, while the tendency of a drug to activate the receptor is called its **efficacy**.

Drugs that have intermediate levels of efficacy are called **partial agonists**. **Full agonists** can produce the maximal tissue response, and therefore have maximal efficacy. Full agonists work by increasing the rate of signal transduction when they bind to receptors, whereas **inverse agonists** decrease the rate of signal transduction. There are only a few known inverse agonists.

A few drugs bind permanently to receptors by covalent bonds. A **competitive antagonist** will reversibly bind to the same site as an agonist, whereas a **noncompetitive antagonist** will bind irreversibly, generally by the formation of a covalent bond.

3.4.1 Receptor regulation and drug tolerance

The affinity of receptors for ligands and drugs can be reduced if there is continuous or repeated exposure of the receptor to agonists. This reduction in affinity is called **desensitisation** or **tachyphylaxis**. The number of receptors (density) on the cell surface can also be reduced; this is known as **down-regulation**.

Continuous or repeated exposure to antagonists can result in **supersensitivity**, which is an increased response of the receptor. Antagonists may also induce **up-regulation** of the number of receptors on the cell surface.

Drug tolerance may be pharmacodynamic or pharmacokinetic in nature. Pharmacokinetic tolerance can result if there is accelerated drug elimination. Pharmacodynamic tolerance is due to adaptions at a receptor level, for example receptor down-regulation.

Some diseases also alter the number and function of receptors altering the body's response to certain drugs.

3.4.2 Activity 3.2

Do the following activity and add it to your portfolio.

a) Define the terms "agonist", "antagonist", "affinity" and "efficacy".
b) What is the difference between a competitive antagonist and a noncompetitive antagonist?

c) Describe how drug tolerance occurs at a cellular level.
d) Under what conditions may the number of receptors be up-regulated, and under what conditions may the number of receptors be down-regulated?

3.5 DOSE–RESPONSE RELATIONSHIPS

Recommended reading: the section entitled "Dose–response relationships" on pages 30–32 in chapter 3 of Brenner and Stevens

The relationship between the drug concentration at the receptor site and the effect of the drug is called the dose–response relationship. It is useful to compare the potencies of different drugs that produce similar effects by examining dose–response curves showing the relationship between the dose of drug and the magnitude of the effect of the drug. Refer to Figure 3-5A in Brenner and Stevens, which shows a graded dose–response graph.

The **potency** of a drug is typically expressed in terms of the **median effective dose** (ED50), which is the concentration of drug required to produce 50% of the maximal response. The lower the ED50 value, the more potent the drug. More potent drugs typically have a greater affinity for their receptors, and so less drug is needed to elicit an effect.

The maximal response produced by a drug is called its **efficacy**. Drugs that have maximal efficacy are called **full agonists**, and those that produce less than maximal efficacy are known as **partial agonists**. No matter how high the dose of drug administered, a partial agonist will never have maximal efficacy (refer to Figure 3-5A in Brenner and Stevens; drug T is a partial agonist). Even if a partial agonist were to bind every available receptor, it would not result in a maximal response.

An antagonist has no efficacy, but may have an effect on the dose–response curve of an agonist. The effect of the antagonist will depend on whether it is competitive or noncompetitive (refer to Figure 3-5B in Brenner and Stevens).

In the section above we have been describing a **graded dose–response** relationship, where the percentage of maximal response can be calculated and plotted against log of the dose of drug. A **quantal dose–response** relationship is the percentage of patients that have exhibited a defined all- or-none response at different doses of drug. Refer to Figure 3-6 showing a quantal dose–response relationship.

Quantal relationships can be used to calculate the **therapeutic index** (TI) and the **certain safety factor** (CSF) of a drug.

3.5.1 Activity 3.3

Do the following activity and add it to your portfolio.

a) Define the terms "maximal response", "potency", "efficacy" and "median effective dose" as they relate to drugs.
b) Describe the difference between a graded dose–response relationship and a quantal dose–response relationship.
c) What is the difference between a full agonist and a partial agonist?
d) If a partial agonist is administered with a full agonist, maximal efficacy may not occur. Why is this?
e) How do competitive and noncompetitive antagonists affect an agonist's dose–response curve? Give reasons for your answer.
f) Explain what the therapeutic index of a drug is, and how it can be determined.

g) Explain what the certain safety factor (CSF) of a drug is, and how it can be determined.

3.5.2 Feedback on activity 3.3

If a partial agonist is administered with a full agonist, maximal efficacy may not occur, because the partial agonist will bind the receptor and act as an antagonist, blocking the full agonist from binding enough receptors to elicit the maximal response.

Competitive antagonists bind reversibly. Therefore, if the dose of agonist is high enough, it will be able to displace all the antagonist drug molecules and a maximal response will occur. This means that competitive antagonists shift the curve to the right, but the maximal response is not reduced.

The effects of noncompetitive antagonists cannot be overcome by increasing the agonist concentration, as the antagonist binds to the receptor in such a way that the effects of the agonist are reduced. Therefore the curve shifts to the right, and a maximal response will never occur.

LEARNING UNIT 4

Drug development, safety and interactions

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4.1 INTRODUCTION

Before any drug enters the market for clinical use it needs to be thoroughly tested for efficacy and safety. This process is a long and expensive exercise, and many drugs that appear promising in the early stages of testing need to be discarded because they either do not work or are unsafe.

Some drugs interact with each other, causing unwanted effects that may be life threatening. Many drugs cause side effects. The reasons for the adverse effects of drugs are numerous and typically depend on various biological factors of the individual who is taking the drug. Neonates and the elderly are specifically susceptible to drug toxicity, as they cannot metabolise and excrete all drugs as effectively as healthy adults.

In this learning unit we will look at the process of drug design, clinical trials, the potential adverse effects of and the interactions that can occur between certain drugs. You need to understand what causes the adverse effects of drugs and what factors affect drug safety and efficacy. To complete the study unit, you will need to refer to **chapter 4** in Brenner and Stevens.

4.2 LEARNING OUTCOMES

Upon completion of this learning unit you should be able to:

- discuss the process of drug development
- explain the difference between phase I, phase II and phase III clinical trials
- discuss the potential side effects of drugs and the reason for these side effects
- discuss the different types of interactions that can occur between drugs and explain the mechanisms of these interactions
- discuss the effects of age, disease status and pregnancy on drug safety and efficacy

4.3 DRUG DEVELOPMENT

Recommended reading: the section entitled "Drug development" on pages 34–36 in chapter 4 of Brenner and Stevens

Drug development and approval in different countries share similar features. In South Africa the Medicines Control Council (MCC) is a statutory body that regulates the implementation of clinical trials and registration of drugs for use in South Africa. Because the textbook deals with drug development in the United States, we will discuss drug development in that country. Keep in mind that although drug development procedures in South Africa will be similar, there may nevertheless be a few differences.

Figure 4-1 in Brenner and Stevens outlines the process of drug development from drug discovery to postmarketing surveillance. New drugs can be isolated from natural sources or may be synthesised de novo. These drugs then need to be tested to determine their pharmaceutical properties. The drug now enters the pre-clinical stage where it is tested in animals for toxicity, teratogenesis, mutagenesis and carcinogenesis. The pharmacokinetic and pharmacodynamic properties are also investigated. As animals have a different physiology from humans, animal studies do not always expose all the adverse effects that may occur in humans.

If the drug passes all the above-mentioned tests, then clinical trials in humans may be started. Clinical trials are divided into three phases.

- Phase I – determine pharmacokinetic properties and safety in healthy human subjects
- Phase II – determine the efficacy and safety of the drug in human subjects who have the disease that the drug being tested targets
- Phase III – determine the safety and efficacy of the drug in large numbers of people

Once a drug passes all the clinical trials, it then needs to be approved for marketing to the general public. Each country will have its own organisation that will either approve or reject a drug for use in that country after reviewing all the data on the drug.

Once a drug is marketed, postmarketing surveillance is important. This is sometimes referred to as phase IV. During phase IV, uncommon drug reactions that were not seen in the clinical trials may become apparent. Some of these reactions may be life threatening, and may therefore necessitate removal of the drug from the market.

4.4 DRUG SIDE EFFECTS

Recommended reading: the section entitled "Adverse effects of drugs" on pages 38–39 in chapter 4 of Brenner and Stevens.

Many drugs have side effects. Adverse side effects are typically due to:

- excessive pharmacologic effects
- hypersensitivity reactions
- adverse effects on organs and tissues

Many of the adverse effects of drugs are difficult to predict because their manifestation depends on the drug susceptibility of the individual patient. Refer to Table 4-2 in Brenner and Stevens for a list of some drug-induced organ toxicities.

4.4.1 Activity 4.1

Do the following activity and add it to your portfolio.

Remember, these activities serve as part of your summary to use in preparing for the exam!

Read the section "Adverse effects of drugs" on pages 38–39 and answer the following questions.

a) What is meant by "excessive pharmacologic effects"? How can these effects be managed?
b) What is a hypersensitivity reaction?
c) Describe the four different types of hypersensitivity reactions that can occur when a person is taking drugs.
d) Discuss haematopoiesis, hepatotoxicity and nephrotoxicity.
e) What are idiosyncratic reactions?

4.5 DRUG INTERACTIONS

Recommended reading: the section entitled "Drug interactions" on pages 39–41 in chapter 4 of Brenner and Stevens.

Drug interactions occur when a drug interacts with another drug or food, and this changes its pharmacologic effect. Refer to Table 4-3 in Brenner and Stevens, which lists the types and mechanisms of drug interactions.

Pharmaceutical interactions are the **chemical reactions** that occur **between two drugs before they are administered or absorbed**. This may be a problem if two drugs are combined to be given intravenously or if somebody takes two sets of tablets simultaneously, as a result of which the pharmaceutical agents mix in the gut. Most drugs do not react with each other, but some do, and this reduces their efficacy.

Pharmacodynamic interactions are interactions that occur when **two drugs have an additive, synergistic or antagonistic effect on a tissue, organ system, microbe or cancer cell**.

Pharmacodynamic interactions can occur when two drugs interact with the same receptor or affect the same physiological function due to actions on different receptors.

Pharmacokinetic interactions occur as a result of:

- altered drug absorption
- altered drug distribution
- altered drug biotransformation
- altered drug excretion

Various mechanisms may be responsible for pharmacokinetic interactions. You will see some of these in Table 4-3 in Brenner and Stevens.

The **clinical significance of drug interactions** depends on the drugs being administered. In some cases the drugs should never be administered concurrently, while in other instances the dosage of drugs can be adjusted to avoid adverse reactions. Refer to Table 4-4 in Brenner and Stevens, which describes some clinically significant drug interactions.

4.5.1 Activity 4.2

Do the following activity and add it to your portfolio.

a) Explain the difference between an additive and a synergistic effect.
b) Explain what an antagonistic effect is.

c) Describe the various interactions that can alter drug absorption, drug distribution, drug biotransformation and drug excretion. Give specific examples.
d) Describe how antibiotics can affect the pharmacological action of contraceptives. Be sure to mention enterohepatic cycling.

4.6 DRUG SAFETY

Recommended reading: the section entitled "Factors affecting drug safety and efficacy" on pages 42–43 in chapter 4 of Brenner and Stevens.

A person's response to a particular drug can vary depending on several factors, such as age and disease status. Pregnancy and the effects of drugs on the unborn foetus also need to be taken into account when determining the safety of a drug.

