

**A retrospective analysis of phentermine in the
private healthcare sector of South Africa:
Duration and drug-drug interactions**

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PREFACE

This dissertation is presented in the format of a manuscript, with the results of the study discussed in Chapter 3.

The dissertation is divided into four chapters:

- Chapter 1 presents the introduction, background and research methodology of the study as well as ethical aspects that needs to be taken into consideration to successfully complete the study.
- Chapter 2 provides a comprehensive literature review, addressing all relevant topics, such as the pharmacological classification, indication, as well as the pharmacokinetic (PK) and pharmacodynamic (PD) properties of phentermine. The contraindications, drug-drug interactions (DDIs), along with international and national prescribing guidelines of phentermine is discussed in detail. Drug utilisation reviews (DURs) are briefly discussed where after the chapter concludes with a chapter summary.
- Chapter 3 comprises of the empirical investigation results, presented in the format of two manuscripts. The manuscripts are compiled according to the specifications and requirements set out by the South African Medical Journal (SAMJ) for possible publishing.
- Chapter 4 provides the conclusions made from the objectives of the study, including the study's limitations and strengths. Recommendations for potential future research is also provided in this chapter.

A reference list and annexure are provided at the end of the dissertation, while the proof of language editing for the dissertation and manuscripts, Turnitin report and acknowledgements are provided in the subsequent section.

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ABSTRACT

Title: A retrospective analysis of phentermine in the private healthcare sector of South Africa: Duration and drug-drug interactions

Background: Phentermine is the preferred appetite suppressant amongst South African healthcare prescribers. Guidelines are available to assist prescribers in rational and safe prescribing of the drug. The long-term (LT) use of phentermine possibly linked to amphetamine-like side effects justifies why the duration of use thereof is, as specified in the prescribing guidelines, limited to a period not surpassing 12 consecutive weeks. These guidelines also refer to certain drugs phentermine should not be co-prescribed with as it may result in mild, moderate or even severe drug-drug interactions (DDIs) and thus causing adverse drug reactions (ADRs). Phentermine continues to be prescribed LT and for other indications, consequently increasing the risk of adverse drug events (ADEs) and DDIs.

Objectives: To analyse the duration of therapy (DOT) with phentermine (15 mg and 30 mg respectively) and to determine the prevalence of potential drug-drug interactions (PDDIs) amongst LT phentermine consumers in private healthcare.

Method: A quantitative, retrospective analyses was conducted using approved and paid claims data for phentermine from 1 January 2015 to 31 December 2019. Information of the age, gender and prescriber's speciality of patients receiving 15 mg and 30 mg phentermine were considered and evaluated. The total number of consecutive days 15 mg and 30 mg phentermine was supplied for, respectively, was used to determine the DOT and to identify the patient group that received phentermine LT. Drugs co-prescribed with phentermine were extracted and the top 20 drugs, which may have caused PDDIs, most frequently prescribed to LT phentermine consumers were listed accordingly. These PDDIs were categorised according to severity as mild, moderate or severe, using a drug interaction checker from Drugs.com.

Results: There were 3 361 patients receiving phentermine over the study period of which 2 848 (84.74%) patients were female and 35-59 years of age ($n = 1\,952$; 58.08%). Patients mostly received phentermine short-term (ST) ($n = 2\,472$; 73.55%) and 889 (26.45%) patients received the drug LT. The average DOT with 15 mg phentermine was 57.26 (58.72) days and with 30 mg phentermine it was 67.10 (52.01) days ($p < 0.001$; d -value = 0.17). The DOT with 15 mg and 30 mg phentermine varied from 5-720 days and 1-360 days, respectively.

The top 20 drugs most frequently co-prescribed with phentermine, amongst LT consumers, demonstrated no mild PDDIs. There were 15 (75%) drugs which may have possibly caused moderate DDIs; with dextromethorphan most frequently (n = 282; 31.72%) and formoterol (n = 52; 5.85%) least prescribed to patients in this group. The residual 25% of drugs may have potentially caused severe DDIs and tramadol (n = 416; 46.79%) was most frequently prescribed to patients. The drug least prescribed in this group was phenylpropanolamine (n = 69; 7.76%).

Conclusion: In South Africa, the DOT with phentermine, in private healthcare, is not restricted to ST use. Patients receive LT therapy and are therefore exposed to the risk of experiencing amphetamine-like side effects, PDDIs and ADRs. Prescribers should use prescribing guidelines when prescribing phentermine as it eliminates irrational drug prescribing and prevents PDDIs and ADRs.

Keywords: adverse drug reactions, anti-obesity, appetite suppressant, drug-drug interactions, duration of therapy, long-term, phentermine, South Africa.

LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine/Serotonin
5-HT syndrome	Serotonin syndrome
5-HTP	5-hydroxytryptophan
5-HTT	5-hydroxytryptamine/Serotonin transporter
ADE	Adverse drug event
ADHD	Attention-deficit/hyperactivity disorder
ADR	Adverse drug reaction
AHFS	American Hospital Formulary Service
AKA	Also known as
ANOVA	Analysis of variance
ANS	Adrenergic nervous system
ASBP	American Society of Bariatric Physicians
ATS	Amphetamine-type stimulants
AUC	Area under the curve
BBB	Blood-brain barrier
BMI	Body mass index
CC	Central compartment
CCOHS	Canadian Centre for Occupational Health and Safety
CER	Cation-exchange resin complex

CDL	Chronic disease list
C _{max}	Maximum/peak concentration
CNS	Central nervous system
CV	<i>Curriculum vitae</i>
CVS	Cardiovascular system
CYP	Cytochrome
DA	Dopamine
DAT	Dopamine transporter
DDI	Drug-drug interaction
DEA	Drug Enforcement Administration
DOT	Duration of therapy
DPP-4	Dipeptidyl peptidase-4
DUR	Drug utilisation review
ECG	Electrocardiogram
EM	Essential Medical
EP	Epinephrine
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GI	Gastrointestinal
GIT	Gastrointestinal tract
GLP-1	Glucagon-like peptide 1

GP	General practitioner
HMDB	Human Metabolome Database
HPA	Hypothalamus-pituitary axis
HREC	Health Research Ethics Committee
ICD-10	International Classification of Diseases and Related Health Problems (10 th revision)
IER	Ion-exchange resin
IUPAC	International Union of Pure and Applied Chemistry
IV	Intravenous
LT	Long-term
MAO	Monoamine oxidase
MAOI	Monoamine oxidase inhibitor
MAT	Monoamine transporters
MI	Myocardial infarction
MIMS®	Monthly Index of Medical Specialities
MUSA	Medicine Usage in South Africa
NAcSh	Nucleus accumbens shell
NAPPI	National Pharmaceutical Product Index
NE	Norepinephrine
NET	Norepinephrine transporter
NH ₂	Amidogen (amino group)
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases

NWU	North-West University
NWU-HREC	North-West University Health Research Ethics Committee
OCD	Obsessive-compulsive disorder
PAH	Pulmonary arterial hypertension
PBM	Pharmacy benefit management
PC	Peripheral compartment
PD	Pharmacodynamic
PDDI	Potential drug-drug interaction
PDR	Prescribers' Digital Reference
PIL	Patient information leaflet
PK	Pharmacokinetic
PNS	Peripheral nervous system
QRS	Q wave, R wave, S wave
QT	Q wave, T wave
S	Scheduling status
SAHPRA	South African Health Products Regulatory Authority
SAMF	South African Medicines Formulary
SAMJ	South African Medical Journal
SAS®	Statistical Analysis System®
SD	Standard deviation
SNS	Sympathetic nervous system

SSRI	Selective serotonin reuptake inhibitor
ST	Short-term
TCA	Tricyclic antidepressant
$t_{1/2}$	Half-life
USA	United States of America
Vd	Volume of distribution
VMAT	Vesicular monoamine transporter
vs	Versus
VTa	Ventral tegmental area
WHO	World Health Organization

LIST OF DEFINITIONS

Adsorption	The process where molecules, ions or atoms stick to the surface of a solid matter (Brandani <i>et al.</i> , 2016:262).
Adverse effect	An unwanted, unpredictable reaction that appears during treatment with a medical product and there is a reasonable possibility that the medicinal agent is the cause of the reaction (Sharma, 2021:802; Yeung, 2020).
Adverse drug event	Any medicine-related injury, including adverse drug reactions (ADRs), medication errors, overdoses and allergic reactions that may appear during treatment with a medicinal product (Leheny, 2017; Office of Disease Prevention and Health Promotion, 2021).
Adverse drug reaction	An undesirable, unpredicted reaction resulting from a medicinal agent during standard clinical treatment, which can foresee potential risks associated with future consumption and merits: prevention of certain treatments or modification of the administered quantity, retraction of the causative agent (Park, 2018:56).
Agitation	A physiological process of severe motor activity that causes feelings of irritability or extreme restlessness (Siddiqui <i>et al.</i> , 2020).
Amphetamine	A central nervous system (CNS) stimulant which stimulates receptors in the brain, enhance the activity of several neurotransmitters, particularly dopamine (DA) and norepinephrine (NE), and has a significant potential to cause misuse in individuals (Newman, 2017; Rossiter, 2016:70).
Anaphylaxis	An acute yet deadly hypersensitivity condition, described as a widespread, fast-developing, multi-systemic hypersensitive reaction (McLendon & Sternard, 2021).
Anorectic drug	A medicine that reduces appetite, for the purpose of weight loss, by acting on the signalling pathway responsible for appetite control (Thompkins, 2017:1).

Anorexia nervosa	A serious mental illness where an individual develops an eating disorder as well as a metabolic disease which is caused by self-starvation of the individual, resulting in extreme weight loss and severe thinness (McQuillan, 2019; Shiel, 2018a).
Catecholamines	Hormones (such as adrenaline, DA and noradrenaline (NA)) produced by the brain, nerve tissue and adrenal glands that are released when the body experiences emotional or physical anxiety. They control the “fight-or-flight” response in the body, also known as parasympathetic innervation (Smith, 2020).
Comorbidities	The supplementary effects caused by additional diseases with reference to a particular chronic disease in an individual where more than one chronic disease occurs (Tugwell & Kottner, 2019:5).
Descriptive research	Research that correctly and systemically defines a population, situation or event (McCombes, 2019).
Drug-drug interaction (DDI)	When two or more medicines are taken simultaneously, and one drug changes the effect of the other on the body. This interaction either postpones, reduces or heightens the absorption of either drug, which may lead to the reduction or incline of the action of any or both medicines and lead to adverse effects (AIDSinfo, 2018).
Elimination half-life	The amount of time needed for the concentration of a drug to reduce to 50% of its starting concentration, in the body (Hallare & Gerriets, 2020).
Glaucoma	A disorder where the intraocular pressure in the eye increases and may advance to a loss of vision (Dietze <i>et al.</i> , 2021).
Gluconeogenesis	A set of metabolic reactions that function to maintain a constant concentration of glucose in the blood throughout fasting conditions (Chourpiliadis & Mohiuddin, 2021).
Glycogenolysis	The breakdown of glycogen into glucose-1-phosphate and glycogen (Paredes-Flores & Mohiuddin, 2021).

Hyperpyrexia	Characterised by extremely high fever (higher than 41.5°C), which may appear amongst individuals with severe infections (Balli, 2021).
Hypertension	A medical condition where the force exerted (via circulating blood) against the arterial walls in the body is too high. It can be diagnosed if the systolic blood pressure reading is greater than or equal to ($\geq$) 140 mmHg and/or the diastolic blood pressure is $\geq$ 90 mmHg, on 2-3 office visits at intervals of 1-4 weeks (Unger <i>et al.</i> , 2020:1336; World Health Organization (WHO), 2019a).
Hypertensive crisis	A medical emergency caused by a potentially life-threatening increase in blood pressure which can cause organ damage when the blood pressure levels rise to $\geq$ 180/110 mmHg (Stöppler, 2018).
Hypertensive emergency	A swift and stern upsurge in blood pressure (systolic blood pressure is greater than ($>$) 180 mmHg and the diastolic blood pressure is $>$ 120 mmHg) which results in new and liberal end-organ impairment (Hopkins, 2018; Suneja & Sanders, 2017:467).
Hypertensive urgency	A meaningful increase (blood pressure reading of $\geq$ 180/110 mmHg) in blood pressure lacking proof of acute end-organ impairment (Beckerman, 2019; Breu & Axon, 2018:860).
Hyperthyroidism	A medical condition in which there is an excess thyroid hormone production, which may speed up the body's metabolism, consequently resulting in unintended weight loss and a fast or abnormal heartbeat (Mathew & Rawla, 2021, Mayo Clinic, 2020b).
International Classification for Diseases and Related Health Problems (10 th revision)	A diagnostic classification coding system that defines diseases, disorders, grievances and other health-related conditions, from scripted medical and health material, into customary codes (WHO, 2004).

Insomnia	A sleeping disorder whereby an individual can be diagnosed as an insomniac if they have difficulty falling asleep or staying asleep for a minimum of three nights a week for $\geq$ three months and if these difficulties impair their normal daily functioning (Kalmbach <i>et al.</i> , 2016:2102).
Lipolysis	The metabolic breakdown, via hydrolysis, of triacylglycerols into their fundamental molecules, glycerol and free fatty acids (Edwards & Mohiuddin, 2021).
Medication side effect	A predictable reaction that arises when treatment with a medicinal product exceeds the desired therapeutic outcome or any effect resulting additive to the therapeutic outcome (Shiel, 2018b).
Micturition	The vital process of urination where metabolic products and toxic wastes, permeated by the kidneys, are excreted from the body (Cortes & Flores, 2021).
Mydriasis	When the pupils become dilated (Ma & Liao, 2017:1).
National Pharmaceutical Product Index (NAPPI) code	A universally distinctive national coding technique used for all pharmaceutical, surgical and healthcare consumable goods in South Africa. These codes allow the provider to request products by using a unique code recognised by medical schemes (MediKredit, 2018).
Neurons	Cells in the brain and the nervous system that receive sensory input from the exterior environment of the body. They send motor instructions to the muscles and alter and communicate electrical signals at every intermediate level (Woodruff, 2019).
Observational research	Non-experimental research where the researcher studies continuing behaviour (Fuel Cycle, 2019).
Obstructive uropathy	An interference with regular urinary outflow, which can be caused by several physical and functional aetiologies (Rishor-Olney & Hinson, 2021).

Off-label drug use	The use of medicinal agents for an indication, age group, in quantities or administration route, other than which is approved by regulatory authorities or specified in the prescribing material of the specific drug (Gor <i>et al.</i> , 2019:31). For this specific study, off-label drug use refers to when phentermine is used for longer than 12 consecutive weeks.
Perfusion-rate diffusion	Drug delivery from the systemic circulation to a particular organ or tissue, where the delivery rate depends on the blood flow inside that organ or tissue (Kok-Yong & Lawrence, 2015).
Permeability	A characteristic of being permeable, i.e., being able to penetrate or pass through, e.g., a cellular membrane (Bennion <i>et al.</i> , 2017:5228).
Pharmacodynamics	The study of biochemical, molecular and physiological effects, including dose-dependent: receptor binding, post-receptor effects and chemical interactions between the drug and the body, which causes a pharmacological effect in the body (Farinde, 2019).
Pharmacoepidemiology	Large quantities of individuals are studied for interactions that occur between medication and the individual human being. It uses different epidemiological techniques to study the advantages, risks and utilisation of medicines in real-life circumstances, and it concerns the process and/or thought of pharmacology and epidemiology (Montastruc <i>et al.</i> , 2018).
Pharmacokinetics (PKs)	The effect of the body on a drug is studied with the focus on the absorption, bioavailability, distribution, metabolism and excretion of the drug throughout the body (Le, 2019).
Pharmacovigilance	Drug pharmacology and patient activities are evaluated to discover, evaluate, comprehend and avoid adverse effects and any other potential drug-associated complications to ensure individual and public safety. Thus, pharmacovigilance (PV) operations should identify the existence of inadequate and reduced quality medicines, especially when they may cause adverse events in individuals (Olsson <i>et al.</i> , 2015:449; WHO, 2002:7).

Phentermine	An amphetamine-like substance that encourages neurons to emancipate or sustain elevated concentrations of a specific group of neurotransmitters, well-known as catecholamine, to decrease appetite (including DA and NE) (Human Metabolome Database (HMDB), 2013).
Polypharmacy	The concomitant and repetitive consumption of five and/or more medications (for this study, individuals with multimorbidity will be excluded), which includes over-the-counter-, prescription- and/or traditional- and complementary medication consumed by the patient (WHO, 2019b).
Q wave, T wave (QT) interval	Represents, on an electrocardiogram (ECG), the length of the ventricular action potential, which physiologically associates with the length of the ventricular depolarisation and repolarisation, i.e., it translates to the time it takes for the cardiac muscle to contract and then relax (Al-Akchar & Siddique, 2021).
Quantitative research	Research used to measure and analyse outlined variables in order to formulate facts and discover prototypes in research (DeFranzo, 2011).
Retrospective cohort study	Observational research where the researcher reviews previous self-reported data to retrospectively investigate whether the risk of condition was distinctive between an exposed and a non-exposed group (El-Masri, 2014).
Side effect	Any effect caused by a drug in addition to the intended effects thereof (Law & Martin, 2020).
Solubility	The highest concentration of a solute that is able to disperse in a solvent at a specified temperature (Lu <i>et al.</i> , 2020).
Steady state	A dynamic equilibrium where a drug's concentration constantly stays within therapeutic perimeters for an unknown yet extensive period of time (Wadhwa & Cascella, 2021).

Sympathomimetic agent	An agent that moderately or entirely imitates the activities of endogenous NE or epinephrine in the sympathetic nervous system (SNS) (AMBOSS, 2020).
Synergistic interaction	The effect that comes about when the joint effect of two substances is larger than the sum of each substance's distinctive action (Canadian Centre for Occupational Health and Safety (CCOHS), 2019).
Thermogenesis	The process in which skeletal muscles and brown adipose tissue dissipate energy to produce heat (Ikeda & Yamada, 2020:2).
Torsade de Pointes	A form of polymorphic ventricular tachycardia, which indicates oscillatory changes in the amplitude of the QRS (Q wave, R wave, S wave) complexes surrounding the isoelectric line on an ECG (Cohagan & Brandis, 2020).
Urticaria or hives	A medical disorder characterised by a red, itchy rash on the skin and mucous membranes (Kayiran & Akdeniz, 2019:93).
Volume of distribution	A pharmacokinetic (PK) component characterising a specific drug's tendency to either stay in the plasma or move to different tissue compartments, i.e., it indicates to what extent a drug can go into organ tissue and cause a pharmacological effect in the body (Mansoor & Mahabadi, 2020).
Xerostomia	The sensation of dryness in the oral cavity, also known as dry mouth, occurs when the salivary glands fail to produce adequate saliva to prevent the mouth from drying out (Talha & Swarnkar, 2021).

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CHAPTER 1: STUDY OVERVIEW AND BACKGROUND

1.1 Introduction and background to the study

Obesity is an extremely common medical disorder that continues to be a global burden to public health (Arroyo-Johnson & Mincey, 2016:571). It describes a condition where an individual has an excessive amount of body fat, and a person can be classified as obese if they have a body mass index (BMI) of 30 kg/m² or higher ($\geq$) (Arroyo-Johnson & Mincey, 2016:571). The BMI can be calculated by dividing an individual's weight (in kilogram) by their height (in metre) squared (height x height) (Yanovski & Yanovski, 2014:75). Obesity negatively affects almost all of the body's physiological functions, which increases a person's risk of developing various chronic health problems such as diabetes, heart conditions and certain cancers (Chooi *et al.*, 2019:6; Dugdale, 2019). It is an immense health (disproportionate healthcare expenses) and economic (loss of individual productivity) burden for society, and since it is classified as a disease, it should be treated as such (Tremmel *et al.*, 2017:436; Upadhyay *et al.*, 2017).

There are different ways in which obesity can be managed and treated. This includes implementing changes in an individual's current lifestyle and behaviour, initiating pharmacological interventions and sometimes performing weight loss (bariatric) surgery (Cleveland Clinic, 2020). Of these, the most important step in managing obesity is changing the individual's current lifestyle. The three main elements of a complete lifestyle intervention include changing the individual's diet, increasing physical activities and initiating behavioural therapy (Webb & Wadden, 2017:1753). However, it is often difficult for patients to lose weight and maintain satisfactory weight loss with just lifestyle and behavioural interventions. Then adjunctive therapies, such as pharmacological interventions, are needed (Yanovski & Yanovski, 2014:75).

Pharmacological interventions such as anti-obesity medication should be initiated, in conjunction with to a medically approved diet, physical exercise and emotional interventions, if the patient has a BMI of ≥ 30 kg/m² or if the patient has a BMI of ≥ 27 kg/m² with complications related to the adiposity (amount of body fat) (Wharton *et al.*, 2020:884). The main purpose of anti-obesity medication is to enhance a patient's welfare and quality of life (Yanovski & Yanovski, 2014:9). The most frequently prescribed anti-obesity medication worldwide is phentermine (Coulter *et al.*, 2018:7; Manasrah *et al.*, 2022:1).

Phentermine (trading as Duromine® in South Africa) is a prescription medication used to suppress an individual's appetite for the purpose of weight loss (Rossiter, 2016:70). It is identified as a schedule five (S5) medicine in South Africa, which was certified in 1959 by the United States of

America's (USA) Food and Drug Administration (FDA) for the short-term (ST) management of obesity (Nicolai *et al.*, 2018:386; Rossiter, 2016:70). A medication is scheduled as S5 in South Africa, if the agent is known to have a low to moderate possibility to cause misuse or dependence and requires a medical diagnosis along with management and control over the supply (via a prescription) (South African Health Products Regulatory Authority (SAHPRA), 2019).

Phentermine is a central, indirect-acting sympathomimetic stimulant related to amphetamine (Human Metabolome Database (HMDB), 2013; Kiortsis, 2013:508; iNova Pharmaceuticals, 2007). Amphetamine is a central nervous system (CNS) stimulant that has a significant ability to cause abuse (Rossiter, 2016:70). Although phentermine is a derivative thereof, the phenylethylamine side chain (of amphetamine's molecule) has been substituted with an α -methyl group (to produce phentermine), which results in less CNS stimulation and makes the agent less likely to cause abuse (Coulter *et al.*, 2018:7; Rossiter, 2016:70).

Phentermine is the most frequently prescribed anti-obesity agent, and its popularity can be attributed to its very slim ability to cause abuse (Coulter *et al.*, 2018:7). An anonymous survey was sent out to the physicians of the American Society of Bariatric Physicians (ASBP). Of the 98% of the physicians that responded, 97% prescribed phentermine to manage obesity (Hendricks, 2016:142). When a South African study investigated the dispensing patterns of prescription-only anti-obesity preparations in South Africa, the researcher found that phentermine accounted for 92.44% of all the anti-obesity prescriptions, making phentermine the most popular prescription-only anti-obesity preparation in South Africa (Truter, 2016:139).

As given by Rossiter (2016:71), the recommended use of phentermine is 15-30 mg orally before breakfast, and therapy should not exceed 12 consecutive weeks as only the safety and efficacy of ST use has been established. A USA survey-based study was done over 10 years, and the self-reported use of phentermine indicated that 42% of the respondents used phentermine for longer than 12 consecutive weeks (Hampp *et al.*, 2013:1306). This provoked concern in the USA regarding possible abuse and addiction since the duration exceeds the recommended guidelines (Hampp *et al.*, 2013:1306). Furthermore, once therapy has been initiated, it should only be continued if the patient loses and maintains a weight loss of 5% (Rossiter, 2016:70). It is evident that phentermine is often used for longer periods than the recommended duration; therefore, it is important that drug surveillance ensues (Keller *et al.*, 2012).

Drug surveillance can be attained through pharmacovigilance (PV) by healthcare professionals. Pharmacovigilance can be described as the discovery, evaluation, understanding and refrainment of any drug-associated problem (World Health Organization (WHO), 2002:7). It serves as a

platform to successfully analyse drug consumption patterns as they are the foremost determining factor in drug safety (WHO, 2002:28). Pharmacovigilance can successfully be achieved if the pharmacological properties of a drug (i.e., its pharmacodynamics and pharmacokinetics) are understood (Berger & Iyengar, 2011:129). The pharmacodynamic (PD) and pharmacokinetic (PK) properties of a medicine are important since they can assist in managing and avoiding potential drug-associated problems, such as medication side effects, adverse drug reactions (ADRs) and drug-drug interactions (DDIs) (Cascorbi, 2012:547).