Age

The factors influencing drug disposition in individuals of different ages is summarised in Table 4-5 in Brenner and Stevens. The elderly and neonates tend to have a reduced capacity to metabolise and excrete drugs, and this needs to be taken into account when determining dosages.

Disease

A number of diseases can affect an individual's capacity to absorb, metabolise and excrete drugs. Hepatic and renal diseases may have a significant influence on a person's ability to metabolise and excrete drugs, and may require that the dose be adjusted to reduce the chance of toxicity.

Pregnancy

Many drugs can have an unfavourable effect on a foetus during pregnancy or an infant that is being breastfed. Between 1 and 5% of foetal malformations can be linked to the use of drugs during pregnancy. Drug-induced developmental abnormalities are called **teratogenic effects**. The greatest risk of teratogenic effects occurs in the fourth to tenth week of gestation. Refer to Table 4-6 in Brenner and Stevens, which gives some examples of teratogenic drugs.

Drugs are divided into 5 categories according to their safety in pregnant women:

- Category A – demonstrated to pose no risk to the human foetus
- Category B – no risk in human studies, some effects in animal studies
- Category C – adverse effects in animals, insufficient data relating to humans
- Category D – evidence of risk to foetus
- Category X – contraindicated in pregnancy

Some drugs pose a risk of toxicity to infants that are being breastfed.

4.6.1 Activity 4.3

Do the following activity and add it to your portfolio.

Read the section, "Factors affecting drug safety and efficacy" on pages 42–43 in Brenner and Stevens and answer the following questions.

a) Discuss the effect of age and disease status on drug metabolism and elimination.
b) Describe why many drugs are contraindicated during pregnancy.

LEARNING UNIT 5

Neurotransmission and the peripheral nervous system

CONTENTS

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5.1 INTRODUCTION

The nervous system is made up of the **central nervous system (CNS)** and the **peripheral nervous system (PNS)**. The **CNS** consists of the **brain** and **spinal cord**. We will be discussing it in learning unit 7. The **peripheral nervous system** includes the **autonomic** and **somatic nervous system**.

Drugs that affect the nervous system typically do so by influencing **neurotransmitters**.

- They may affect the synthesis, storage, release, activity or neuronal uptake of neurotransmitters, or
- they may block or activate the neurotransmitter receptors.

If a drug interacts with a specific neurotransmitter, its effects will depend on the **distribution** of the neurotransmitter and its receptors in the nervous system. Some drugs will therefore affect the **entire** nervous system, whereas others will be more **specific** for either the peripheral or the central nervous system.

In this learning unit we will look at the anatomy and physiology of the peripheral nervous system and how drugs can be used to affect nervous system function. To complete the study unit, you will need to refer to **chapter 5** and the beginning sections of **chapters 6, 8 and 9** in Brenner and Stevens.

5.2 LEARNING OUTCOMES

Upon completion of this learning unit you should be able to:

- describe the function of the peripheral nervous system
- explain how neurotransmission occurs
- describe the different types of acetylcholine receptors
- describe the different types of adrenoceptors
- discuss how drugs can influence cholinergic neurotransmission
- discuss how drugs can influence adrenergic neurotransmission

5.3 THE PERIPHERAL NERVOUS SYSTEM

Recommended reading: the section entitled "Anatomy and physiology of the peripheral nervous system" on page 46 in chapter 5 of Brenner and Stevens.

The peripheral nervous system includes the **autonomic** and **somatic** nervous system.

- The autonomic nervous system is **unconsciously controlled**, and regulates functions such as heart rate, digestion, respiratory rate, perspiration, pupil dilation, and many metabolic activities.
- The somatic nervous system controls voluntary body movements via **skeletal muscle contraction**.

Both are ultimately controlled by the central nervous system.

The autonomic nervous system can be divided into three sub-systems:

- the parasympathetic nervous system,
- the sympathetic nervous system and
- the enteric nervous system.

The parasympathetic nervous system and the sympathetic nervous system often have opposite effects on organ function (refer to Figure 5-2).

- The **"fight or flight"** response is activated by the **sympathetic** nervous system (note its effects on the organs in Figure 5-2, for example increased heart rate).
- The **parasympathetic** nervous system is the **"rest and digest"** system and results in reduced heart rate and increased digestion.
- The **enteric** nervous system regulates **gastrointestinal mobility and secretion**.

Activation of the parasympathetic nervous system **stimulates** the enteric nervous system, and activation of the sympathetic nervous system **inhibits** the enteric nervous system.

5.4 NEUROTRANSMISSION

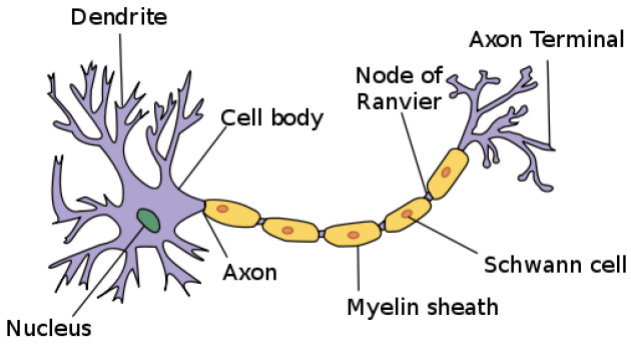
Figure 5.1 below shows the structure of a typical neuron. Neurons can be divided into three main parts:

- the cell body (soma),
- the dendrites and
- the axon.

Two neuronal cells interact with each other by synapses, which are membrane junctions that allow signals to be passed from one neuron to the next. The synaptic signals from one of the neurons are collected by the dendrites and soma of the other neuron. These signals may be either **excitatory** or **inhibitory**. If the net signal is a large enough excitatory signal, then the neuron generates an electrical impulse called an **action potential**. The action potential travels down the axon and activates the axon termini, passing the signal to the next neuron.

FIGURE 5.1

Typical neuron of the peripheral nervous system



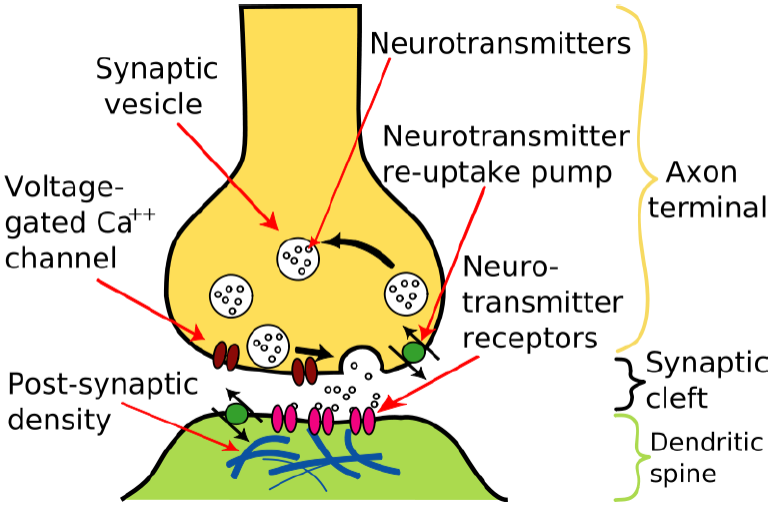
(http://en.wikipedia.org/wiki/File:Neuron_Hand-tuned.svg)

Signals are transmitted through the synaptic space by the action of neurotransmitters that are released by the neurons. Neurotransmitters are produced in neuronal cells and are stored in neuronal vesicles. The neurotransmitters are released when there is membrane depolarisation due to calcium flux into the cell. The calcium causes the neuronal vesicles to fuse with the membrane of the cells, and they are released by exocytosis (refer to Figure 5.2 below). These molecules then bind and activate receptors of another neuron, triggering a post-synaptic action potential. The neuron that releases the signals is called the **presynaptic** neuron, and the neuron that the neurotransmitters bind to is called the **postsynaptic** neuron.

The neurotransmitters are either **removed** through reuptake into the presynaptic neuron by neurotransmitter uptake pumps, or they are **degraded** by enzymes found in the cell membranes or cytoplasm in both the presynaptic and post-synaptic cells. Refer to Figure 18-1 in Brenner and Stevens. This process is repeated every time an action potential reaches the axon terminal of the presynaptic neuron.

FIGURE 5.2

Neurotransmitter release



(http://en.wikipedia.org/wiki/File:Synapse_Illustration2_tweaked.svg)

The following online video describes neurotransmission in very basic terms. It is not essential that you watch it, but you may find it helpful.

http://science. education. nih. gov/supplements/nih2/addiction/activities/lesson2_neurotransmission.htm or https://www.youtube.com/watch?v=p5zFgT4aofA

5.5 SPECIFIC NEUROTRANSMITTERS AND RECEPTORS

Recommended reading: the section entitled "Neurotransmitters and receptors" on pages 47–48 in chapter 5 of Brenner and Stevens.

The main neurotransmitters of the peripheral nervous system are:

- acetylcholine, released by cholinergic neurons, and
- norepinephrine, released by adrenergic neurons.

Epinephrine is another important neurotransmitter of the nervous system.

Acetylcholine interacts with acetylcholine receptors, of which there are two main types:

- muscarinic receptors – found mainly at parasympathetic neuroeffector junctions
- nicotinic receptors – found in all autonomic ganglia

The receptors for norepinephrine and epinephrine are called adrenoceptors, and can be divided into two types:

- α-adrenoceptors
- β-adrenoceptors

5.5.1 Acetylcholine receptors

Recommended reading: the section entitled "Overview of cholinergic pharmacology" on pages 53–54 in chapter 6 of Brenner and Stevens.

Muscarinic receptors

Muscarinic receptors are located at parasympathetic neuroeffector junctions in smooth muscle, cardiac tissue, and glands. They are also located in the CNS, on presynaptic sympathetic ganglia and parasympathetic ganglia. Neurotransmitter release is inhibited when the muscarinic receptors on presynaptic ganglia of the autonomic nervous system are activated.

There are **five** subtypes of muscarinic receptors, M1– M5, based on their molecular structures and pharmacological properties. The main subtypes are M1, M2 and M3. Their properties are given in Table 6-1 in Brenner and Stevens. Activation of muscarinic receptors results in the activation of signal transduction pathways, which will result in different effects depending on the cell affected and the type of receptor.

Nicotinic receptors

The nicotinic receptors are acetylcholine-gated sodium channels (refer to Figure 6-1 in Brenner and Stevens) and are located on all autonomic ganglia, at somatic neuromuscular junctions (muscles), and in the central nervous system (brain). Their activation causes sodium to enter the cell, which causes membrane depolarisation.

- In the autonomic ganglia, activation causes excitation, triggering the release of neurotransmitters at postganglionic neuroeffector junctions.
- In somatic nerves, activation leads to the contraction of muscles.
- In the brain (CNS), activation causes excitation of presynaptic and postsynaptic neurons.

5.5.2 Adrenoceptors

Recommended reading: the sections entitled "Overview", "Adrenoceptors" and "Signal transduction" on pages 69–71 in chapter 8 of Brenner and Stevens.

The adrenoceptors are G protein-binding receptors which, upon activation, result in an increase or decrease in the formation of secondary messengers in signal transduction pathways.

α-adrenoceptors

α-adrenoceptors can be divided into two groups, depending on their location and function.

- The α_1-adrenoceptors are found in smooth muscle at sympathetic neuroeffector junctions, exocrine glands and the central nervous system. They mediate smooth muscle contraction, causing vasoconstriction, dilation of the pupils and contraction of the bladder sphincter muscle.
- The α_2-adrenoceptors, when activated, inhibit the release of norepinephrine from sympathetic neurons and decrease the secretion of insulin.

β-adrenoceptors

There are three types of β-adrenoceptors.

- β_1-adrenoceptor activation results in cardiac stimulation with increased heart rate (positive chronotropic effect), increased contractibility (positive inotropic effect) and increased cardiac impulse conduction velocity (dromotropic effect). Activation also increases renin secretion.
- B_2-adrenoceptor activation in smooth muscle results in relaxation including bronchial, uterine and vascular smooth muscle. Activation of β_3-adrenoceptors in the liver results in glycogenolysis, which releases glucose into the blood.
- Activation of β_3-adrenoceptors results in lipolysis in the body.

The primary tissue locations of α-adrenoceptors and β-adrenoceptors is illustrated in Figure 8-1 in Brenner and Stevens. The properties of the α-adrenoceptors and β-adrenoceptors are listed in the same table.

5.6 SITES OF DRUG ACTION

Recommended reading: the section entitled "Neurotransmission and sites of drug action" on pages 48–51 in chapter 5 of Brenner and Stevens.

As you already know, during neurotransmission a number of steps take place. They are:

1. neurotransmitter synthesis
2. neurotransmitter storage
3. neurotransmitter release
4. neurotransmitter interaction with receptors
5. neurotransmitter breakdown or reuptake

Drugs can affect neurotransmission by interfering with any of these steps. Refer to Table 5-1 in Brenner and Stevens, which describes the mechanism of action of some drugs that affect neurotransmission. I will now say more about some specific drugs that affect cholinergic and adrenergic neurotransmission and their effects.

5.6.1 Drugs affecting cholinergic neurotransmission

Acetylcholine is stored in vesicles after being synthesised from acetate and choline by choline acetyltransferase. If a neuronal cell is stimulated, the action potential causes calcium to enter the neuron. The increased calcium levels then facilitate the release of the neurotransmitter by exocytosis. The released acetylcholine then binds the postsynaptic neuron receptors. In the synapse it is quickly hydrolysed into choline and acetate by cholinesterase. The choline is then taken back into the presynaptic neuron. The presynaptic neuron also has autoreceptors for acetylcholine that signal the cell to stop releasing acetylcholine.

There are many different mechanisms of drug action that affect cholinergic neurotransmission. (Refer to Figure 5-3A in Brenner and Stevens, which illustrates the sites of drug action.) None of the drugs that block choline transport into the neuron or prevent the storage of acetylcholine are used clinically. Black widow spider venom and botulinum toxin A are two agents that affect cholinergic neurotransmission by affecting the release of acetylcholine.

Drugs that bind directly to acetylcholine receptors, activating them, are called **direct acting agonists**. Refer to Table 6-2 in Brenner and Stevens for examples of direct-acting acetylcholine receptor agonists. **Indirect acting agonists** are drugs that increase the concentration of acetylcholine or enhance acetylcholine signal transduction rather than binding directly to the receptors. The cholinesterase inhibitors are indirect acting, as they prevent the breakdown of acetylcholine in the synapses. This results in increased activation of the acetylcholine receptors. Refer to Table 6-3 in Brenner and Stevens for examples of cholinesterase inhibitors. Take note of their diverse clinical use.

The acetylcholine receptor antagonists block either muscarinic receptors or nicotinic receptors, and inhibit cholinergic neurotransmission. The muscarinic receptor antagonistic drugs can be used to relax smooth muscle, decrease exocrine gland secretions and increase heart rate. The nicotinic receptor antagonists are typically used to relax skeletal muscle.

5.6.2 Drugs affecting adrenergic neurotransmission

The synthesis of norepinephrine is shown in Figure 18-3.

- In the initial step, **tyrosine** is converted to **dopa**, which is then converted to **dopamine**.
- In the final step, the **dopamine** is converted to **norepinephrine**.

When the neuron is stimulated, the norepinephrine is released into the synapse by calcium- mediated exocytosis. In the synapse the norepinephrine interacts with adrenoceptors of the postsynaptic neuron and with autoreceptors on the presynaptic neuron. Interaction with autoreceptors inhibits the further release of norepinephrine.

Norepinephrine is removed from the synapses by a catecholamine transporter in a process called **reuptake**. Most of the norepinephrine that is taken up is collected in storage vesicles and recycled. Two enzymes,

- catechol-O-methyltransferase (COMT) and
- monoamine oxidase (MAO)

inactivate (break down) excess norepinephrine.

The various agents that affect adrenergic neurotransmission and their sites of action are shown in Figure 5-3B.

Drugs that affect the activity of tyrosine hydroxylase, the enzyme that converts tyrosine to dopa, will inhibit the synthesis of epinephrine and norepinephrine. Other drugs can affect the storage of norepinephrine or the release of norepinephrine when the nerve is stimulated. Drugs that influence the synthesis, storage or release of norepinephrine are called **neuronal blocking agents**.

Adrenoceptor agonists can be divided into three groups:

- the direct acting agonists,
- the indirect acting agonists and
- the mixed-acting agonists.

Because they mimic the effects of activation of the sympathetic nervous system, they can be called **sympathomimetic drugs**. The direct acting agonists include the drugs dobutamine and albuterol. They work by binding directly to the adrenoceptors, causing nerve stimulation. The indirect acting agonists enhance the activation of adrenoceptors by increasing the concentration of epinephrine at the synapse. Cocaine inhibits the catecholamine transporter, and therefore reduces reuptake of norepinephrine, increasing the duration of action of the norepinephrine. Amphetamines also increase the synaptic concentration of norepinephrine. Other drugs can inhibit the breakdown of norepinephrine by inhibiting catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO).

Too much sympathetic nervous system activation can play a part in certain cardiovascular disorders such as hypertension, angina pectoris and cardiac arrhythmias. Therefore drugs that reduce sympathetic stimulation, the most important being **adrenoceptor antagonists**, can be used in the treatment of **cardiovascular disease**.

The adrenoceptor antagonists can block α-adrenoceptors, β-adrenoceptors, or both. The α-adrenoceptor antagonists relax smooth muscle and reduce vascular resistance, and the β-adrenoceptor antagonists reduce cardiac output and heart rate. Both can therefore be used in the treatment of **hypertension**.

The selective α_1-blockers may be used to treat chronic hypertension and urinary obstruction. The nonselective α-blockers block both α_1- and α_2-adrenoceptors, and are used primarily to treat **hypertensive episodes caused by pheochromocytoma**.

The β-blockers can be used to treat **migraine headaches**, **angina pectoris**, **hypertension**, **cardiac arrhythmias** and **glaucoma**.

5.6.3 Activity 5.1

Do the following activity and add it to your portfolio.

a) What effect does black widow spider venom have on the body?
b) Discuss botulinum toxin A. What is its mechanism of action, and how is it used medicinally?
c) Discuss the difference between a direct acting agonist, an indirect acting agonist and a mixed- acting agonist.
d) In your own words, describe cholinergic neurotransmission.
e) Discuss neurotransmission by norepinephrine and the different types of drugs that can be used to effect norepinephrine neurotransmission.

5.6.4 Feedback on activity 5.1

The effects of black widow spider venom and botulinum toxin A are described on page 50 in Brenner and Stevens.

You would have found the information you needed to answer the question on the difference between the direct acting agonists, the indirect acting agonists and the mixed-acting agonists in the section, "Classification of adrenoceptor agonists" on page 71 in Brenner and Stevens.

LEARNING UNIT 6

The central nervous system

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6.1 INTRODUCTION

The central nervous system (CNS) is the portion of the nervous system comprising the **brain** and **spinal cord**. The peripheral nervous system (PNS) consists of the **nerves** and **ganglia** that lead to and from the CNS. The PNS essentially connects the CNS to the limbs and organs of the body, and is involved in passing communications between the brain and the other areas of the body. These communications are processed by the CNS, along with memories and internal drive states, to produce **cognitive**, **emotional** and **motor reactions**. In people with brain disorders CNS processing is affected, and this results in atypical cognitive, emotional or motor responses.

Drugs can be used to alleviate the symptoms of brain dysfunction, but do not generally fix the underlying disorder. As a result, they are typically taken for life. Short-term drug therapy is sometimes used to treat acute conditions, for example insomnia. Most drugs that act on the CNS alter neurotransmitters or their receptors.

In this learning unit we will review CNS neurotransmission, discuss the different neurotransmitters and receptors found in the CNS and describe some of the mechanisms of action of drugs affecting CNS neurotransmission. To complete the study unit, you will need to refer to **chapter 18** in Brenner and Stevens.

6.2 LEARNING OUTCOMES

Upon completion of this learning unit you should be able to:

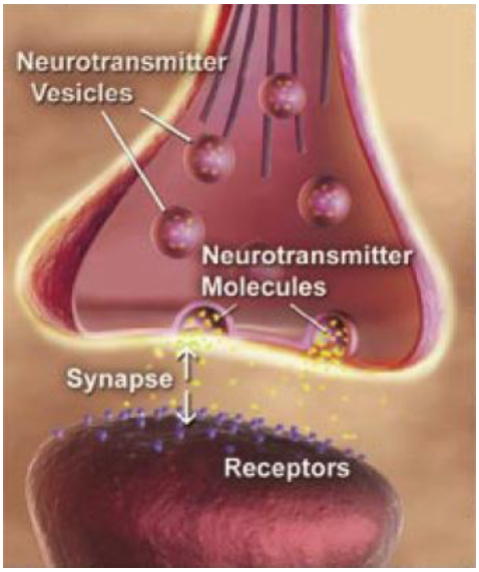
- explain CNA neurotransmission, including:
  - principles of neurotransmission
  - neurotransmitter synthesis and metabolism
  - excitatory and inhibitory neurotransmission
- describe the different neurotransmitters and receptors found in the CNS
- discuss the mechanisms of action of drugs that affect neurotransmission in the CNS

6.3 CNS NEUROTRANSMISSION

Recommended reading: the section entitled "Neurotransmission in the central nervous system" on pages 174–176 in chapter 18 of Brenner and Stevens.

FIGURE 6.1

Diagram illustrating neurotransmission



(http://simple.wikipedia.org/wiki/File:Neurons- axons-dendrites-synapses.PNG)

We discussed the basics of neurotransmission in learning unit 5. Neurotransmission in the CNS is similar to neurotransmission in the PNS. Chemical neurotransmission is well understood in general terms, but we are still finding out more about the details of the process.

Neurons may release more than one type of neurotransmitter. Once they have been released, these neurotransmitters are able to diffuse and affect surrounding neurons at other synapses, not just the direct postsynaptic neuron. All the different neurotransmitters released by the different neurons in a region form a chemical milieu or soup, and the overall effect at any specific synapse will depend on the relative ratios of all the different excitatory or inhibitory neurotransmitters.

Drugs affecting neurotransmission become widely distributed throughout the body and brain and add to the chemical milieu, interacting with neurons and receptors in a number of neuronal tracts.