The PD properties of a drug refers to how the drug affects the body (Glassman & Muzykantov, 2019:570). Phentermine affects the cardiovascular system (CVS), CNS and the gastrointestinal tract (GIT) (iNova Pharmaceuticals, 2007). The effect on the CVS can cause a pressor response along with an increased heart rate and force of contraction (iNova Pharmaceuticals, 2007). Its appetite suppression effect is believed to be exerted via the hypothalamus in the CNS, and this is not the only weight-reducing effect it possesses (iNova Pharmaceuticals, 2007).

As a sympathetic stimulant, phentermine suppresses appetite by indirectly stimulating the CNS, whereby neurons in the hypothalamus of the brain are then again stimulated (Coulter *et al.*, 2018:2; HMDB, 2013). The hypothalamus reacts to the signals sent by the neurons by stimulating the dopaminergic and noradrenergic nervous system to a great extent (iNova Pharmaceuticals, 2007). Thereafter, it causes the release or sustainment of elevated concentrations of a specific group of neurotransmitters (chemical messengers), known as catecholamines (including dopamine (DA), adrenaline and norepinephrine (NE)), outside of the brain, which causes the breakdown of stowed adipose tissue. Norepinephrine plays a role in stress responses (fight-or-flight reactions) and diminishes the sense of hunger (HMDB, 2013).

Phentermine further inhibits the reuptake of noradrenaline (NA), DA and serotonin (5-HT) by inhibiting or reversing the reuptake transporters (HMDB, 2013). It may also possibly cause the inhibition of monoamine oxidase (MAO), resulting in an additional number of neurotransmitters available at the synapses (place of interaction between two neurons) (HMDB, 2013).

Secondarily it may also increase leptin concentrations in the brain, resulting in a state of being sated (HMDB, 2013). It can thus be speculated that an increased concentration of catecholamines is accountable for ceasing neuropeptide Y (a chemical messenger). Neuropeptide Y commences eating, reduces energy expenditure and intensifies fat storage (HMDB, 2013). It can thus be concluded that phentermine stimulates specified brain chemicals, which makes the body think it is full.

Due to severe CNS stimulation, phentermine, just like any other medication, is not entirely free from side effects (Sahu *et al.*, 2014:659). Medication side effects refer to an expected reaction that arises when therapy exceeds the desired outcome. The most common side effects of phentermine include anxiety, agitation, hypertension and insomnia (Rossiter, 2016:70; Shiel, 2018b). More severe medication side effects include heart attack/myocardial infarction, stroke and angina (iNova Pharmaceuticals, 2018). As previously mentioned, phentermine does stimulate not only the CNS but also the CVS and the GIT, which enables it to cause cardiovascular, CNS, gastrointestinal and other types of ADRs, such as micturition disorders, skin rash, impotence, alterations in libido and facial oedema (iNova Pharmaceuticals, 2007). The number of and severity of ADRs rise excessively as the number of drugs taken simultaneously increases (polypharmacy) (Alomar, 2013:84).

Obese patients are commonly associated with polypharmacy because they are especially in danger to acquire chronic diseases, resulting in more drugs that are taken simultaneously (National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 2015; Slater *et al.*, 2018:8). When several drugs are taken concurrently, it makes room for more potential drug-drug interactions (PDDIs) to arise (Alomar, 2013:85). Therefore, polypharmacy should be observed critically in order to avoid DDIs, which affect an individual's health status, compliance and therapeutic outcomes (Alomar, 2013:90).

Some patients encounter clinically relevant life-threatening reactions when facing DDIs, while others are not necessarily affected (Das *et al.*, 2019:64). Such interactions can be classified as mild, moderate or severe (Shahabudin *et al.*, 2012:1258).

A mild DDI is of little significance and these reactions may cause distress to the individual who experiences it (Marsh, 2018). It can worsen the frequency or severity of adverse effects and does not usually call for therapy changes (Shahabudin *et al.*, 2012:1258). Such DDIs become moderate DDIs if the individual experiencing the reaction considers it to be markedly annoying, stressful or unbearable (Marsh, 2018). Moderate DDIs, on the other hand, normally call for a change in therapy and can exacerbate a patient's disease (Shahabudin *et al.*, 2012:1258). Severe DDIs require immediate medical attention or intervention as these can be life-threatening (Shahabudin *et al.*, 2012:1258). It can thus be concluded that minor DDIs are not always of clinical significance as they do not require a change in therapy, whereas moderate and severe DDIs require medical attention as well as a change in therapy.

Drug-drug interactions may also occur if contraindicated drugs are taken simultaneously (Kapp *et al.*, 2013:83). The term contraindicated refers to a certain situation in which a medication,

procedure or operation should be avoided due to the harmful effects it may have on an individual (MedlinePlus, 2019). Phentermine has known DDIs and is, therefore, contraindicated in concurrent use with several medicinal agents. An understanding of the essential mechanisms of DDIs provides an opportunity for early detection or prevention of possible harmful courses of therapy since early decision-making regarding the use or termination of the drugs can be made (Sahasrabudhe *et al.*, 2015:111). Drugs that should not be used together with phentermine include the following:

- **Other agents for weight reduction:** the safety and efficacy thereof have not yet been established (iNova Pharmaceuticals, 2000).
- **Cough and cold preparations containing pseudoephedrine, phenylpropanolamine or phenylephrine (iNova Pharmaceuticals, 2018):** they enhance the elevating effect on blood pressure and heart rate caused by phentermine (Drugs.com., 2021a). When phentermine is used simultaneously with other sympathomimetic drugs (such as phenylephrine), the possibility for additive side effects such as a hypertensive crisis or cardiac arrhythmias arises, and this can be classified as a severe drug interaction (Prescribers' Digital Reference (PDR), 2020).
- **Thyroid hormones:** this causes extra strain on the adrenals resulting in a further reduction in thyroid function (Childs, 2019). The combination of thyroid hormones and sympathomimetic drugs can be classified as a moderate drug interaction since both parties augment the effects on the cardiovascular system (PDR, 2020).
- **Medication used to lower high blood pressure (clonidine, methyldopa and guanethidine) (iNova Pharmaceuticals, 2018) and adrenergic neuron blocking agents:** it decreases the hypotensive effect of these agents (iNova Pharmaceuticals, 2000).
- **Insulin and oral hypoglycaemic medication:** the requirements may be adjusted (Teva Pharmaceuticals, 2020). According to the PDR (2020), both insulin and phentermine increase the blood glucose levels when administered orally, resulting in a moderate drug interaction.
- **Medicines used to treat mental disorders (depression or obsessive-compulsive disorder) (iNova Pharmaceuticals, 2018):** medicine such as fluoxetine, sertraline, paroxetine, ergot-like migraine preparations like ergotamine and clomipramine because of the association these drugs have with cardiac valvular disease (iNova Pharmaceuticals, 2000).

- **Alcohol:** this may result in an ADR and is classified as a moderate drug interaction since the concomitant use of phentermine with alcohol may intensify the risk of cardiovascular side effects (Drugs.com., 2021a, Teva Pharmaceuticals, 2020).
- **Monoamine oxidase inhibitors (MAOIs):** or within 14 days of administration thereof, as this can result in a hypertensive crisis (Thomas *et al.*, 2015:435). Co-administration of MAO and phentermine is considered as a severe drug interaction due to cardiac stimulation and vasopressor effects that may implore a hypertensive reaction. Monoamine oxidase may interact with serotonergic agents, increasing the risk for serotonin syndrome (5-HT syndrome) (PDR, 2020).

It can thus be concluded that the PD properties of phentermine can explain the mechanism of side effects, certain ADRs and DDIs.

Moreover, the PK properties of a drug describe the effect that the body has on a drug (Glassman & Muzykantov, 2019:570). The body processes drugs via absorption, distribution, metabolism and elimination (Glassman & Muzykantov, 2019:570). Phentermine is practically completely absorbed from the GIT and extends to a maximum concentration (C_{max}) (optimal activity) after 3 to 4.4 hours. It has an elimination half-life ($t_{1/2}$) of approximately 25 hours (Teva Pharmaceuticals, 2020), i.e., after 25 hours the drug will reach half the concentration of that of the starting dose in the body. The medication undergoes hepatic metabolism (in the liver), is eliminated via the kidneys, and the cumulative urinary excretion of the unaffected drug (fraction of the drug the GIT did not absorb) ranges from 62.7%-84.8% within 72 hours (iNova Pharmaceuticals, 2007), i.e., after 72 hours 62.7%-84.8% of the unabsorbed drug will be excreted in the urine. Therefore, it can be expected that exposure to the drug may increase in patients with renal impairment and it should be used with attentiveness when administered to such patients (Teva Pharmaceuticals, 2020).

In conclusion: phentermine is the most popular prescription-only anti-obesity medicine in South Africa. The prescribing thereof sometimes exceeds the recommended duration of therapy (DOT) and it is often indecorously controlled. Phentermine has various side effects, ADRs, DDIs and contraindications associated with the consumption thereof. Due to the limited studies investigating the prescribing patterns of anti-obesity products in South Africa, this study may result in a valuable contribution to the literature (Truter, 2016:140).

1.2 Problem statement

There is a need to investigate the prescribing pattern of phentermine in the private healthcare sector of South Africa, because of the associated various risks, contraindications with regard to duration and DDIs, which may lead to life threatening adverse drug events (ADEs).

1.3 Research aims and objectives

The aim and objectives of the research study are discussed hereinafter.

1.3.1 Research aim

The study aimed to investigate data, from a South African pharmacy benefit management (PBM) company's database, from 1 January 2015 to 31 December 2019 in order to analyse the duration of phentermine therapy in the private healthcare sector of South Africa and to establish the prevalence of mild, moderate and severe DDIs when therapy exceeds the recommended duration.

1.3.2 Research objectives

The research study consisted of a literature review and empirical investigation objectives in order to fulfil the aim of the study.

1.3.3 Literature review objectives

The literature review of the research study included the following objectives:

- To present an overview on the background, pharmacological classification, therapeutic indication, contraindications and DDIs of phentermine.
- To investigate the PK and PD characteristics of phentermine that may lead to PDDIs and ADRs.
- To investigate the utilisation patterns of phentermine both nationally and internationally.
- To investigate both the international and national specific prescriber guidelines for prescribing phentermine.

1.3.4 Empirical investigation objectives

The empirical investigation of the research study included the following objectives:

- To investigate the duration of phentermine therapy (for patients receiving 15 mg or 30 mg phentermine respectively) on the PBM company's database for the specific study period, stratified by gender, age and prescriber.
- To determine the prevalence of the co-prescribing of different strengths of phentermine with the top 20 drugs most frequently prescribed to long-term (LT) phentermine consumers that may potentially cause mild, moderate or severe DDIs (classified by a drug interaction checker).

1.4 Research methodology

The research study was based on a literature review as well as an empirical investigation.

1.4.1 Literature review

The literature review was conducted to gather information on the background, pharmacological classification, therapeutic indication, PK and PD properties, contraindications, DDIs, international and national prescribing guidelines of phentermine, as well as drug utilisation reviews (DURs). Various resources were used to gather information on the above-mentioned specifics, and the main sources used were articles from both international and national journals. Other sources used were textbooks, prescribing guidelines of package inserts, honourable internet sites and mobile applications.

Journal articles and textbooks were explored through databases accessible via the North-West University (NWU) of Potchefstroom's library system, such as ScienceDirect®, EBSCOhost® and Google Scholar™. Reliable internet sites were also accessed through the NWU's library system and included Drugs.com and Mayo Clinic. The WHO's internet site, Drugs.com's and the Essential Medical (EM) Guidance's mobile application were also used to gather scientific literature for the literature review.

Specific keywords and/or phrases were used to provide literature related to the keywords and literature of relevance. The following keywords and phrases were used as single entities or in combination: "Drug-drug interact*", "phentermine", "study", "adverse drug react*", "adverse effect*", "side effect*", "risk*", "contraindicat*", "anti-obesit*", "weight loss*", "harm*" and "utilis*".

1.4.2 Empirical investigation

The empirical investigation is discussed under the subheadings: study design, study setting and data source, target and study population and inclusion/exclusion criteria.

1.4.3 Study design

A quantitative descriptive observational pharmacoepidemiological study was conducted using retrospective cross-sectional medicines claims data provided by a national representative PBM company in South Africa to assess the data of patients that received phentermine. Available data from 1 January 2015 to 31 December 2019 were used.