6.3.1 Neurotransmitter synthesis, release and effects

Neurotransmitters are **synthesised** in the **neuronal cell soma** or **terminals** and are **stored** in **neuronal vesicles**. Membrane depolarisation and calcium influx into the cell results in the release of the neurotransmitters into the synapse. The calcium binds with the membrane of the synaptic vesicles and causes the vesicles to fuse with the membrane. This leads to the release of the neurotransmitter into the synaptic cleft by exocytosis. Refer to Figure 18-1 in Brenner and Stevens.

Once the neurotransmitters are released they diffuse into the synaptic cleft and can interact with receptors on the postsynaptic and presynaptic membranes. The neurotransmitters can also diffuse from their synapse of origin and interact with other neurons in the surrounding region. When neurotransmitters bind to receptor molecules, they trigger effects within the neuronal cell. Neurotransmitters can be described as either **excitatory** or **inhibitory**. Whether the effect is excitatory or inhibitory depends on the **specific type of receptor** that is activated.

The only direct action of a neurotransmitter is to **activate a receptor**.

- If the receptors they interact with **increase** the probability that the target cell will fire an action potential, then they are classified as **excitatory**. If there is a depolarisation of the postsynaptic neural membrane, an excitatory postsynaptic potential will result. If it reaches firing threshold, an action potential will be conducted along the axonal membrane, causing the release of neurotransmitter from the nerve terminal. These neurotransmitters will then interact with receptors on another cell. In this way, the signal is transmitted through the nervous system.
- However, if the receptors that they interact with **reduce** the chance that the target cell will fire an action potential, then they are classified as **inhibitory**. If there is a hyperpolarisation of the neuronal membrane, the firing of an action potential is inhibited.
- Some neurotransmitters interact with both excitatory and inhibitory receptors, depending on which receptors are present on the cell. These receptors **cannot then be classified as either excitatory or inhibitory**.

Receptors in the presynaptic membrane are called **autoreceptors**, and they modulate the release of neurotransmitters from the neuron.

Multiple neurotransmitters at a specific location in a neuronal tract all interact, resulting in a complex interplay of signals, which will govern whether neurotransmission occurs or not. Refer to Box 18-1. If the release of an inhibitory neurotransmitter is **inhibited**, then the chance of neurotransmission in the target neuron will be **increased**. Therefore, the effects of a neurotransmitter on a neuronal system depend on the **connections** of the **neurons** that use the transmitter, and the **chemical properties** of the **receptors** that the transmitter binds to. From this you can see that drugs that either affect the release of neurotransmitters or affect the receptors for those neurotransmitters will have an effect on neurotransmission.

The postsynaptic potentials produced by all neurotransmitters are brief, and neurotransmission is terminated by reuptake or degradation of the neurotransmitters. During reuptake special transporter molecules in the presynaptic membrane move neurotransmitters from the synaptic cleft back into the cytoplasm.

6.3.2 Specific neurotransmitters and receptors found in the CNS

Recommended reading: chapter 18, the section entitled "Neurotransmission in the central nervous system – Neurotransmitters and receptors" on pages 176–180 in chapter 18 of Brenner and Stevens.

You will find the major neurotransmitters of the CNS, their receptors and function listed in Table 18-1 in Brenner and Stevens. There are four main types of neurotransmitter in the CNS:

- acetylcholine,
- amino acids,
- biogenic amines and
- neuropeptides.

The receptors can be divided into two groups:

- ionotropic receptors (ligand-gated ion channels) and
- metabotropic receptors (typically G protein-coupled receptors).

The stimulation of ionotropic receptors changes the influx of ions (calcium, sodium, potassium or chloride) into the cell, resulting in excitatory or inhibitory membrane potentials. The movement of ions into the cell causes a **depolarisation** of the membrane, and is **excitatory**. The movement of ions out of the cell causes **hyperpolarisation** and is **inhibitory**.

The activation of metabotropic receptors with G proteins:

- alters the activity of adenylyl cyclase, affecting cAMP levels
- or results in activation of phospholipase C
- and may also modulate ion channel activity through secondary messengers.

The mechanisms of signal transduction for neurotransmitters in the CNS are similar to those in the autonomic nervous system, which we discussed in learning unit 3.

Let's discuss the neurotransmitters of the CNS in more detail.

6.3.2.1 Acetylcholine

In learning unit 5 you learnt that acetylcholine interacts with two different types of receptors, namely nicotinic and muscarinic receptors. Drugs can affect acetylcholine neurotransmission by either **blocking** or **activating acetylcholine receptors** or by **inhibiting cholinesterase**, which catalyses the hydrolysis of acetylcholine into choline and acetic acid.

In the CNS acetylcholine may be either excitatory or inhibitory, and is involved in **memory**, **sensory processing** and **motor coordination**.

6.3.2.2 Amino acids

The amino acids:

- glutamate,
- aspartate,
- GABA (γ-aminobutyric acid) and
- glycine are important neurotransmitters in the CNS.

GABA and glycine are **inhibitory**, and glutamate and aspartate are **excitatory**.

GABA is produced from **glutamic acid** and is the most common **inhibitory** neurotransmitter in the **brain** and **spinal cord**. GABA interacts with ionotropic GABAA receptors and metabotropic GABAB receptors. Drugs that influence GABA neurotransmission typically activate or inhibit the GABAA receptors (GABAA-chloride ion channel complex). Drugs can activate the GABAA-chloride ion channel complex by increasing the amount of available GABA or by activating the receptors, and typically have

an **anti-anxiety** or **sedative** effect. They include benzodiazepines, barbiturates, general anaesthetics and alcohol.

Glycine is an important **inhibitory** neurotransmitter in the **spinal cord**. Its receptors are sensitive to strychnine, which is a convulsant poison.

Glutamate and **aspartate** act as **excitatory** neurotransmitters in the **brain** and **spinal cord**. They interact with three different types of receptors: NMDA (N-methyl-D-aspartate), AMPA (α-amino-3- hydroxy-5-methyl-4-isoxazole propionate) and kainite receptors. They both play a role in long-term potentiation, which is important for **learning** and **memory**. Antagonists of the glutamate and aspartate receptors are used to treat **seizures** and are used in the treatment of **epilepsy**.

6.3.2.3 Biogenic amines

Dopamine, norepinephrine, serotonin and histamine are **monoamines** that act as neurotransmitters in the CNS.

Dopamine is an important neurotransmitter of the CNS and binds to five types of receptor (D_1–D_5). D_1 and D_5activate adenylyl cyclase, **increasing** cAMP levels, where D_2, $D_3$and D_4**decrease** cAMP levels. Dopamine is involved in **regulation of motor behaviour**, **emesis**, **mood states** (emotional arousal), **prolactin release** and **olfaction**. Individuals with Parkinson's disease generally have low levels of dopamine, and so drugs that increase levels of dopamine in the brain are used to treat **Parkinson's disease**.

Norepinephrine plays a role in the **regulation of anxiety**, **cerebellar function**, **learning**, **memory**, **mood**, **sensory processing** and **sleep**. Drugs that activate or block norepinephrine receptors or that inhibit its reuptake alter norepinephrine neurotransmission.

Serotonin can function as either an excitatory or an inhibitory neurotransmitter. It is involved in **pain** and **emotional processing** and can affect appetite, sleep, memory and learning, mood and behaviour. Drugs alter serotonin neurotransmission by either activating or blocking its receptors or by inhibiting its reuptake.

Histamine plays a role in the **sleep– wake cycle**, **cardiovascular control**, **learning**, **memory** and **regulation of the hypothalamic-pituitary-adrenal axis**. There are no important drugs that alter histamine neurotransmission in the CNS that are used for therapeutic reasons.

6.3.2.4 Neuropeptides

Some peptides can function as neurotransmitters or neuromodulators. They are released by neuronal cells and are removed by a number of peptidases, and do not undergo reuptake. Some peptides act as co-transmitters by prolonging or amplifying the effects of other neurotransmitters. Some examples include the opioid peptides (endorphins) and tachykinins.

6.3.2.5 Other neurotransmitters of the CNS

Nitric oxide, carbon monoxide, appetite-regulating peptides and purines may also act as neurotransmitters in the CNS.

6.3.3 Activity 6.1

Do the following activity and add it to your portfolio.

Remember, these activities serve as part of your summary to use in preparing for the exam!

a) What is strychnine? What effect does it have on neurotransmission and the body?
b) What do NMDA and AMPA stand for?
c) $D_1$and D_5activate adenylyl cyclase, increasing cAMP levels, where D_2, D_3 and D_4 decrease cAMP levels. What effect does this have on the cell?
d) What role do the opioid peptides (endorphins) and tachykinins play in the CNS?

6.3.4 Feedback on activity 6.1

Strychnine interacts with glycine receptors. You would have found the answer in the section on glycine as a neurotransmitter.

We discussed signal transduction and cAMP levels in learning unit 3, and there is information about this on page 28 in Brenner and Stevens.

6.4 MECHANISMS OF DRUG ACTION

Recommended reading: the section entitled "'Mechanisms of drug action" on pages 180–181 in chapter 18 of Brenner and Stevens.

Drugs that modify neurotransmission in the CNS typically act by:

- altering the synthesis, storage or release of neurotransmitters
- blocking the reuptake of neurotransmitters
- inhibiting the degradation of neurotransmitters
- activating or blocking neurotransmitter receptors

Some CNS drugs block membrane ion channels directly or change the neuronal cell membranes directly, **inhibiting neurotransmission**. Lithium has a unique mode of action in that it directly blocks signal transduction within the cell without interacting with the receptors.

6.4.1 Activity 6.2

Do the following activity and add it to your portfolio.

Refer to the section entitled "Mechanisms of drug action" on pages 180–181 in chapter 18 of Brenner and Stevens, and answer the following questions.

a) Discuss some examples of drugs that act by altering the synthesis, storage or release of neurotransmitters.
b) Discuss drugs that either block the reuptake of neurotransmitters or inhibit the degradation of neurotransmitters.
c) Describe receptor activation or blockade by drugs.
d) Drugs can sensitise, desensitise or change the number of receptors on the cell surface. Explain under what conditions this may occur and the effects of increased or decreased receptor numbers. Refer to Figure 18-4 to help you answer the question.

6.5 NEURONAL SYSTEMS IN THE CNS

Recommended reading: the section entitled "Neuronal systems in the CNS" on pages 181–183 in chapter 18 of Brenner and Stevens.

There are six general areas of functional processing carried out by the CNS. They are:

- cognitive processing
- memory
- emotional processing
- sensory processing
- motor processing
- autonomic processing

Various diseases and drug treatments affect these processes.

- Antipsychotics, CNS stimulants, sedative-hypnotics and hallucinogens affect **cognitive processing.**
- Cholinesterase inhibitors and the benzodiazepines affect **memory**.
- Anxiolytic (antianxiety) drugs, antidepressants, antipsychotics, CNS stimulants, opioids and all addictive drugs affect **emotional processing** in some manner.
- Antidepressants, hallucinogens and anaesthetics are examples of drugs that affect **sensory processing**.
- Some examples of drugs affecting **motor processing** include antispasmodics, CNS stimulants, muscle relaxants and sedative-hypnotics.
- Antidepressants, antipsychotics and drugs for Alzheimer's disease all affect **autonomic processing**.

In the next learning unit we will discuss a few disorders of the CNS and the drugs that are typically used to treat them.

6.5.1 Activity 6.3

Do the following activity and add it to your portfolio.

Write a brief description of cognitive processing, memory, emotional processing, sensory processing, motor processing and autonomic processing as carried out by the CNS.

LEARNING UNIT 7

Disorders of the CNS and their treatment

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7.1 INTRODUCTION

Disorders of brain function are a major concern of human society, and many different drugs have been developed to treat CNS disturbances. CNS disorders are treated according to their **symptoms** rather than causative factors, as in many instances the causative factors are unknown. Because many of the disorders of the CNS are caused by different mechanisms, individuals respond to drugs in different ways, and a drug that works to treat a set of symptoms in one individual may not work to treat the same set of symptoms in another individual.

In this learning unit we discuss the pharmacokinetics and mechanism of action of different classes of drugs that are used to treat anxiety, insomnia, epilepsy, schizophrenia and affective disorders. To complete the study unit, you will need to refer to **chapters 19, 20** and **22** in Brenner and Stevens.

7.2 LEARNING OUTCOMES

Upon completion of this learning unit you should be able to:

- discuss the sedative-hypnotic drugs and their use in the treatment of anxiety and insomnia
- describe the different types of epilepsy and the various classes of drugs used to treat epilepsy, their mechanisms of action and their pharmacological characteristics
- describe the pharmacokinetics and mechanism of action of a number of drugs used to treat schizophrenia
- describe the pharmacokinetics and mechanism of action of a number of classes of drugs used to treat depression, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs)
- discuss bipolar disorder and its treatment

7.3 SEDATIVE-HYPNOTIC AND ANXIOLYTIC DRUGS

Recommended reading: the section entitled "Overview" on page 186 in chapter 19 of Brenner and Stevens.

The sedative-hypnotic drugs are used extensively worldwide. They achieve calming, antianxiety (anxiolytic) effects. Many, if they are used at high enough concentrations, will promote sleep or hypnosis (the medical term for sleep). **Newer** anxiolytic drugs have been developed that have anxiolytic effects **without inducing sedation or hypnosis**. The most commonly used drugs for anxiety and sleep disorders are the **benzodiazepines**, although many new drugs are now being developed and used.

7.3.1 Anxiety and sleep disorders

Recommended reading: the sections entitled "Anxiety disorders" and "Sleep disorders" on pages 186–189 in chapter 19 of Brenner and Stevens.

Anxiety is characterised by apprehension and fear of some perceived threat, sympathetic nervous system arousal and hypervigilance.

Anxiety disorders can be classified into a number of different types:

- acute anxiety
- panic disorder
- phobic disorder
- obsessive-compulsive disorder
- generalised anxiety disorder
- post-traumatic stress disorder

The treatment of anxiety disorders depends on the **type** of anxiety disorder, and may involve **psychotherapy** as well as **medication**. **Benzodiazepines** are commonly used for most forms of anxiety disorder.

Insomnia is a sleep disorder. Patients with this disorder find it hard to fall asleep or stay asleep at night.

- If the reason for the insomnia is purely **medical**, then it is typically treated with **benzodiazepines** or other sedative-hypnotic drugs such as **zolpidem**, **zaleplon**, **eszopiclone**, and **ramelteon**.
- If the insomnia is due to **psychological disturbances**, then treatment is typically with **psychotherapy** and **medication**.

7.3.2 Sedative-hypnotic drugs

Recommended reading: the section entitled "Sedative-hypnotic drugs" on pages 189–195 in chapter 19 of Brenner and Stevens.

The sedative-hypnotic drugs include the benzodiazepines, barbiturates, certain antihistamines, and the additional agents zolpidem, zaleplon, eszopiclone, and ramelteon. The pharmacokinetic properties and clinical uses of these drugs are listed in Table 19-1, and the adverse effects and drug interactions are summarised in Table 19-2.

The most frequently used class of sedative-hypnotic drugs is the benzodiazepines. The barbiturates were extensively used in the past, but with the development of newer drugs they are no longer used much to treat anxiety or sleep disorders.

Zolpidem, zaleplon and eszopiclone are the new drugs of choice for insomnia, as they have fewer adverse effects than the benzodiazepines. Ramelteon interacts with selective melatonin receptors, and is used to treat sleep-onset insomnia.

7.3.3 Activity 7.1

Do the following activity and add it to your portfolio.

Remember, these activities serve as part of your summary to use in preparing for the exam!

a) List and briefly discuss the different types of anxiety disorders and the drugs that are typically used to treat them.
b) Describe the pharmacokinetics, mechanism of action and pharmacologic effects of the benzodiazepines.
c) Long-term use of the benzodiazepines can result in physical dependence. What does this mean?
d) Discuss the adverse effects of the benzodiazepines and their interactions with other drugs.
e) Why are the drugs zolpidem, zaleplon and eszopiclone preferred to the benzodiazepines for treating insomnia?
f) Briefly discuss the use of melatonin and ramelteon in the treatment of sleep disorders.

7.3.4 Feedback on activity 7.1

Did you identify and discuss all the different types of anxiety disorder (acute anxiety, panic disorder, phobic disorder, obsessive-compulsive disorder, generalised anxiety disorder and post-traumatic stress disorder) and the drugs that are used to treat them?

When describing the mechanism of action of the benzodiazepines, did you mention binding of benzodiazepines to GABAA receptor-chloride ion channels, allosteric binding, increased frequency of opening and neuronal membrane hyperpolarisation? It is also important to note that the benzodiazepines can cause anterograde amnesia, and that they exhibit a ceiling effect with regard to CNS depression.

We will discuss physical dependence on drugs in greater detail in learning unit 9.

7.4 EPILEPSY

Recommended reading: the section entitled "Overview" on pages 198–199 in chapter 20 of Brenner and Stevens.

Epilepsy is a disorder of the CNS. It affects between 0.5 and 1 % of the population, and is characterised by epileptic seizures in which the patient experiences abnormal behaviour and strange sensations, and may lose consciousness. Seizures may be short-lived and nearly undetectable, or may be lengthy, accompanied by vigorous shaking. Typically there is no recognisable cause, although patients may develop epilepsy after stroke, trauma, infection or tumour growth.

Epileptic seizures are associated with neuronal discharges of impulses by a group of neurons (called the **seizure focus**) in the brain, typically in the cerebral cortex. The abnormal discharges then spread to other areas of the brain. The site of the seizure focus and the extent of spread determine the symptoms that occur. Symptoms may be **mild**, with a brief lapse in attention, to **full-blown convulsive fits** or **strange sensations, thoughts and behaviours**. Epileptic seizures can be confirmed with an EEG (electroencephalogram) (refer to Figure 20-1 on page 200 of Brenner and Stevens). The different types of seizure result in different distributions of abnormal discharge.

Types of epileptic seizures

Epileptic seizures can be classified as either:

- partial or
- generalised.

If the seizure originates in **one** cerebral hemisphere, it is called a **partial** seizure. A **generalised** seizure originates in **both** hemispheres of the brain, and the individual typically **loses consciousness**. Refer to Table 20-1 in Brenner and Stevens, which shows the classification of partial and generalised seizures.

7.4.1 Neural mechanisms of epilepsy

The neural mechanisms leading to epileptic seizures are poorly understood. One possibility is that glutamate activates N-methyl-d-aspartate (NMDA) receptors, causing calcium influx into the postsynaptic cell (refer to Figure 20-2 in Brenner and Stevens). This results in increased synthesis of nitric oxide, which diffuses into the presynaptic neuron. This then stimulates the release of more glutamate, resulting in further NMDA receptor activation. All this leads to a depolarisation shift with prolonged action potentials with spikelets. The depolarisation shift causes the adjacent neurons to discharge synchronously, and a seizure results.

7.4.2 Antiepileptic drugs

Epilepsy can be treated with a number of drugs, although it remains difficult to treat in some patients. Epilepsy can be controlled completely with antiepileptic drugs in about 75% of cases. Antiepileptic drugs are also used to treat and prevent convulsions caused by other brain diseases.

Antiepileptic drugs have three main mechanisms of action:

1. inhibition of sodium or calcium ion-channels, causing neuronal depolarisation
2. enhancement of inhibitory GABA neurotransmission
3. inhibition of excitatory glutamate transmission

Table 20-2 lists a number of antiepileptic drugs and their mechanism of action.

There are many other drugs that can be used to treat epilepsy. Refer to Table 20-3 in Brenner and Stevens, which lists some antiepileptic drugs, adverse effects and contraindications. (You do not need to learn these drug names.)

We will now briefly discuss two antiepileptic drugs as representative examples. They are:

- carbamazepine, which is used to treat partial seizures and tonic-clonic seizures, and
- ethosuximide, which is used to treat generalised absence seizures.

Valproate is another important drug that is used in the treatment of epilepsy.

7.4.2.1 Carbamazepine

This is one of the most widely used antiepileptic drugs.

Pharmacokinetics:

- well absorbed after oral administration
- biotransformed to the active metabolite carbamazepine epoxide
- drug is excreted in the urine and faeces

Mechanisms and effects:

Blocks voltage sensitive sodium channels in neuronal cell membranes, inhibiting spread of abnormal discharges from seizure focus. Carbamazepine can cause drowsiness, dizziness, ataxia and gastrointestinal side effects.

Interactions: It induces cytochrome P450 enzymes that metabolise a number of drugs. It therefore increases the metabolism of certain other drugs and itself, reducing the effects of these drugs.

Indications: It is indicated for use for

- partial seizures
- generalised tonic-clonic seizures
- trigeminal neuralgia
- bipolar disease

7.4.2.2 Ethosuximide

It is used clinically to treat absence seizures.

Pharmacokinetics:

- well absorbed after oral administration
- metabolised into inactive compounds and excreted in urine
- has a long half-life (approximately 55 hours in adults)

Mechanisms and effects:

Its main effect is to inhibit T-type calcium channels in thalamic neurons. Ethosuximide can cause dizziness, drowsiness, nausea and gastric side effects. The side effects can be modulated by starting with a low dose of drug, and slowly increasing the concentration until the desired level is reached.

Interactions: Valproate (another antiepileptic drug) inhibits its metabolism, increasing its serum levels. Ethosuximide also interacts with haloperidol, which is an antipsychotic drug.

Indications: It is indicated for use in generalised absence seizures in children.

7.4.2.3 Activity 7.2

Do the following activity and add it to your portfolio.

a) Briefly discuss the difference between a simple partial seizure and a complex partial seizure.
b) Explain what a tonic-clonic (grand mal) seizure and an absence (petit mal) seizure are.
c) Describe how antiepileptic drugs that effect ion channels work to reduce seizures in epileptics. Give three examples of drugs that work by this mechanism of action.
d) Explain why drugs that increase GABA neurotransmission can act as antiepileptic drugs. Give the names of two classes of drugs that work in this manner.
e) Give the names of three drugs that work by inhibiting glutamate neurotransmission.
f) What is ataxia?
g) Discuss the pharmacokinetics, mechanisms of action, pharmacologic effects and indications of the drug valproate.
h) Read the case study in Box 20-1 on page 207 in Brenner and Stevens.

7.5 SCHIZOPHRENIA

Recommended reading: the section entitled "Schizophrenia" on pages 221– 228 in chapter 22 of Brenner and Stevens.

Schizophrenia is one of the most important forms of severe psychiatric illness, and affects approximately 1% of the world's population. The main clinical features of the disease include hallucinations, delusions, thought disorder, emotional abnormalities and abnormal disorganised behaviour. The symptoms can be divided into **positive** symptoms and **negative** symptoms (refer to Box 22-1 in Brenner and Stevens). The clinical features vary widely from individual to individual, especially with regard to the balance of positive and negative symptoms, which has an influence on the efficacy of drug treatment.