The study was a quantitative study, since the research focused on numeric and unchangeable data, and statistical models were used to explain what was detected (Bhandari, 2020). Descriptive studies aim to define the frequencies of factors and to recognise patterns or trends under certain circumstances (Parab & Bhalerao, 2010:189). This study investigated the prescribing patterns of phentermine, specifically the DOT with the drug (15 mg and 30 mg phentermine, respectively) and where the duration exceeds 12 consecutive weeks (off-label prescribing), the prevalence of mild, moderate and severe DDIs, explaining why this was a descriptive study design.

Furthermore, the study was an observational study as no intervention by the researcher took place during the duration of the study (Parab & Bhalerao, 2010:188). This study analysed the obtained data, as mentioned above, having no influence on the participants whatsoever. Pharmacoepidemiology involves the study of the consumption and effects of medicine in a large population. It gives an approximate possibility of favourable effects and adverse effects of a medicine in a large number of people, which justifies why this was a pharmacoepidemiologic research study (Montastruc *et al.*, 2018). A retrospective study studies something that occurred in the past, and a cross-sectional study design aims to determine the prevalence of this phenomenon (Unite For Sight, 2015).

1.4.4 Study setting and data source

The collected data were obtained from a national representative PBM company's medicine database in South Africa (the name is protected under a confidentiality agreement). This specific PBM company offers services to medical schemes and capitation provider clients to manage medicines dispensed by diverse healthcare dispensers in South Africa. Currently, 98% of all dispensing practitioners, as well as all South African pharmacies, are linked to the PBM company. Moreover, the PBM company has longitudinal data of patient medical claims that exceed

1.8 million medical scheme beneficiaries. Data from 1 January 2015 to 31 December 2019 were used.

The data fields from the database that were utilised included the:

- Active ingredient of the medicine
- National Pharmaceutical Product Index (NAPPI) code of the medicinal item
- Trade/registered name of the medication
- Date that the prescription was dispensed
- Number of the patients receiving phentermine during the study period (1 January 2015 to 31 December 2019)
- Patient's date of birth
- Gender of the patient
- Total number of days that the drug was supplied for within the study period
- Prescriber's speciality.

1.4.5 Target and study population

The target population of the study included all patients in the private healthcare sector of South Africa that had an active member status of any medical aid scheme.

The study population included data of all patients on the PBM company's medicine claims database who had paid claims for 15 mg or 30 mg phentermine as from 1 January 2015 up to 31 December 2019.

1.4.6 Inclusion/exclusion criteria

The following inclusion and exclusion criteria were applied to the study population.

Inclusion criteria:

Inclusion criteria provide an adequate number of participants who are likely to influence and assist in achieving the outcome of the study (Cummings *et al.*, 2007:30). It describes the main elements

of the study population that relates to the research question and are listed below (Cummings *et al.*, 2007:30):

- **National Pharmaceutical Product Index (NAPPI) code:** All prescriptions containing the NAPPI codes for either 15 mg (721786-006) or 30 mg (721794-009) phentermine
- **Time period:** 1 January 2015 to 31 December 2019
- **Date the prescription was filled:** The DOT with phentermine and the period extending longer than 12 consecutive weeks (given a grace period of 5 days for early/late collection of prescriptions)
- **Phentermine use exceeding the 12-week period:**
 - Data containing the co-prescription of phentermine with those drugs that may cause severe DDIs, as specified by the DDI checker:
 - ✓ Non-selective monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs) and appetite suppressants as categorised by the Monthly Index of Medical Specialities (MIMS®) classification system
 - ✓ Active ingredients duloxetine and venlafaxine (5-HT and NA reuptake inhibitors), bupropion (NA (and DA) reuptake inhibitor), rasagiline (anti-Parkinson agent), tramadol hydrochloride and tapentadol (analgesics), phenylpropanolamine (antitussives and expectorant) and linezolid (antibacterial agent), as classified by the MIMS® classification system
 - ✓ Water-soluble, nephrotrophic low osmolar X-ray contrast media iohexol and iopamidol
 - ✓ Antidote methylene blue
 - Data containing the co-prescription of phentermine with those drugs that may cause moderate DDIs, as specified by the DDI checker:
 - ✓ Tricyclic antidepressants (TCAs), butyrophenones, other positive inotropic agents, sympathetic nervous blockers, dipeptidyl peptidase-4 (DPP-4) antagonists and glucagon-like peptide 1 (GLP-1) agonists as categorised by the MIMS® classification system
 - ✓ Active ingredients chlorpromazine (phenothiazine), amisulpride (atypical antipsychotic), sulpiride, zuclopenthixol and flupentixol (anti-psychotics), topiramate (anti-epileptic), fentanyl, ketamine, remifentanyl and sufentanyl (parenteral anaesthetics), pethidine, dihydrocodeine tartrate and

pentazocine (narcotic analgesics), adrenaline (sympathomimetic), promethazine hydrochloride and trimeprazine (anti-histamines), dobutamine and DA (positive inotropic agents), methyldopa (central acting sympathetic nervous system (SNS) inhibitor), dextromethorphan hydrobromide, ephedrine, methadone, promethazine and pseudoephedrine (antitussives and expectorants), formoterol, indacaterol, salbutamol, salmeterol and terbutaline (sympathomimetic bronchodilators), polyethylene glycol (laxative), phenylephrine hydrochloride (mydriatic), biosynthetic isophane human insulin, insulin aspart, insulin detemir, insulin glargine, insulin glulisine and insulin lispro (insulins), acarbose, glibenclamide, gliclazide, glimepiride, glipizide, metformin hydrochloride and pioglitazone (oral anti-diabetic agents), levothyroxine sodium and liothyronine sodium (thyroid), as categorised by the MIMS® classification system

- Data containing the co-prescription of phentermine with those drugs that may cause minor DDIs, as specified by the DDI checker (evening primrose).

Exclusion criteria:

Exclusion criteria describe the process of establishing which research subjects and articles must be extracted from the literature that has been gathered due to their irrelevance to the study (Salkind, 2010).

The empirical investigation consisted of the following exclusion criteria:

- Insufficient data regarding the prescriber's speciality
- Data where the patients' date of birth/gender was not known.

1.4.7 Classification systems

The following classification systems were used to fulfil the purpose of the study.

MIMS® classification:

The MIMS® is a resource that categorises the active ingredients and registered trade names of indices according to their pharmacological classification. It provides information that is accumulated by package inserts and provided by pharmaceutical companies (Snyman, 2014:5).

The MIMS® classification group 1.4.1 was thus used for TCAs, groups 1.4.3.1 for non-selective monoamine oxidase inhibitors, group 1.4.4 for SSRIs, group 1.5.2 for butyrophenones, group 7.1.2 for other positive inotropic agents, group 7.3.5 for sympathetic nervous blockers, group 12.2 for appetite suppressants, group 19.1.2.1 for DPP-4 antagonists and group 19.1.3 for GLP-1 agonists.

NAPPI code:

The NAPPI codes are exclusive 9-digit codes that are applied with electronic transactions in mind (Snyman, 2014:216). These codes incorporate the products name, strength, package size, manufacturer and exclusions. The MIMS® was used to identify the NAPPI codes for phentermine 15 mg (721786-006) and 30 mg (721794-009). These respective codes for phentermine were used to identify the products on the database.

1.4.8 Study variables

The following independent and dependent variables were applied to the study.

Independent variables:

- Age: Each patient's age was calculated by using the date of birth and the date the prescription was filled. The age of the patients was thus the exact age of the patient on the calendar date on which the prescription was dispensed. The age groups were then categorised in accordance with existing literature as (Truter, 2016:140; Truter, 2014:33):
 - Age group 1: ≤ 18 years
 - Age group 2: 19-34 years
 - Age group 3: 35-59 years
 - Age group 4: ≥ 60 years.
- Gender: The gender of the patients was gathered from the database and depending on their information on the database, patients were categorised as either male or female.
- Prescriber: The prescriber's speciality was gathered from the database and categorised as general practitioners or specialists.
- Duration of therapy exceeding 12 consecutive weeks: The total number of days the drug was supplied was used to determine whether the DOT exceeded the recommended 12-week period. A grace period of five days was given for early or late collection of prescriptions.

Dependent variables:

- Duration of therapy: The overall number of days that 15 mg and 30 mg phentermine was supplied for, respectively, was used to establish the DOT with the drug.
- Drug-drug interactions: Drugs that may potentially cause DDIs when co-administered with phentermine were categorised according to the severity of the DDI as described by Drugs.com's interaction checker (Drugs.com., 2021a). According to Drugs.com (2021a), DDIs can be classified as mild (i.e., the reaction is of little clinical significance and does not require a change in therapy), moderate (i.e., it is of clinical significance as it may cause distress to patients and these DDIs usually necessitates a change in therapy) and severe (i.e., the interactions are of major clinical significance as they may be life-threatening and they require a change in therapy) (Shahabudin *et al.*, 2012:1258).

1.4.9 Data analysis

A retrospective DUR study was performed by using a South African PBM medicine claims database. Data on the prescribing patterns of phentermine were extracted to analyse the DOT with 15 mg and 30 mg phentermine, respectively. Where the DOT exceeded 12 consecutive weeks, the co-prescribing of phentermine with drugs that may potentially cause DDIs were then analysed. The data analysis plan is provided in Annexure A.

1.4.10 Statistical analysis

The researcher made use of descriptive statistics to summarise the data. The analyses were performed in Statistical Analysis System® (SAS®) 9.4 (SAS® Institute, Cary NC). The statistical analyses of each empirical objective are listed in Table 1-1.

Table 1-1: Statistical analyses per study objective

Objective	Descriptive statistics
To investigate the duration of phentermine therapy (for patients receiving 15 mg or 30 mg phentermine respectively) on the PBM company's database, stratified by gender, age and prescriber.	Minimum Maximum Mean and standard deviation The results of the descriptive statistics will also be stratified by: Gender Age Prescriber

To determine the prevalence of the co-prescribing of different strengths of phentermine with the top 20 drugs most frequently prescribed to LT phentermine consumers that may potentially cause mild, moderate or severe DDIs (classified by a drug interaction checker).	Frequency and percentage
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1.4.11 Descriptive statistics

Descriptive statistics were used to analyse the data.

Mean value:

The mean value, also known as the average, is the most popular measurement of central tendency (Sykes *et al.*, 2016:277). It can be calculated by adding up all the entries in a dataset and dividing that amount by the number of entries which was added together (Sykes *et al.*, 2016:277). For the purpose of the study, the mean was calculated to determine the average DOT with 15 mg and 30 mg phentermine:

- for the study population
- amongst male and female patients
- amongst the different age groups
- as prescribed by a general practitioner and a specialist.

Standard deviation:

The standard deviation determines the difference from the group's average, i.e., it provides an understanding of how much variation occurs within a group of figures (Sykes *et al.*, 2016:277). It can be calculated by applying a square root to the variance, which is an amount in square units that has little significance to the data (Sykes *et al.*, 2016:277). The standard deviation is thus a measurement of the variability expressed in the same entities as the data. If the standard deviation has a low value, it indicates that the data fragments are near the mean, and the opposite is also true (Sykes *et al.*, 2016:277). The standard deviation for the different groups, as discussed above, were calculated.

Frequency and percentage:

Frequency (n) can be defined as the number of times in which a particular observation occurred in a set of data (Manikandan, 2011:54). The frequency and percentage were used to indicate the number of patients on the database that received phentermine, and for longer than 12 consecutive weeks, during the study period. It was also used to numerise the prevalence of DDIs with phentermine when the DOT has been exceeded.

1.4.12 Inferential statistics

The inferential statistics that were used in the study are discussed below.

Two sample t-test:

A two-sample t-test (or an independent t-test) is a sort of statistical test that is utilised to compare the averages of two groups (Kim, 2015:540). This test was used to assess whether the mean DOT with 15 mg and 30 mg phentermine respectively, was significantly different between male and female and between the prescribing practices of those of a general practitioner and specialist.

One-way ANOVA:

The one-way analysis of variance (ANOVA) is a statistical method used to establish whether there is a difference in the averages of three or more groups (Kim, 2017:22). This test was utilised to determine whether there is a difference in the average DOT with 15 mg and 30 mg phentermine respectively for different age groups.