There are many hypotheses as to the causes of schizophrenia. The one with the most evidence is the **dopamine hypothesis**, which suggests that abnormalities in dopamine neurotransmission result in schizophrenia. Read the section on the dopamine hypothesis on pages 222–223 in Brenner.

7.5.1 Antipsychotic drugs

More than 30 different antipsychotic drugs that reduce psychotic symptoms in schizophrenic patients are available for clinical use. The different antipsychotic drugs influence several neurotransmitter systems. Refer to Table 22-1 in Brenner and Stevens for a list of mechanisms of drug action that are responsible for the therapeutic and adverse effects of the antipsychotic drugs, and to Box 22-2, which discusses the sites of drug action. From the table you can see that the therapeutic effects result from competitive blockage of dopamine receptors and serotonin (5-HT) receptors.

The reason why the blockage of dopamine and serotonin receptors helps reduce the symptoms of schizophrenia is not fully understood.

Many of the antipsychotic drugs have adverse effects – you will find a summary of these in Tables 22-1 and 22-2 in Brenner and Stevens. **Neuroleptic malignant syndrome** can occur as a result of drug toxicity, and is life threatening.

Depending on their pharmacologic properties, antipsychotic drugs can be divided into two groups:

- the typical (first-generation) and

- atypical (second-generation) antipsychotic drugs.

The **typical** antipsychotics include **chlorpromazine**, **fluphenazine**, **thioridazine** and **haloperidol**. These four drugs have similar therapeutic effects, but differ in their strength and side effects. Refer to Tables 22-2 and 22-3 in Brenner and Stevens. Read the section on the typical antipsychotic agents on pages 225–227 in Brenner and Stevens.

The **atypical** antipsychotic agents include **clozapine** and **olanzapine**. They produce fewer extrapyramidal side effects than older antipsychotic drugs. Certain drugs of this class are also approved for the treatment of manic episodes associated with bipolar disorder. Read the section on the atypical antipsychotic drugs clozapine and olanzapine on page 227 in Brenner and Stevens.

7.5.2 Activity 7.3

Do the following activity and add it to your portfolio.

a) Which are more difficult to treat, the positive or negative symptoms of schizophrenia?
b) Discuss the dopamine hypothesis and how abnormalities in dopamine neurotransmission may result in schizophrenia.
c) What are extrapyramidal symptoms?
d) What is neuroleptic malignant syndrome? How is it managed when it occurs as a result of the administration of antipsychotics?
e) Discuss the pharmacokinetics, mechanisms of action and pharmacologic effects of typical antipsychotic agents.
f) Discuss the antipsychotic drugs clozapine and olanzapine.

7.6 AFFECTIVE DISORDERS

Recommended reading: the section entitled "Affective disorders" on pages 228–229 in chapter 22 of Brenner and Stevens.

Affective disorders are **mood** disorders, the two most common being **major depressive disorder** and **bipolar disorder**.

- **Depressive** disorder results in depressed mood, loss of pleasure and interest in life, feelings of worthlessness, sleep disturbances, a reduced ability to concentrate and thoughts of suicide.
- **Bipolar** disorder, also known as manic-depressive disorder, is a mental illness characterised by periods of elevated mood (manic phase) and periods of depression, which may last several weeks or months. During rapid cycling bipolar disorder the periods of mania and depression can change within hours or days.

One hypothesis explaining the mood disorders is the **biogenic amine hypothesis**, which proclaims that mood disorders result from irregularities in serotonin, norepinephrine or dopamine neurotransmission. Read the section on the biogenic amine hypothesis on page 228 in Brenner.

7.6.1 Antidepressant drugs

Recommended reading: the section entitled "Antidepressant drugs" on pages 229–234 in chapter 22 of Brenner and Stevens

There are a number of different types of antidepressant drugs on the market, the most common being the:

- tricyclic antidepressants (TCAs)
- selective serotonin reuptake inhibitors (SSRIs)
- monoamine oxidase inhibitors (MAOIs)

Antidepressant drugs are used to treat **all forms of depression**, and may also be successfully used in the treatment of **sleep disorders** and several **anxiety disorders**, for example, **panic** disorders, **phobic** disorders and **obsessive-compulsive** disorder. Certain antidepressants may also be used to treat chronic pain syndrome, and SSRIs have also been used to treat **depression**, **eating disorders**, **anxiety disorders**, **fibromyalgia**, **autism** and **premenstrual dysphoric disorder**.

Tricyclic antidepressants (TCAs)

Amitriptyline, clomipramine, desipramine, imipramine, and nortriptyline are all examples of TCAs that are used in the treatment of depression. They are unfortunately associated with **adverse effects** and are highly **toxic** if excess is consumed (refer to Table 22-5 in Brenner and Stevens). Read the section on tricyclic antidepressants on page 230 in the textbook.

Selective serotonin reuptake inhibitors (SSRIs)

The SSRIs are the most extensively used drugs for the treatment of depression, and include fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram. They are **effective** in treating depression and have **fewer side effects** than the TCAs (refer to Table 22-5 in the textbook). They selectively block serotonin neuronal reuptake, with little effect on the reuptake of norepinephrine. The short- and long-term effects of taking SSRIs is illustrated in Figure 22-2 in Brenner and Stevens. Read the section on selective serotonin reuptake inhibitors on pages 230–232 in Brenner and Stevens.

Monoamine oxidase inhibitors (MAOIs)

The MAOIs interact with many different drugs and foods, and are therefore **not** the drug of choice for treating depression. They are used only if other drug treatments do not work. Read the section on monoamine oxidase inhibitors on page 232 in Brenner and Stevens.

A number of interactions can occur between the different types of antidepressant drugs and other types of drugs. Read the section on adverse interactions of antidepressant drugs on page 233 in Brenner and Stevens.

7.6.2 Mood-stabilising drugs

Recommended reading: the section entitled "Mood-stabilizing drugs" on pages 234–235 in chapter 22 of Brenner and Stevens.

A number of different medications can be used to treat bipolar disorder. Lithium is the most common drug, and is effective in reducing both acute manic episodes and depressive symptoms, normalising the patient's mood. Carbamazepine and valproate are two additional drugs that have been found to be effective in treating bipolar disorder.

Treatment commonly includes psychotherapy in conjunction with medication.

7.6.3 Activity 7.4

Do the following activity and add it to your portfolio.

a) What support is there for the biogenic amine hypothesis?

b) Describe the pharmacokinetics, mechanism of action and pharmacologic effects of the tricyclic antidepressants.
c) Describe the pharmacokinetics, mechanism of action and pharmacologic effects of the SSRIs.
d) Discuss the difference between the adverse effects of the SSRIs and TCAs that are used to treat depression.
e) Describe the pharmacokinetics, mechanism of action and pharmacologic effects of the MAOIs.
f) Describe some of the adverse interactions that can occur between the three main types of antidepressant drugs (TCAs, SSRIs and MAOIs).
g) Describe the pharmacokinetics, mechanism of action, pharmacologic effects and adverse effects of lithium.

LEARNING UNIT 8

Hypertension as an example of cardiovascular disease

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8.1 INTRODUCTION

We say that a person has high blood pressure or hypertension when they have a systolic blood pressure of over 140 mm Hg or a diastolic blood pressure over 90 mm Hg. Untreated hypertension can damage blood vessels, increases a person's risk for atherosclerosis, and causes left ventricular hypertrophy. These conditions may ultimately lead to ischemic heart disease, stroke, renal failure and heart failure.

It is estimated that over 50 million people in the United States have hypertension.

In this learning unit we will study the antihypertensive drugs as examples of drugs used to treat cardiovascular disease. To complete the study unit, you will need to refer to **chapter 10** in Brenner and Stevens.

8.2 LEARNING OUTCOMES

Upon completion of this learning unit you should be able to:

- define hypertension

- describe how blood pressure is regulated by the body
- discuss the use of diuretics in the treatment of hypertension
- describe the sympatholytic drugs (α- and β-adrenoceptor antagonists) used in the treatment of hypertension
- discuss the two types of angiotensin inhibitors, ACE and ARBs, used to reduce blood pressure
- discuss the use of vasodilators in the treatment of hypertension

8.3 HYPERTENSION

Recommended reading: the section entitled "Overview" on pages 88–89 in chapter 10 of Brenner and Stevens.

95% of cases of hypertension cannot be linked to a specific cause, although genetic and lifestyle factors may play a role. This type of hypertension is referred to as **primary hypertension**.

The other 5% of cases are as a direct result of other disease conditions or identifiable causes. This type of hypertension is called **secondary hypertension**. In some instances secondary hypertension can be treated by treating the underlying condition.

Lifestyle factors associated with hypertension include:

- obesity
- lack of exercise
- metabolic syndrome
- high salt intake in the case of susceptible people
- excessive alcohol consumption

The classification of hypertension is shown in Table 10-1. Treatment of hypertension will depend on the severity of the hypertension. Blood pressures over 180/110 mm Hg need to be treated immediately.

Blood pressure is regulated by the **sympathetic nervous system** and the **kidneys**, as they control cardiac output and peripheral vascular resistance (PVR).

Cardiac output is influenced by the **stroke volume** and **heart rate**, which is increased by activation of β_1-adrenoceptors in the heart (sympathetic stimulation). The kidneys regulate blood volume, and therefore influence cardiac filling pressure and stroke volume.

Peripheral vascular resistance (PVR) is controlled by the **resistance of blood flow** through the arterioles. Activation of α_1-adrenoceptors stimulates arteriolar smooth muscle contraction, causing vasoconstriction.

The **short-term regulation of blood pressure** is through the **baroreceptor reflex**, which changes the heart rate if there is a sudden change in blood pressure. If an increase in blood pressure is detected, then the baroreceptor reflex causes the heart rate to decrease, resulting in a decrease in the blood pressure. A decrease in blood pressure causes an increase in heart rate, raising the blood pressure. The baroreceptor reflex can be controlled in fractions of a second, and is important in controlling blood pressure changes that occur as a result of changes in posture. It is modulated by the autonomic nervous system.

The **long-term regulation of blood pressure** is controlled predominantly by the **kidneys**. In individuals with normal blood pressure, if the blood pressure increases, the kidneys increase the excretion of water and sodium. This reduces the blood volume, allowing the blood pressure to return to normal levels. In hypertensive individuals this process may be defective, and the blood pressure is not reduced to low enough levels.

The kidneys and sympathetic nervous system therefore **work together** to maintain the arterial blood pressure, changing it as needed when a person is at rest, changing postures or physically active.

8.3.1 Activity 8.1

Do the following activity and add it to your portfolio.

Remember, these activities serve as part of your summary to use in preparing for the exam!

a) What is atherosclerosis, left ventricular hypertrophy, ischemic heart disease, stroke, renal failure and heart failure?
b) List three identifiable causes of secondary hypertension.
c) Describe the baroreceptor reflex. Refer to Figure 5-4, at the end of chapter 5, to help you.

8.4 DRUGS FOR HYPERTENSION

Recommended reading: the sections entitled "Diuretics", "Sympatholytic drugs", "Angiotensin inhibitors" and "Vasodilators" on pages 89–98 in chapter 10 of Brenner and Stevens.