1.4.13 Effect size

Effect size gives the extent of the difference between groups (Sullivan & Feinn, 2012:279). The study made use of Cohen's d-value to specify the effect size of results that were statistically significant, computed as a two-sided p-value of 0.05, i.e., if p is < 0.05 , there is a statistically significant difference in the mean values of groups and if p is > 0.05 , we accept that there is no difference in the mean values between groups.

Cohen's d-value:

Cohen's d-value assists in reporting the two-sample t-test and the ANOVA, where it computes the extent of the disparity between the average values of two or more study variables comparative to the extent of their standard deviations (Sullivan & Feinn, 2012:280). A d-value of 0.2, 0.8 and ≥ 0.8 suggests a small, medium and large effect, respectively (Sullivan & Feinn 2012:80).

1.5 Ethical considerations

The ethical consideration of the research study is discussed further in the subsequent paragraphs.

1.5.1 Permission and informed consent

In 2011, the research niche-area Medicine Usage in South Africa (MUSA) was granted permission to use the PBM company's data for research purposes. Informed consent was obtained from the PBM's Boards of Directors, which was done through a formal agreement between the PBM and MUSA. The proposal was submitted to MUSA's scientific committee for review and the study commenced after ethical approval was granted by the Health Research Ethics committee (HREC) of the Faculty of Health Science of the NWU (ethics no. NWU-00179-14-A1-11) (see Annexure B).

When a member voluntarily becomes an associate of a medical scheme, they are obligated to supply personal information to the medical schemes when they use the services, products, amenities, apparatuses or benefits offered by the medical scheme. A patient's personal information may only be disclosed, gathered and processed if the patient has given written permission or if permitted or obligated to do so by law.

If a medical scheme registers a patient as a beneficiary, the patient supplies the medical scheme with transcribed consent to share private information inside the medical scheme or with a third participant, like a PBM, Council of Medical Schemes, universities and other researchers. However, the patient membership form of the medical schemes states that information will only be shared with a third party if it is kept truly confidential and if all data (such as patient, prescriber, etc.) will be depersonalised. The medical scheme must ensure that all information is depersonalised before it is obtained by the PBM.

Informed consent was therefore not relevant to this study since the researcher worked with retrospective data and no patients, medical aid, prescribers or providers could be identified. Individual researchers and statistical consultants only accessed the data after they had signed a confidentiality agreement which is kept in a tamper-proof cabinet in MUSA's office.

1.5.2 Anonymity

The PBM (which is not identified in this study) gains data through medical schemes which assure confidentiality by erratically assigning "dummy" member numbers to each patient record. Each medical scheme ensures that all information is depersonalised before it is obtained by the PBM,

thereby ensuring anonymity and confidentiality, as no individual, medical scheme, plan option, provider or prescriber can be identified.

1.5.3 Privacy and confidentiality

The PBM providing the data was not identified throughout the study and it complied with all privacy and security policies as well as local, provincial and nation-wide policies. The research assistant of MUSA, along with Prof MS Lubbe, the permitted researchers (Dr JM du Plessis, Dr M Julyan and Ms CS Mostert) and the statistician (Ms M Cockeran) was able to access the data once they had signed the designated confidentiality agreement which the research assistant keeps in a tamper-proof cabinet in MUSA's office.

Only data related to the study was extracted from the database and included the following: the number of the prescriptions containing phentermine from 1 January 2015 to 31 December 2019, the active ingredient of the medicine, patient's date of birth, gender of the patient, date that the prescription was dispensed, NAPPI code of the medicinal item, trade/registered name of the medication, the total number of days that the drug was supplied for as well as the speciality of the prescriber. All personal patient information, medical scheme information or scheme option was de-identified, which ensured confidentiality and its maintenance.

All copies of the datasets kept on laptops or computers were kept under a different file name, and all the data were safely secured with passwords on protected computers (which are secured by a firewall and an anti-virus software programme).

1.5.4 Justification for the study population

The study population consisted of all patients on the PBM's medicine claims database who obtained phentermine from 1 January 2015 to 31 December 2019, and only paid claims were included in the study. The study population was sufficient in reaching the aims and objectives of the study.

1.5.5 Benefit-risk ratio analysis

The study showed no potential for direct risks as no participants took part in conducting the study (retrospective anonymous data). This was a low-risk or minimal-risk study since retrospective medicine claims data were used. Therefore, the benefits outweighed the risks.

1.5.6 Direct benefits

The study did not provide any direct benefits to the study population, as this was an observational, retrospective study.

1.5.7 Indirect benefits

Society, researchers and institutions indirectly benefit from the study by gaining academic knowledge. Patients can also indirectly benefit from this study, as it educates them on the classification, indication, DOT, side effects, ADRs, PDDI's, PK and PD properties of phentermine. Prescribers may benefit from this study since they are provided with statistics regarding the prescribing patterns of phentermine, which may result in prescribers being more vigilant when prescribing phentermine.

The study provides scientific facts on phentermine and allows other researchers to compare their data to ensure an exact representation of the current state of affairs.

1.6 Chapter summary

Obesity is a significant inconvenience for society and has many health risks accompanying the disease. Fortunately, it can be treated both non-pharmacologically and pharmacologically. Treatment with phentermine has been the most popular pharmacological approach, in addition to lifestyle and behavioural interventions, to treat obesity because of the drug's ability to suppress appetite. Phentermine is known for its safety profile, although side effects, ADRs and DDIs occur, which can be attributed to its judicious use over the past few decades. To ensure that the drug retains its popularity, the prescribing patterns ought to be investigated so medication errors and problematic drug prescribing can be detected, resolved and prevented. Maximum patient adherence and outcomes are the main priority in the healthcare sector of South Africa. Therefore, this study investigated the prescribing patterns of phentermine (the DOT with the drug and the prevalence of DDIs when the duration exceeds 12 consecutive weeks) in the private healthcare sector of South Africa, adhering to the ethical aspects discussed above (see section 1.5). The research methodology provided in this chapter was used to fulfil the aim and objectives of this study. The literature review objectives are addressed in the following chapter, chapter 2, followed by the results from the empirical investigation objectives in chapter 3.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction and background of phentermine

Phentermine, a significant amphetamine derivative, was first developed in 1959 by Strassenburg Laboratories in the United States of America (USA) to treat obesity (Haslam, 2016:208; Hendricks, 2017:226). In the same year, the drug got approved by the USA's Food and Drug Administration (FDA) for that indication (not specifying nor restricting the recommended duration of therapy (DOT)) (Haslam, 2016:208; Hendricks, 2017:226). This amphetamine derivative has become the most popular medication prescribed for the treatment of obesity since its FDA approval (Hendricks, 2017:226). Amphetamine is a synthetic central nervous system (CNS) stimulant that is likely to cause abuse and dependence because of the drug's highly addictive and mood-altering properties (Hendricks, 2017:226; Newman, 2017). The addictive properties, which may also lead to the long-term (LT) use thereof, may be associated with augmented sympathetic nervous system (SNS) stimulation, which consequently may result in cardiovascular side effects such as hypertension (Bazmi *et al.*, 2017:32). Concerns arose that phentermine, being structurally related to amphetamine, may also potentially induce dependence and cause severe cardiovascular side effects if used LT (off-label, in this case, more than 12 consecutive weeks) (Kokkinos & Levine, 1993:310). These apprehensions had a significant impact on the prescribing of the drug at that time, causing a decline in the market use thereof (Hampp *et al.*, 2013:1300; Rodgers *et al.*, 2012:622).

In 1962, the Kefauver-Harris modification to the USA's Food, Drug and Cosmetic Act mandated that all drugs that the FDA approved prior to 1962 (thus including phentermine) be re-evaluated based on their safety and efficacy (Haslam, 2016:208; Hendricks, 2017:226). Phentermine was not withdrawn from the market due to the lack of substantial evidence linking the LT use of phentermine to abuse or serious cardiovascular side effects. The FDA re-approved the drug in 1977, only this time it was restricted to short-term (ST) (a period not exceeding 12 consecutive weeks) use only (Haslam, 2016:209; Hendricks, 2017:226).

Disregarding this restriction, USA physicians continued to prescribe phentermine on an off-label, LT basis (Hendricks, 2017:226). The term off-label describes a situation where an FDA-approved medicine (i.e., the medicine is only approved for a specific indication) is used for an unapproved indication (FDA, 2018). The LT prescribing of phentermine might be considered as legal and rather universal, but regardless of the popularity and lawfulness of off-label drug prescribing, The Medicine Act of South Africa classifies it as "risky" since the safety thereof in a specific population

has not been tested (Berry, 2020; Klinck & Trokis, 2020:2). It holds a liability risk for any healthcare professional, and no regulatory approvals will authenticate nor validate its use for particular indications (Klinck & Trokis, 2020:2).

Hendricks *et al.* (2014:297) found that the LT (i.e., longer than 12 consecutive weeks) use of phentermine does not cause abuse nor addiction, nor does it provoke drug cravings, and the sudden cessation of the drug does not cause amphetamine-like withdrawal. In addition to this, Lewis *et al.* (2019:601) found that the LT use of phentermine causes significant larger weight loss when compared to ST treatment, and there is no evidence of increased cardiovascular risks. However, further evidence is essential to undeniably prove the safety and efficacy of LT monotherapy with phentermine (Lewis *et al.*, 2019:601).

The off-label use of prescription medication is not only considered “risky”, but it also increases a person’s risk to experience an adverse drug event (ADE) (Egualé *et al.*, 2016:61). An ADE describes a drug-related injury resulting from a medical intervention (Office of Disease Prevention and Control, 2020). A perfect example of this would be the combination of phentermine with fenfluramine which caused cardiac valve damage (Wellman & Maher, 1999:730). In this context, the ADE refers to the adverse drug reaction (ADR) (cardiac valve disease), which was caused by the synergistic drug-drug interaction (DDI) between phentermine and fenfluramine (Wellman & Maher, 1999:730). Liu *et al.* (2017:3) define an ADR induced by synergistic DDIs as a result of the concurrent interaction amongst two co-administered substances and their target proteins, which produces a greater ADR than that which can be caused by either substance individually. This is known as a pharmacodynamic (PD) DDI since it focuses on the mechanism by which drugs affect each other’s receptor function and physiological processes and whether drugs add or oppose to one another’s physiological effects (Yartsev, 2018b).

The combination of phentermine with fenfluramine or dexfenfluramine was a popular approach to treating obesity in the early 1990s (Li *et al.*, 2003:448). Fenfluramine and dexfenfluramine were both serotonin (5-HT) releasing agents (approved by the FDA in 1973 and 1996 respectively, to treat obesity), which were withdrawn from the market by the manufacturers due to their connotation with primary pulmonary hypertension and valvular heart disease (Leroy, 2017; Roig, 2016; Schwarz, 2020). However, in 2003, Li *et al.* (2003:458) found that whether phentermine was used alone or in combination with fenfluramine, there is no substantial difference in weight loss.

Unlike the combination of phentermine and fenfluramine, a study done by Arrone *et al.* (2013:2170) discovered that the FDA-approved fixed-dose combination of phentermine with

topiramate (extended-release formulation) caused a significantly larger amount of weight loss than that of either constituent does as monotherapy. The exact mechanism through which topiramate exerts its weight-reducing effect is not known, and it is only known to be a common side effect of the drug (Wilding, 2017:1505). The FDA approved this weight-loss combination in 2012, specifying that the dose of phentermine may not exceed a maximum of 15 mg/day (Arrone *et al.*, 2013:2170). Despite this restriction, certain USA prescribers prescribe an additional dose of phentermine to the phentermine/topiramate fixed-dose combination (Hendricks, 2017:230). Neither phentermine nor the phentermine/topiramate combination is approved by the FDA for this specific indication, making it an off-label use thereof (Hendricks, 2017:230).

Another drug that was found to cause significant weight loss when combined with phentermine is lorcaserin, which is a selective agonist on serotonin 2C receptors (5-HT_{2c}) (Giovanni *et al.*, 2020:1). Theoretically, one would expect this combination would lead to adverse serotonergic incidents since lorcaserin is, and phentermine might perhaps be, connected with increased serotonergic activity. Still, Smith *et al.* (2017:856, 863) concluded that this combination does, in fact, not increase the prevalence of such events. Despite this combination being an exceptional approach to weight loss, the FDA requested that lorcaserin be withdrawn from the market due to the drug's possible carcinogenic characteristics outweighing the benefits thereof (FDA, 2020).

When two drugs, which may potentially cause an ADR, are co-administered, the benefit-risk ratio must be considered (MedlinePlus, 2019). For example, fluoxetine augments the anorectic activity of phentermine, but it also enhances the dopamine (DA) concentrations which result in neurotoxic effects (Callahan *et al.*, 2000:476). Fluoxetine is a selective 5-HT reuptake inhibitor (SSRI) and the co-administration with phentermine may cause a severe DDI which can result in serotonin syndrome (5-HT syndrome) (Drugs.com., 2021a; Rossiter, 2016:495). Serotonin syndrome results from an excess 5-HT concentration in the body which causes extreme activity of nerve cells and life-threatening symptoms (Simon & Keenaghan, 2021). Consequently, phentermine and fluoxetine are absolutely contraindicated. The simultaneous use of these two drugs should be avoided due to the significant harm this combination may cause to an individual (MedlinePlus, 2019).

One of the main reasons why phentermine is still a popularly prescribed drug, regardless of the various modern anti-obesity medicines, is because the drug has been used judiciously over the past few decades without severe side effects (Kim *et al.*, 2006:614; WebMD, 2021). It doesn't mean that phentermine is entirely free from side effects; in fact, being a sympathomimetic amine, it stimulates the CNS and may produce side effects that are harmonious with its catecholamine releasing abilities (Isidro & Cordido, 2010:129; Kim *et al.*, 2006:614). Cardiovascular, CNS and

gastrointestinal (GI) side effects can be observed, and they vary in terms of frequency and severity (Kim *et al.*, 2010:614; iNova Pharmaceuticals, 2000). The more severe side effects experienced with phentermine necessitate medical intervention and cessation of drug use. Fortunately, these types of side effects are rare, and the most common, less-severe side effects experienced by patients are (amongst other) (see section 2.5.2): dry mouth (xerostomia) and sleeping obscurities (insomnia) (WebMD, 2021).

When a patient is using medicinal products, the ultimate goal is to minimise any side effects or adverse effects that may occur during treatment, as it ensures maximum patient adherence and outcome (Carver *et al.*, 2020; Hansberry, 2017). This may be achieved by pharmacovigilance (PV), as the goal is to ensure drug safety, and it describes the gathering, investigation, managing and prevention of hostile effects that may occur with medical treatment and certain therapies (Hansberry, 2017). Pharmacovigilance goes hand in hand with drug utilisation reviews (DURs), as DURs assess how the use of drugs may relate to the favourable or adverse effects of drugs (Gama, 2008:68).

Drug utilisation reviews focus on the systemic use of medicine to ensure that medication is used appropriately, safely and efficiently (Carver *et al.*, 2020). It assists in identifying actual and possible medicine-related problems that may interfere with maximum patient adherence and outcome (Carver *et al.*, 2020). The common goal amongst PV and DURs is that both processes aim to optimise patient outcome with medicine. However, only PV focuses specifically on hostile effects, whereas DURs focus on any medicine-related problems that may occur during therapy (Carver *et al.*, 2020; Hansberry, 2017).

Therefore, a DUR of phentermine would be beneficial as it will assist in identifying and resolving medication-related problems, so the drug can continue to be used judiciously in the future, as in the past (Carver *et al.*, 2020; Kim *et al.*, 2006:614). Understanding the pharmacokinetic (PK) and PD properties of the drug will aid in the management and prevention of side effects, ADRs and DDIs related to phentermine. This chapter will, therefore, focus on the pharmacological classification, therapeutic indication, PK and PD properties of phentermine. Attention will also be given to the drug's contraindications, DDIs and the national and international prescribing guidelines thereof.

2.2 Pharmacological classification

Phentermine is mainly classified as an anorexigenic appetite suppressant since it consists of CNS stimulating properties that suppresses an individual's appetite (i.e., the drug acts on the brain to

suppress the appetite) (Drugs.com, 2021b; Rossiter, 2016:70). The drug's chemical structure plays an important role in the classification thereof, and it can further be classified as an amphetamine derivative since it has a chemical structure similar to that of amphetamine, a phenylethylamine core (Drugs.com, 2021b; iNova Pharmaceuticals, 2000; Rossiter, 2016:70). Figure 2-1 gives a representation of the different chemical structures of phentermine and amphetamine as adapted from Hong *et al.* (2016:1406) and Sanchez-Ramos (2015:133), and it also emphasises the similarities in the two structures.

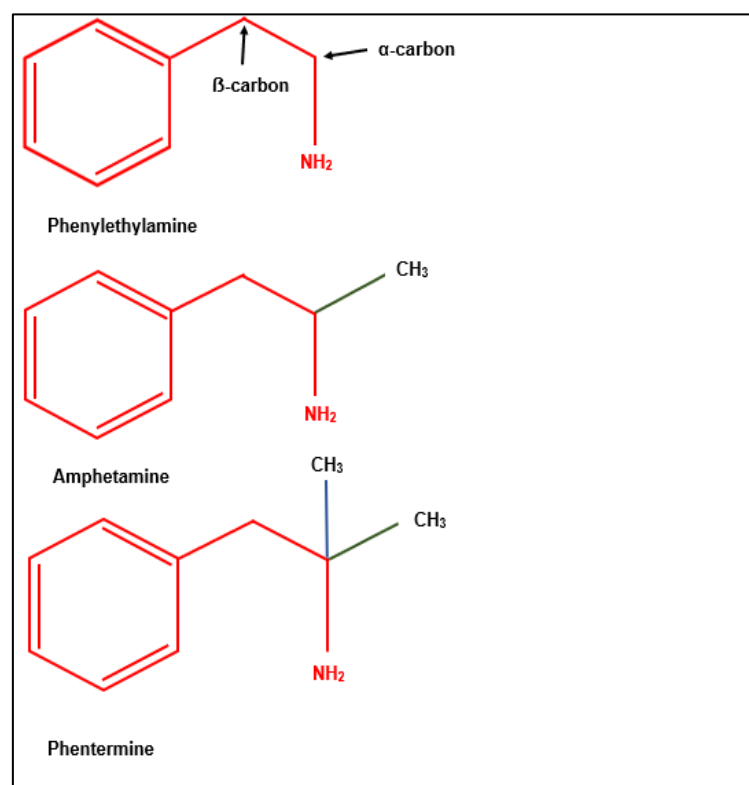


Figure 2-1: Chemical structures of phentermine and amphetamine

As seen in Figure 2-1, both drugs have the same phenylethylamine core. Phenylethylamine is a natural chemical that is made by the body, and it plays an essential role in depression and other psychiatric disorders (WebMD, 2020a). When a methyl group is added to the α -carbon, the molecule becomes a selective monoamine oxidase A inhibitor (MAOI-A) and the structure represents that of amphetamine's (Reyes-Parada *et al.*, 2020:5). Amphetamine is a potent sympathomimetic CNS stimulant and an anorexic drug with severe abuse potential and several toxic side effects (Stăcescu *et al.*, 2020:78). However, when a second methyl group is added to the α -carbon (of amphetamine's structure), the molecule will cause less CNS stimulation, it will

be less likely to cause abuse, and the structure now corresponds to phentermine's chemical structure (Coulter *et al.*, 2018:7).

Moreover, when a hydroxide (OH⁻) atom is added to the β -carbon of the phenylethylamine core in amphetamine's structure, the chemical structure is called D-nor-pseudoephedrine or cathine (Sanchez-Ramos, 2015:133). Cathine is also an amphetamine derivative that is less potent and less addictive than amphetamine (Kalyanasundar *et al.*, 2020:2; Sanchez-Ramos, 2015:132). The drug is available in South Africa (trading as Nobese No.1[®], Eatless[®] SR, Leanor[®] and Relislim[®]) as a CNS appetite suppressant and is classified in the same pharmacological class as phentermine; that is, anorexigenic appetite suppressants (Rossiter, 2016:70; Sanchez-Ramos, 2015:133).

Other anorexigenic appetite suppressants available in South Africa are amfepramone or diethylpropion hydrochloride (trading as Tenuate Dospan[®]) and phendimetrazine or D-phendimetrazine barbiturate (trading as Obex-LA[®] and Obesan X[®]) (Rossiter, 2016:70). Both amfepramone and phendimetrazine can also be classified as amphetamine derivatives, although they do not share the same phenylethylamine core (Stăcescu *et al.*, 2020:77). Figure 2-2 is adapted from Stăcescu *et al.* (2020:77) and Sanchez-Ramos (2015:133) and gives the similarities and differences in the chemical structures of the different anorexigenic appetite suppressants that are available in South Africa.

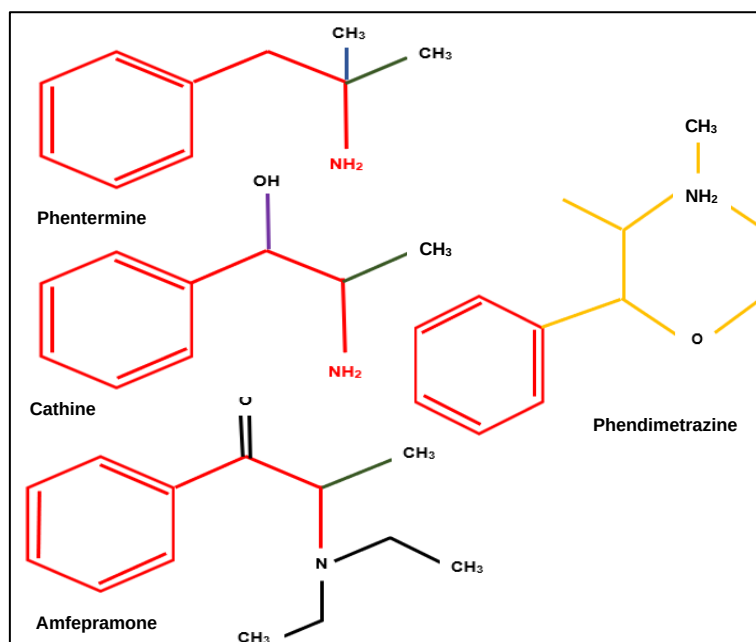


Figure 2-2: Chemical structures of phentermine, cathine, amfepramone and phendimetrazine

Phentermine, cathine, amfepramone and phendimetrazine are all classified as amphetamine derivative anorexigenic appetite suppressants that differ in terms of chemical structures, resulting in them having different potencies, abuse potentials and safety profiles (Rossiter, 2016:70; Stăcescu *et al.*, 2020:77). Cathine, amfepramone and phendimetrazine are all scheduled as schedule six (S6) substances since they have a moderate to high possibility to cause abuse and dependence, and they may not be prescribed nor supplied for a period longer than 30 days (Rossiter, 2016:70; South African Health Products Regulatory Authority (SAHPRA), 2019:9). In other words, if the authorised prescriber chooses to continue therapy with these drugs, a new prescription will need to be filled out every time (or every 30 days) the medication ought to be dispensed (Truter, 2016:142). Phentermine, on the other hand, is scheduled as a schedule five (S5) substance since the drug has a low to moderate possibility to cause abuse or dependence (SAHPRA, 2019:8).

Schedule five substances may be prescribed for a maximum of six consecutive months; however, phentermine is restricted to a maximum of three months only (Hendricks, 2017:226; SAHPRA, 2019:8). Phentermine's lower scheduling status can be attributed to the second methyl group on the α -carbon (as previously discussed), which results in less severe CNS stimulation and consequently the lower risk for developing dependence in individuals (Coulter *et al.*, 2018:7). For this exact reason, phentermine is found to be the most popular anorectic drug prescribed for the treatment of obesity in South Africa (Truter, 2016:143).

Furthermore, apart from structurally being similar to amphetamine and therefore also being classified as a natural monoamine alkaloid derivative, phentermine's chemical structure is also similar to that of certain endogenous neurotransmitters (Reyes-Parada *et al.*, 2020:5; Sanchez-Ramos, 2015:133; Willard *et al.*, 2017:116). These neurotransmitters include DA, norepinephrine (or noradrenaline) (NE or NA) and epinephrine (or adrenaline), and they all share the same phenylethylamine core as seen in amphetamine, phentermine and cathine (Sanchez-Ramos, 2015:133). Figure 2-3 gives the chemical structure of phentermine, DA, NE and epinephrine, respectively, to point out the similarities in the structures of these neurotransmitters and phentermine (adapted from Sanchez-Ramos, 2015:133; and Stăcescu *et al.*, 2020:77).