There are four main categories of drugs used to reduce blood pressure. They are the:

- diuretics
- sympatholytic drugs
- angiotensin inhibitors
- vasodilators

They reduce blood pressure by acting on the kidneys, sympathetic nervous system, renin-angiotensin-aldosterone axis or vascular smooth muscle. The pharmacological effects of the different drugs are summarised in Tables 10-2 and 10-3 in Brenner and Stevens. Table 10-4 lists the adverse effects, contraindications and drug interactions of antihypertensive medications.

Most blood pressure drugs are taken orally, although in hypertensive emergencies they may be given parenterally.

In the next sections I will tell you more about each of the four main categories of drugs used to reduce hypertension.

8.4.1 Diuretics

- Potassium-sparing,
- thiazide and
- related diuretics

are the most common diuretics used to treat hypertension.

Diuretics work by **increasing renal sodium excretion**, which results in a **decrease in blood pressure**. The process of increased renal sodium excretion is called **natriuresis** or the **natriuretic effect**.

Thiazide diuretics have a moderate natriuretic effect and are often used in the treatment of hypertension. They reduce blood pressure by two mechanisms (refer to Figure 10-2 in Brenner and Stevens).

- In the short term the drugs decrease blood volume, and therefore cardiac output.
- In the long term they decrease PVR (peripheral vascular resistance), which decreases blood pressure.

Hydrochlorothiazide is the most commonly used thiazide diuretic. It can be used in combination with other antihypertensive drugs. The common adverse effects and drug interactions of the thiazide diuretics are described in Table 10-4, the most problematic adverse effect being the tendency to cause **hypokalaemia**.

Loop diuretics are less effective than thiazide diuretics in the treatment of most cases of hypertension.

8.4.2 Activity 8.2

Do the following activity and add it to your portfolio.

a) Discuss the use of diuretics to treat hypertension.
b) Describe the use of potassium-sparing diuretics in the treatment of hypertension.
c) Discuss the potential adverse effects of diuretic drugs.

8.4.3 Sympatholytic drugs

- α-adrenoceptor antagonists,
- β-adrenoceptor antagonists and
- centrally acting adrenoceptor agonists

are the sympatholytic drugs that may be used to treat hypertension. Their pharmacologic effects are described in Tables 10-2 and 10-3 in Brenner and Stevens. The common adverse effects and drug interactions are described in Table 10-4.

α-adrenoceptor agonists

The drugs doxazosin, prazosin and terazosin are some α_1-blockers that can be used to treat hypertension. They work by inhibiting sympathetic stimulation of arteriolar contraction, which results in vasodilation and decreased vascular resistance. They may have unwanted effects, and are not recommended for the initial treatment of hypertension in most patients.

β-adrenoceptor agonists

The β-blockers block β_1-adrenocepters in the heart and other tissues, in that way reducing blood pressure. The blocking of the heart β_1-adrenocepters decreases cardiac output by reducing the heart rate and contractibility. β-blockers are effective at reducing blood pressure in most patients, and have additional benefits for people with pre-existing heart disease. However, there is evidence that the β-blockers are less likely to prevent stroke, myocardial infarction and death in patients that do **not** have heart disease and, therefore, other hypertensive drugs may be better for these patients.

Most patients require more than one form of hypertensive drug to reduce blood pressure to low enough levels. In such cases, β may be used in combination with other types of hypertensive drugs.

Centrally acting adrenoceptor agonists

The centrally acting sympatholytic drugs tend to cause more side effects than other antihypertensive drugs. They are generally used only if other hypertensive drugs do not work or in hypertensive emergencies.

8.4.4 Activity 8.3

Do the following activity and add it to your portfolio.

a) Discuss the side effects and disadvantages of using α-blockers in the treatment of hypertension.
b) What additional benefits are there in administering β-blockers to people with pre-existing heart disease?
c) Not all β-blockers are the same. Discuss the difference between selective, nonselective and third-generation β-blockers.
d) Discuss how the centrally acting sympatholytic drugs work, and the adverse effects of these drugs.

8.4.5 Angiotensin inhibitors

There are three types of angiotensin inhibitors:

- the angiotensin converting enzyme (ACE) inhibitors,
- the angiotensin receptor blockers (ARBs) and
- a direct renin inhibitor called aliskiren.

These drugs are often used for the **initial** treatment of hypertension. Their pharmacologic effects are described in Tables 10-2 and 10-3 in Brenner and Stevens. Their common adverse effects and drug interactions are described in Table 10-4, and their pharmacokinetic properties are summarised in Table 10-5.

These drugs function by altering the renin-angiotensin-aldosterone axis, as shown in Figure 10-3 in Brenner and Stevens. The renin-angiotensin-aldosterone axis is a hormone system that regulates blood pressure and fluid (water) balance in the body.

Renin is secreted if there is:

- a reduction in arterial pressure in renal afferent arterioles
- a fall in sodium chloride concentration in the distal renal tubule
- sympathetic nervous system activation of β1-adrenoceptors on renal juxtaglomerular cells

Therefore, if there is a drop in blood pressure, renin will be secreted, initiating a sequence of events that raise the blood pressure to normal levels. Renin is a **protease** that **converts angiotensinogen to angiotensin I**. The angiotensin I is then converted to **active angiotensin II** by ACE (refer to Figure 10-3 in Brenner and Stevens). Angiotensin II activates the angiotensin receptors, AT1 and AT2, resulting in:

- contraction of vascular smooth muscle, bringing about generalised vasoconstriction
- secretion of aldosterone from the adrenal cortex
- increased reabsorption of sodium from the proximal tubule
- increased release of norepinepshrine from sympathetic nerves
- stimulation of cell growth in the arteries and heart

Vasoconstriction results in a direct increase in blood pressure. The reabsorption of sodium and water in the kidneys increases the volume of fluid in the body, which also increases blood pressure. ACE also inactivates bradykinin, an endogenous vasodilator peptide,

enhancing vasoconstriction. If the renin-angiotensin-aldosterone axis is atypically active, blood pressure will be **too high**.

Any drugs that **interrupt any of the steps** in the renin-angiotensin-aldosterone system will result in a **reduction** in blood pressure.

8.4.5.1 Angiotensin inhibiting drugs

Angiotensin converting enzyme (ACE) inhibitors

There are a number of ACE inhibitors that all work to reduce blood pressure through a similar mechanism of action. Inhibition of ACE affects the renin-angiotensin-aldosterone axis, blocking the formation of angiotensin II, which results in a lowering of blood pressure.

Angiotensin receptor blockers (ARBs)

The angiotensin receptor blockers selectively block AT1 receptors, reducing:

- vasoconstriction,
- aldosterone secretion,
- sodium reabsorption by the proximal tubule, and
- norepinephrine release from sympathetic nerve terminals.

This results in a drop in blood pressure. They may be used alone or with other antihypertensive drugs.

Direct renin inhibitor

Aliskiren, a direct renin inhibitor, binds to the active site of renin, stopping it from cleaving angiotensinogen to form angiotensin I. It therefore lowers the levels of angiotensin I and angiotensin II in the plasma (refer to Figure 10-3 in Brenner and Stevens). Aliskiren appears to be a safe and effective drug that can be used for the treatment of hypertension.

8.4.6 Activity 8.4

Do the following activity and add it to your portfolio.

a) Describe how the angiotensin-converting enzyme inhibitors result in a reduction in blood pressure.
b) Can ACE inhibitors and ARBs be used in pregnancy?

8.4.7 Vasodilators

The vasodilators include the calcium channel blockers (CCBs) and other drugs such as hydralazine, minoxidil, nitroprusside and fenoldopam. Their pharmacologic effects are described in Tables 10-2 and 10-3 in Brenner and Stevens. The common adverse effects and drug interactions are given in Table 10-4.

Calcium channel blockers

As well as being used to treat hypertension, CCBs can be used to treat angina pectoris, peripheral vascular disorders and cardiac arrhythmias. They work by blocking calcium ion channels in the plasma membranes of smooth muscle. This results in relaxation of vascular

smooth muscle, causing vasodilation. Their effect on blood pressure is principally produced by a reduction in PVR.

They are typically used for the initial treatment of hypertension, alone or in combination with other hypertensive drugs, as they have few adverse effects.

8.4.8 Activity 8.5

Do the following activity and add it to your portfolio.

a) Describe the mechanism of action of the CCB drugs diltiazem and amlodipine.
b) Briefly describe the use of the vasodilators hydralazine, minoxidil, nitroprusside and fenoldopam.

8.4.9 Management of hypertension

Recommended reading: the section entitled "The management of hypertension" on pages 98–100 in chapter 10 of Brenner and Stevens.

Hypertension can sometimes be managed through lifestyle changes such as increased exercise, weight loss and reduced sodium intake. If hypertension is not severe, it is best managed through lifestyle changes before drugs are prescribed, as lifestyle changes will increase overall health.

In instances where drugs are recommended, a **thiazide diuretic** is generally the **first choice** for the initial therapy. This is because thiazide diuretics are relatively safe and have been shown to reduce complications of hypertension (stroke and coronary heart disease). They are also relatively inexpensive. When thiazide diuretics cannot be used, other drug classes, for example angiotensin converting enzyme inhibitors, ARBs and CCBs (calcium channel blockers) can be used in initial therapy. B-blockers are recommended in initial treatment only if patients have **coronary heart disease**, **heart failure** and **specific arrhythmias**.

Many patients require more than one drug to control hypertension effectively. In these cases there are a number of combination drug products. Drug combinations typically result in reduced blood pressure, with **lower doses of the individual drugs** reducing adverse side effects.

In patients with specific traits or diseases, certain drugs are recommended. Refer to Table 10-6 on page 105 in Brenner and Stevens.

8.4.9.1 Activity 8.6

Do the following activity and add it to your portfolio.

Discuss the use of antihypertensive drugs in patients with specific traits or diseases.

LEARNING UNIT 9

Drugs of abuse

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9.1 INTRODUCTION

When a person repeatedly takes a drug for non-therapeutic or non-medical effects, resulting in harm to the person taking the drug or others, we speak of drug abuse or substance abuse. Drug abuse is a worldwide problem, as drug use often leads to criminal or anti-social behaviour when the person is under the influence of the drug.

Some of the most commonly abused drugs are alcohol, barbiturates, benzodiazepines, amphetamine derivatives, cocaine, cannabis, nicotine and opioids. It is estimated that there are 120 million users of hard drugs such as cocaine, heroin, and other synthetic drugs worldwide, resulting in medical, legal and social problems.

In this learning unit we will look at the various types of drugs that people take by choice. To complete the study unit, you will need to refer to **chapter 25** in Brenner and Stevens.

9.2 LEARNING OUTCOMES

Upon completion of this learning unit you should be able to:

- explain what drug abuse is
- discuss the difference between physical and psychological drug dependence
- describe various central nervous system depressants that are abused by people
- describe some common central nervous system stimulants that are abused by people
- discuss the management of drug abuse and some drugs that may be used to aid in the treatment of drug dependence

9.3 DRUG ABUSE AND DEPENDENCE

Recommended reading: the section entitled "Overview" on pages 260–261 in chapter 25 of Brenner and Stevens.

What is classified as drug abuse is determined by **cultural attitudes** and **legal restrictions**. In many countries the use of ethanol, nicotine and caffeine is socially acceptable, but the use of marijuana, cocaine and other psychoactive drugs is illegal. In other countries the use of marijuana is acceptable, but the use of ethanol is not.