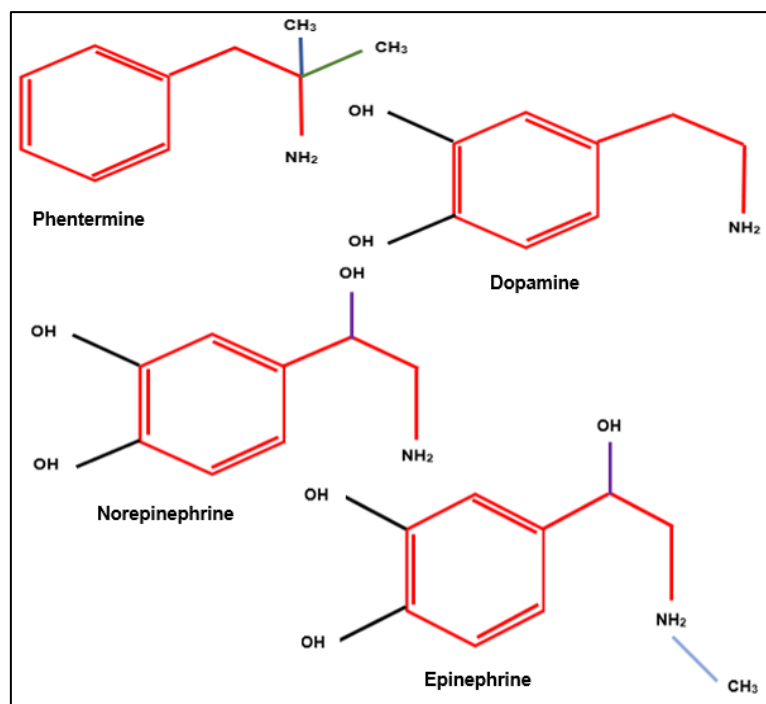


Figure 2-3: Chemical structures of phentermine, dopamine, norepinephrine and epinephrine

The similarities in their chemical structures allow for phentermine to indirectly produce effects that mimic those of DA, NE and epinephrine (Campbell & Young., 2017:20; Sanchez-Ramos, 2015:137). As a result, appetite is suppressed in the brain (Stăcescu *et al.*, 2020:80) (see section 2.5.1 for detailed discussion). This explains why phentermine is a sympathomimetic amine (mimicking the effects of these neurotransmitters) exerting CNS stimulating properties that suppress appetite (Campbell & Young., 2017:20; Rossiter, 2016:70). It, therefore, also justifies phentermine's FDA approved therapeutic indication for obesity (Hendricks, 2017:226).

2.3 Therapeutic indication

Phentermine is indicated for the ST management of obesity if a patient has a body mass index (BMI) of $\geq 30 \text{ kg/m}^2$ and has not been able to lose clinically satisfactory weight after a sufficient weight-reducing programme has been followed for at least 3-6 months (iNova Pharmaceuticals, 2000; Rossiter, 2016:70). A patient is said to have lost a meaningful amount of weight if s/he has lost 5% of their initial body weight, i.e., for an individual weighing in at 100 kg, clinically satisfactory weight loss would be 5 kg (5% of 100 kg); therefore, if the individual fails to lose this amount of body weight over a 3-6-month period, phentermine may be initiated (iNova Pharmaceuticals, 2000; Williamson *et al.*, 2015:2319).

Treatment may also be initiated if the patient has a BMI of $\geq 27 \text{ kg/m}^2$ with complications related to the patient's adiposity (amount of body fat) (Wharton *et al.*, 2020:884). These complications are often associated with obesity and include (amongst others): diabetes (high glucose or sugar levels in the blood), cardiovascular diseases and cancer (Kinlen *et al.*, 2018:440). Obesity, along with these complications, is responsible for a high mortality rate worldwide (Kinlen *et al.*, 2018:438). Kinlen *et al.* (2018:438) support this statement as he found that patients within the BMI range of 20 kg/m^2 to 25 kg/m^2 have the lowest mortality rate when compared to individuals in the overweight and obese category, as their mortality rate increases significantly with an increase in the BMI value. These findings emphasise the importance of managing and maintaining a healthy body weight (BMI ranging from 18.5 kg/m^2 to 24.9 kg/m^2) and warrants why pharmacotherapy ought to be initiated, in addition to healthy lifestyle adjustments, amongst overweight and obese patients (Dasinger 2021; Wharton *et al.*, 2020:884).

However, pharmacotherapy with phentermine may only be initiated in patients with cardiovascular disease and/or diabetes if the benefit outweighs the risk thereof since phentermine affects the cardiovascular system (CVS) as well as glucose levels in the body (Lee & Dixon, 2017:473; Prescribers' Digital Reference (PDR), 2020). The contraindications of phentermine will be discussed more in detail.

Phentermine should further only be prescribed if all subordinate organic causes of obesity have been eliminated by diagnosis (iNova Pharmaceuticals, 2000). In other words, the authorised prescriber ought to ensure that other factors (other than behavioural factors, such as disease, genetics and medicine-related factors) are not the cause of the obesity prior to pharmacotherapy being initiated (iNova Pharmaceuticals, 2000; Upadhyay *et al.*, 2017:3). Disease, genetics and medication that may cause obesity includes, but are not limited to, depression, Cushing syndrome, hypothyroidism, Prader-Willi syndrome, Bardet Biedl syndrome, mental retardation, corticosteroid use and medication to lower high blood pressure and blood glucose levels, respectively (Upadhyay *et al.*, 2017:3). These factors should, therefore, be eliminated as the possible causative agents of obesity prior to initiating pharmacotherapy with phentermine (Upadhyay *et al.*, 2017:3).

Prescribers also prescribe phentermine off-label for several indications other than the specific FDA approved one (Hendricks, 2017:226). These off-label uses include using phentermine (Hendricks, 2017:226-227, 230):

- For periods longer than 12 consecutive weeks. Truter (2016:142), however, found that phentermine was mostly prescribed for short periods in South Africa.

- In doses greater than the recommended threshold (i.e., > 30 mg phentermine base). A survey indicated that the average dose of phentermine used in the USA is 60 mg/day and some prescribers even prescribed up to 112 mg/day.
- In patients that have excess body fat with a BMI below the cut-off value. A person is said to be overweight and obese if they have a BMI of $\geq 27 \text{ kg/m}^2$ and $\geq 30 \text{ kg/m}^2$, respectively (Wharton *et al.*, 2020:884). The cut-off value would thus be a BMI of $< 27 \text{ kg/m}^2$ in patients with an increased risk of developing health issues.
- To treat obese patients with attention-deficit/hyperactivity disorder (ADHD). High doses of phentermine have the same moderate effect on NE plasma levels than that of amphetamine in the treatment of ADHD.
- Together with or despite label contraindications.

The off-label use of medication is not supported by SAHPRA, as there is seldom scientific evidence that supports its use (Klinck & Trokis, 2020:2). When a prescriber does, in fact, choose to prescribe a drug off-label, the patient should be fully informed to allow for mutual decision-making to occur and to ensure that informed consent, meeting ethical and medico-legal requirements, is obtained (Klinck & Trokis, 2020:7).

2.4 Pharmacokinetic properties

Pharmacokinetics refer to the specific actions the body has on a drug and is classically illustrated using the processes of absorption, distribution, metabolism and elimination (Glassman & Muzykantov, 2019:570). The PK properties of phentermine will be discussed using the subheadings chemical properties, absorption, distribution, metabolism and elimination.

2.4.1 Chemical properties

Phentermine is a colourless, mobile, oily liquid that is slightly soluble in water and soluble in chloroform, acetone, ether and diluted acids (Olsson & Hoover, 1976:824; Pharma Professional Services, 2016). The International Union of Pure and Applied Chemistry's (IUPAC) name for phentermine is 2-methyl-1-phenylpropan-2-amine, as it is a substituted phenethylamine that is structurally similar to amphetamine (Human Metabolome Database, 2012; Wilding, 2017:1505).

The drug was initially manufactured as a resin complex, and it was only later in 1970 that the hydrochloride (salt) form became available (Leroy, 2017). Preparations can either contain phentermine hydrochloride or phentermine resin (available as Duomine® in South Africa) (Du Toit *et al.*, 2012). The hydrochloride (salt form) of phentermine is formulated to improve the

dissolution, absorption and efficiency thereof, and the resin is formulated to ensure GI sustained release where prolonged drug dissolution and absorption from the resin will occur throughout the gastrointestinal tract (GIT) (Anderson, 2020; Gaur *et al.*, 2014:305).

Phentermine, just like any other medication, ought to be stored according to the manufacturer's specifications (Shafaat *et al.*, 2013:2500). Phentermine hydrochloride tablets and capsules, and phentermine resin capsules should be kept in tight containers at or less than 30°C; or between 15°C and 30°C (American Hospital Formulary Service (AHFS), 2012; iNova Pharmaceuticals, 2000; Teva Pharmaceuticals, 2020). The medication should be stored in its original packaging until it is ready to be used since the packaging is designed to protect the product from heat, moisture, air and light, which may influence the stability, and thus the safety and efficacy of the product (Alqurshi, 2020:1418; iNova Pharmaceuticals, 2000; Mansour *et al.*, 2018:36; Medsafe, 2014:36; Shafaat *et al.*, 2013:2500).

Exposure to these factors may result in chemical and thermal degradation of the product, and/or alterations in the physicochemical properties of the drug, and/or the formation of toxic by-products, which may result in: the drug being less efficient, being harmful to individuals and/or shorten the shelf-life of the product (Alqurshi, 2020:1418; Mansour *et al.*, 2018:36; Medsafe, 2014:36). The physicochemical properties, such as the solubility, of a drug, are of critical importance since they influence drug absorption, distribution and, in turn, the bioavailability of the drug (Malan *et al.*, 2002:385; Saeui *et al.*, 2018:716).

2.4.2 Absorption

The absorption of a drug describes the process where a drug is transferred from an extravascular site of administration into the bloodstream (Lavielle, 2017). Phentermine is administered via the oral route and will, therefore, be absorbed via the GIT (Alagga & Gupta, 2021). The rate and extent to which drug absorption occurs (i.e., the rate and extent to which drug molecules reach the bloodstream) is known as the bioavailability of the drug, and it is dependent on the drug's dissolution rate (Lavielle, 2017; Sakai, 2009:30). The dissolution of a drug describes the process through which the drug becomes available for absorption (i.e., the process through which the drug is released from its formulation so it can dissolve in the immediate medium) and the rate thereof is affected by both the manufacturing process as well as the solubility of the drug (Sakai, 2009:30; Shekhawat & Pokharkar, 2017:262).

Phentermine is a weak base, i.e., a neutral molecule or a molecule with no charge, that can form a cation (a molecule with a positive charge) by merging with a proton (particle with a positive

charge) (Katzung, 2015:9). During manufacturing, phentermine is adsorbed (i.e., phentermine's molecule is adhered to the surface of a solid) onto a proton, which in this case is an ion-exchange resin, to form a cation-exchange resin complex (CER) (Brandani *et al.*, 2016:262; Gaur *et al.*, 2014:310; iNova Pharmaceuticals, 2000:1). The resin acts as a medium for ion exchange, which means that it will reversibly exchange its cations with ions of like charge; that is, cations so that phentermine can be released from the formulation (dissolution) (Venkatesh *et al.*, 2013:4764). In other words, the phentermine molecules attached to the resin will be released therefrom if the drug molecules can be exchanged or replaced, by cations. Ion-exchange resins (IER) are especially popular in drug delivery systems due to their physicochemical stability and (amongst other qualities) their equilibrium driven drug discharge in ionic environments (Venkatesh *et al.*, 2013:4766).

Since phentermine is administered orally, and drug absorption will occur via the GIT, the drug will reach the stomach first since it is the first organ that encounters orally ingested preparations (Vertzoni *et al.*, 2019:158). This is also the first place where the CER (after the capsule containing the CER has dissolved) will be introduced to the GI fluids of the gastric environment (Vertzoni *et al.*, 2019:158). The GI fluids are present throughout the GIT and consist of a constant ionic concentration of ions such as potassium, hydrogen and sodium (Gaur *et al.*, 2014:307). Keep in mind that the CER will only release phentermine from the formulation if there are cations, which can replace phentermine's position on the resin (Venkatesh *et al.*, 2013:4764). Evidently, once the loaded CER reaches the extremely ionic setting of the stomach, the cations of the resinate will continuously exchange their cations with the cations of the environment and phentermine will be released into the GI fluid (Gaur *et al.*, 2014:307).