From a pharmacological perspective, the use of a drug that is **harmful to the health of the drug user, other people or society in general** is classified as **drug abuse**.

Drug dependence is the condition in which drug taking becomes compulsive, taking precedence over other needs. Dependence on drugs may be either **psychological** or **physical**. If there is physical dependence on a drug, then the user will suffer withdrawal symptoms if he or she stops taking the drug.

The effects of some commonly abused drugs and the signs and symptoms of withdrawal are summarised in Tables 25-1 and 25-3 in Brenner and Stevens.

Addiction to drugs is related to dependence on the drug, and is generally associated with a preoccupation with using the drug, coupled with neglect of other responsibilities.

9.3.1 Activity 9.1

Do the following activity and add it to your portfolio.

Remember, these activities serve as part of your summary to use in preparing for the exam!

Discuss psychological and physical dependence on drugs. Refer to the textbook for help.

9.4 CENTRAL NERVOUS SYSTEM DEPRESSANTS

Recommended reading: the section entitled "Central nervous system depressants" on pages 261–265 in chapter 25 of Brenner and Stevens

9.4.1 Alcohols

Alcoholism is a big problem in South Africa and results in health problems, lost work hours and criminal activity. The alcohols most commonly abused are **ethanol** and

methanol. Even in small quantities, methanol can be highly toxic and cause health problems.

Pharmacokinetics

Ethanol is almost completely absorbed from the gut and has a volume of distribution that is equivalent to the volume of total body water, which indicates that it is widely distributed to the tissues. Its metabolism is shown in Figure 25-1 in Brenner and Stevens. Most ethanol metabolism exhibits zero-order kinetics (unless the ethanol concentration is extremely low) because the enzyme alcohol dehydrogenase is saturated at relatively low concentrations of ethanol.

Central nervous system effects, mechanisms and interactions

Ethanol consumption results in sedative-hypnotic, anxiolytic, amnesic and anticonvulsant effects. Ethanol inhibits the release of acetylcholine from CNS neurons, inhibits the antidiuretic hormone and causes vasodilation. Ethanol acts synergistically with barbiturates and benzodiazepines, and therefore their use together can produce fatal CNS depression. Ethanol at low concentrations causes mild euphoria and disinhibition. Ethanol impairs psychomotor skills, which is why driving while intoxicated is illegal in many countries.

Alcoholics can develop various metabolic disorders leading to cirrhosis, impaired glycogenolysis and tissue damage. Although ethanol is an anticonvulsant, long-term use may result in seizures.

9.4.2 Activity 9.2

Do the following activity and add it to your portfolio.

Refer to your textbook and answer the following questions.

a) Describe how ethanol is metabolised and explain which metabolic pathway contributes to alcohol tolerance in heavy drinkers.
b) Ethanol inhibits the release of acetylcholine from CNS neurons, inhibits the antidiuretic hormone and causes vasodilation. What effect does each of these actions have on the body?
c) Consumption of ethanol produces a number of central nervous system effects, autonomic effects and cardiovascular effects. Describe these effects.
d) What is foetal alcohol syndrome?
e) Discuss the effects of methanol on the body, and how methanol poisoning is treated.

9.4.3 Barbiturates, benzodiazepines and opioids

Barbiturates and benzodiazepines are sedative-hypnotic drugs that are typically prescribed for the treatment of anxiety and insomnia. Several different benzodiazepines are used illegally.

Flunitrazepam has been used as a date rape drug because of its ability to produce anterograde amnesia.

Heroin is the most commonly abused opioid. It is water soluble and is typically injected, causing an intense euphoric feeling called a rush. Long-term heroin use results in drug tolerance and physical dependence. Oxycodone, a prescription opioid tablet, can be crushed and injected, resulting in a rush.

9.4.4 Activity 9.3

Do the following activity and add it to your portfolio.

Refer to your textbook and answer the following question.

Discuss the pharmacologic effects of the benzodiazepines, and explain why they have been associated with date rape.

9.4.5 Feedback on activity 9.3

We discussed the benzodiazepines in learning unit 8. They are described in in the section entitled "Sedative-hypnotic drugs" on pages 190– 192, in chapter 19 of Brenner and Stevens.

The benzodiazepines have the ability to cause anterograde amnesia. Victims of rape who have been given the drug do not recall what happened to them.

9.5 CENTRAL NERVOUS SYSTEM STIMULANTS

Recommended reading: the section entitled "Central nervous system stimulants" on pages 265–267 in chapter 25 of Brenner and Stevens.

9.5.1 Amphetamine and its derivatives

Amphetamine and its derivatives increase the synaptic concentration of the catecholamines, norepinephrine and dopamine. It does this by three methods:

- causing the release of the catecholamines from the presynaptic vesicles
- causing the reverse transport of the catecholamines out of the neuron and into the synapse through the reuptake transporter
- inhibiting monoamine oxidase

The use of amphetamines produces a range of effects, including:

- euphoria
- insomnia and decreased fatigue
- psychomotor stimulation
- anxiety
- loss of appetite
- increased concentration
- respiratory stimulation
- hyperthermia
- mydriasis
- tachycardia
- hypertension

They are medically prescribed for attention-deficit/hyperactivity disorder, narcolepsy, other sleep disorders and obesity.

9.5.2 Activity 9.4

Do the following activity and add it to your portfolio.

Refer to your textbook and answer the following questions.

a) Discuss the illegal use of methamphetamine.

b) MDMA, or ecstasy, is an amphetamine derivative. Discuss the adverse effects of MDMA usage.

9.5.3 Cocaine, nicotine and caffeine

Cocaine

The effects of cocaine are due to the inhibition of the neuronal uptake of norepinephrine and dopamine. It does this by binding to the neurotransmitter reuptake proteins. This causes a conformational change that reduces their capacity to transport the neurotransmitters dopamine and norepinephrine. This in turn increases the synaptic concentration of these neurotransmitters. Cocaine has a number of adverse effects, including cardiovascular, pulmonary and neural toxicity.

The signs and symptoms of cocaine use and withdrawal are summarised in Tables 25-1 and 25-3 in Brenner and Stevens.

Nicotine

Nicotine is found in various tobacco products. It is swiftly absorbed and distributed to the brain. It interacts with cholinergic nicotinic receptors in the central and peripheral nervous systems, and inhibits monoamine oxidase, producing a wide range of effects including:

- mild euphoria
- increased arousal and concentration
- improved memory
- appetite suppression

Caffeine

Caffeine is a methylxanthine that blocks adenosine receptors in the CNS, enhancing dopamine neurotransmission (adenosine inhibits dopamine release). The use of caffeine produces a wide range of effects including:

- reduced fatigue
- elevated mood
- increased alertness
- increased concentration
- increased motivation
- enhanced talkativeness

9.5.4 Activity 9.5

Do the following activity and add it to your portfolio.

Refer to your textbook and answer the following questions.

a) Discuss the absorption of cocaine by the different mechanisms of administration.
b) Describe the effects and adverse effects of cocaine use.
c) Describe the metabolism of nicotine.
d) Describe the effects of high doses of caffeine and the symptoms of withdrawal.

9.6 OTHER PSYCHOACTIVE DRUGS

9.6.1 Cannabis

Cannabis, or marijuana, is a popular drug of abuse. THC (Δ_9-tetrahydrocannabinol) is the main cannabinoid in marijuana, and has multiple effects on neuronal function. The initial effects of marijuana use are mild stimulation, which is then followed by a depressive phase. The use of marijuana has been linked to amotivational syndrome. It is also classified as a gateway drug.

Cannabinoids have been shown to help in the treatment of asthma, glaucoma, anorexia, and nausea and vomiting. A number of prescription cannabinoid drugs are available.

The signs and symptoms of marijuana use and withdrawal are summarised in Tables 25-1 and 25-3 in Brenner and Stevens.

9.6.2 Hallucinogens

Hallucinations are false perceptions that result from abnormal sensory processing. Drugs such as LSD (synthetic ergot derivative), psilocybin (found in specific mushrooms) and mescaline (found in the Peyote cactus) can produce hallucinations without causing delirium. These drugs produce hallucinations within an hour of oral consumption. In the case of LSD, effects last up to 12 hours.

9.6.3 Activity 9.6

Do the following activity and add it to your portfolio.

Remember, these activities serve as part of your summary to use in preparing for the exam!

Refer to your textbook and answer the following questions.

a) How does first-pass metabolism affect the percentage of THC that is absorbed by the body when marijuana is ingested?
b) Discuss the effects of marijuana on neuronal function.
c) What is amotivational syndrome?
d) Define delirium. (You may use a dictionary to help you here.)
e) Discuss the abuse of prescription drugs and steroids.

9.6.4 Feedback on activity 9.6

When discussing the effects of marijuana on neuronal function, did you mention cannabinoid receptors, adenylyl cyclase and modulation of the activity of acetylcholine, dopamine and serotonin? Do you understand what you have written?

9.7 MANAGEMENT OF DRUG ABUSE

The abuse of drugs can lead to problems such as:

- drug intoxication
- overdose
- drug withdrawal
- drug dependence

The extent of the problems differs depending on the type of drug used and the frequency of use.

Drug intoxication and withdrawal

The common signs and symptoms of drug intoxication for a number of common drugs are listed in Table 25-1 in Brenner and Stevens. The common signs and symptoms of drug withdrawal are summarised in Table 25-3.

The treatment of drug intoxication and overdose typically involves supporting cardiovascular and pulmonary functions. The emergency treatment of drug intoxication for a number of drugs is summarised in Table 25-2. As the drug is eliminated from the body, the body experiences withdrawal symptoms. These are managed by substitution therapy and symptomatic relief.

Treatment of drug dependence

Pharmacological treatments may be used to treat drug dependence, but equally important are behavioural therapy and personal motivation to be drug free. A number of 12-step groups, such as Alcoholics Anonymous and Narcotics Anonymous, have been established to help recovering addicts.

Various pharmacological agents can be used to treat drug dependence. These include:

Pharmacological agent	**Used to treat**
disulfiram	alcohol dependence
acamprosate calcium	alcohol dependence
buprenorphine	opioid dependence
naltrexone	alcohol and opioid dependence
nicotine gum, lozenges and patches	smoking dependence
varenicline	smoking dependence

9.7.1 Activity 9.7

Do the following activity and add it to your portfolio.

Refer to your textbook and answer the following questions.

a) What is meant by substitution therapy and symptomatic relief?
b) Discuss the pharmacologic agents disulfiram, naltrexone and varenicline, which are used to treat drug dependence. Describe their mechanism of action, if it is known.

Discussion forums and topics in BMI2605

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Use this forum to discuss general matters amongst yourselves

DISCUSSION 1: INTRODUCE YOURSELF

Use this space to get to know your classmates

In about 250 words, tell us about your current work situation and professional background, and something about yourself as a person.

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Use this space to share your contact details with your classmates and to form study groups.

FORUM 2: LEARNING UNIT CONTENT

Use this forum to discuss specific topics you are trying to understand in the course.

Announcement 1: Welcome and getting started

Dear Student

Welcome to Pharmacology. You should have received a "Getting Started" letter in the mail, explaining what is expected of you as an online student.

Please go to the **Discussion Forums** link on the left-hand side of your screen and access "Forum 1: Student Café". In Discussion 1 we would like you to participate in your first online activity, during which you introduce yourself to your fellow students. Please participate in this discussion during February /July.

We are looking forward to meeting you online!

Your lecturer