The selectively permeable epithelial cells lining the walls of the GIT is now of critical importance since this will determine whether phentermine's drug molecules can cross the barrier and enter the bloodstream, i.e., will the drug molecules be absorbed (Heedes & Ailakis, 1992; Sakai, 2009:31). The epithelial cells are connected to one another through junction complexes, called tight junctions, through which lipophilic drug molecules, such as phentermine, will diffuse via passive diffusion into the bloodstream (Heedes & Ailakis, 1992; Sakai, 2009:31; Schoultz & Keita, 2020:5; Shekhawat & Pokharkar, 2017:262). Passive diffusion describes the natural tendency of substances to move down a concentration gradient (Aryal, 2019). In other words, the lipid-soluble phentermine drug molecules will move from within the GIT (the area that has a high drug concentration), through the epithelial cells, and into the bloodstream (the region with a low drug concentration) (Aryal, 2019). The process of passive diffusion is powered by kinetic energy from

within the molecules and will continue up until the concentration of the drug is more or less equal on either side of the membrane, a state known as equilibria (Aryal, 2019; Sakai, 2009:31).

However, since phentermine is a weak base, and the stomach has an acidic environment (rich in hydrogen ions, H^+) ranging from pH 1.5-3.5, the neutral drug molecules of phentermine will merge with the protons (H^+ ions) in the stomach and become ionised (Katzung, 2015:9; Le, 2020a). The ionised fraction of the drug molecules becomes hydrophilic and unable to readily cross the cell membrane, which results in phentermine being poorly absorbed from this part of the GIT (Akula & Lakshmi, 2018:3; Le, 2020a). Keep in mind that the drug molecules will be released from the CER at a rate that is proportionate to the absorption rate (to maintain equilibrium on either side of the GI membrane); in other words, if poor absorption surfaces, it will consequently result in poor drug release (Lavielle, 2017).

The small intestine is the second part of the GIT in which drug molecules come into contact with, and it consists of an upper segment (duodenum), a middle segment (jejunum) and a lower segment (ileum) (Vertzoni *et al.*, 2019:160). The pH of the small intestine varies or ranges from 6.1-7.0, which means that when phentermine reaches the small intestine, the un-ionised fraction of the drug will be predominant in the basic (or alkaline) fluid of this environment (Akula & Lakshmi, 2018:3; Le, 2020a). The unionised fraction of the drug molecules is now very lipid-soluble and can readily move across the membranes of epithelial cells lining the GIT (the drug molecules will be absorbed) (Heedes & Ailakis, 1992; Sakai, 2009:31; Shekhawat & Pokharkar, 2017:262).

Once absorption occurs, there will be a decline in the concentration of the drug in the GIT as the drug molecules diffuse across the membrane to the portal circulation (the blood that circulates between the GIT and the liver) (Dean & McEntyre, 2004:10). The rate at which phentermine is absorbed is proportionate to the amount of drug in the GIT (Lavielle, 2017). As the drug molecules are absorbed, phentermine is released from the CER at a rate that is proportionate to the number of cations in the GIT to ensure that the drug concentration remains the same in the GIT as in the bloodstream. Since this concentration is constant throughout the GIT, there will be an ongoing dissolution and absorption of phentermine throughout the journey in the GIT (also known as first-order absorption), occurring over a period of 10-14 hours (Gaur *et al.*, 2014:307; iNova Pharmaceuticals, 1991:1; Lavielle, 2017).

The rate at which drug molecules are absorbed from the hydrochloride salt formulation of phentermine is significantly faster than that of the CER (iNova Pharmaceuticals, 2007:1). The hydrochloride form of phentermine is deliberately formulated to increase dissolution, absorption and thus the efficiency of the drug (Anderson, 2020; Gaur *et al.*, 2014:305). The drug molecules

will reach peak concentration in the blood after 3-4.4 hours (Anderson, 2020; Gaur *et al.*, 2014:305; Teva Pharmaceuticals, 2020). The CER, on the other hand (also known and available in South Africa as delayed or sustained-release preparations), is manufactured to postpone dissolution and allow for gradual drug release to occur so it can deliberately extend the process of absorption, which results in a decreased and delayed peak concentration in the blood (Anderson, 2020; Gaur *et al.*, 2014:305; iNova Pharmaceuticals, 2007:1; Sakai, 2009:30) (see section 2.4.1).

Once the drug molecules enter the portal circulation, 17.5% of the drug binds to plasma proteins, and the remaining 82.5% remains unbound (Green *et al.*, 2010:3). Both the bound and unbound fraction of the drug must pass through the liver before it can go into the systemic circulation (Sakai, 2009:31; Teva Pharmaceuticals, 2020). Certain drugs will be metabolised by the liver, i.e., they will be metabolically transformed so they can be more hydrophilic for excretion via the kidneys. Other drugs, such as phentermine, is not subject to this metabolism and the passage thereof through the liver does not affect its bioavailability (Garza *et al.*, 2020; Lavielle, 2017; Sakai, 2009:32).

Phentermine does not have a 100% bioavailability because the drug is not completely absorbed from the GIT (Teva Pharmaceuticals, 2020). We already know that an environment with an acidic pH, such as in the stomach, will cause phentermine to be poorly absorbed (Akula & Lakshmi, 2018:3; Le, 2020a). A drug's transit time through the GIT, gastric emptying and blood flow will also have an impact on the absorption and, thus, the bioavailability of the drug since the majority of the drug is absorbed in the small intestine (Akula & Lakshmi, 2018:3; Alagga & Gupta, 2021; Le, 2020a). The amount of time the drug spends in the GIT will determine how much of the drug is absorbed. For example, if a patient has a fast transit time through the intestine, which is the case when a person has diarrhoea, gastric emptying will occur more often. Therefore, the drug will travel faster through the GIT and less of the drug will be absorbed (Sakai, 2009:33).

On the other hand, high-fat meals will decrease gastric emptying time, which will then cause a decline in the rate of absorption of a drug. However, such high-fat meals do not influence the absorption of phentermine (Akrimax Pharmaceuticals, 2013; Le, 2020a). As individuals age, the surface area of the small bowel decreases and the GIT mobility, as well as the gastric emptying time, becomes slower (Ruscin & Linnebur, 2018). Many orally administered drugs, such as phentermine, are absorbed in the small intestine (larger surface area which results in greater blood flow), and a decrease in the surface area thereof, whether the decline is age-related or a part of it is medically removed, will result in severe impairment of absorption and less of the drug will be available in the systemic circulation (Ruscin & Linnebur, 2018; Sakai, 2009:33).

Nonetheless, phentermine is practically completely absorbed from the GIT, and the fraction of drug that does reach the bloodstream will be distributed via systemic circulation to the bodily tissue, a process known as distribution (Lavielle, 2017).

2.4.3 Distribution

Drug distribution defines the reversible transmission of a substance between the blood plasma (the unsolidified fraction of the blood and lymphatic fluids, which makes up approximately 50% of the total blood volume) and the different tissue compartments of the body as well as the quantity of drug present in the respective tissue sites (Lavielle, 2017; Mansoor & Mahabadi, 2020; Stöppler, 2021). The rate and extent to which drug molecules are distributed to the different bodily compartments vary since the blood perfusion to these respective sites differs (Chillistone & Hardman, 2017:338; Le, 2020b).

The organs in the central compartment (CC) of the body (kidneys, liver, heart and brain) are well perfused, which mean they have a great blood supply relative to their organ weight. The drug will thus be distributed to these organs within the first few minutes after it has been absorbed into the systemic circulation (Akula & Lakshmi, 2018:3; Le, 2020b; Routes, 2004:25). The peripheral compartment (PC), on the other hand, has the less well-perfused organs (fat, bone, muscle and skin) and drug distribution to these sites will occur at a much slower rate than that of the well-perfused organs (Akula & Lakshmi, 2018:3; Le, 2020b; Routes, 2004:25). Table 2-1 is adapted from Comparative pharmacokinetics lectures (2017) and gives the blood perfusion rate to each organ as well as the percentage of cardiac output that each organ receives.

Table 2-1: Blood perfusion rate and cardiac output to each bodily organ

Organ	Blood perfusion rate (mL/min of tissue)	Organ	Percentage of cardiac output to each organ (%)
Kidney	4.00-4.50	Liver	25-27
Liver	0.80-0.95	Kidney	22-24
Heart	0.60	Muscle	15
Brain	0.50-0.55	Brain	14-15
Fat	0.01-0.03	Skin	5-6
Bone	0.02	Bone	5
Muscle	0.025-0.03	Heart	4
Skin	0.04-0.05	Fat	2-4

The kidneys have the highest blood perfusion rate per mL of tissue, followed by the liver, heart, brain, fat, bones, muscle and skin, respectively. In other words, 4-4.5 mL of blood will be distributed to 1 mL of renal tissue each minute, whereas only 0.04-0.05 mL will be distributed to the skin (Comparative pharmacokinetics lectures, 2017). Although the liver receives the greatest percentage (25-27%) of blood ejected by the heart each minute, followed by the kidneys (22-24%), muscles (15%), brain (14-15%), skin (5-6%), bones (5%), heart (4%) and fat (2-4%), the kidneys are considered to be the organs that receive the greatest amount of blood from the heart relative to their tissue mass (Calzia *et al.*, 2005:22; Comparative pharmacokinetics lectures, 2017). The blood perfusion rate will reflect the amount of drug in the plasma, i.e., the higher the blood perfusion rate (per mL of tissue) to the tissue site, the higher the drug concentration in the plasma (Comparative pharmacokinetics lectures, 2017).

The drug's solubility will also determine to what extent it will distribute through the body, i.e., will the drug molecules remain in the blood plasma (hereinafter referred to as plasma), which is in the CC of the body or will it be taken up by the different organ tissues in the CC and the PC of the body (Aryal, 2019; Routes, 2004:23). The pH of the environment (plasma) is of critical importance,

as it will determine whether the ionised or unionised fraction of the drug will be predominant, which in turn influences the solubility, and thus permeability of the drug (Onetto & Sharif, 2021; Aryal, 2019; Routes, 2004:23). If a drug is mostly hydrophilic at physiological pH of the plasma (7.4), i.e., most of the drug is in the ionised configuration, the drug will mainly remain in the plasma and very little will be taken up by organ tissue (Le, 2020b). We refer to this type of distribution as a single compartment model of distribution kinetics since the drug molecules remain in the CC (plasma and highly perfused organs) of the body (Mansoor & Mahabadi, 2020). However, drugs such as phentermine, which is mostly in the unionised lipophilic configuration at physiological pH, will readily leave the plasma (CC) and distribute to the organ tissue in the CC as well as to those in the PC. Therefore, phentermine displays a multi-compartment model of distribution kinetics (Akula & Lakshmi, 2018:3; Le, 2020a; Mansoor & Mahabadi, 2020).

The unionised lipophilic phentermine molecules will thus diffuse, via passive diffusion, from the plasma, into the interstitial space (fluid enclosing target cells of a particular tissue) and finally into the target cells located inside of the tissue at a rate which is directly equivalent to the blood perfusion rate to the site (Kok-Yong & Lawrence, 2015; Mansoor & Mahabadi, 2020; Onetto & Sharif, 2021). The drug molecules obey the process of perfusion-rate diffusion, and the entire process is driven by an equilibrium, i.e., as the free fraction of unionised phentermine molecules leave the plasma, more of the bound fraction will be released from the binding site to maintain the state of equilibria (Aryal, 2019; Kok-Yong & Lawrence, 2015; Sakai, 2009:31). At the same time, the unionised drug will bind to proteins within the interstitial fluid to ensure that the concentration of bound and unbound fractions is equal on both sides of the membrane (Doggrell, 2014; Onetto & Sharif, 2021; Aryal, 2019). The same principle applies to the passage of the drug molecules from the interstitial fluid to the target cells where the free fraction of drug molecules has the ability to bind to receptors and cause a drug-receptor interaction (drug-receptor interactions will be discussed more thoroughly) (Onetto & Sharif, 2021).

As phentermine is extensively taken up by tissue, a decline in the plasma concentration of the drug can be noted, with the overall initial concentration of the drug in the body remaining unchanged (Lavielle, 2017; Mansoor & Mahabadi, 2020). Eventually, phentermine will reach a dynamic equilibrium, also known as a steady state, where the drug has completed its distribution between the CC and PC (Mansoor & Mahabadi, 2020). It is important to remember that phentermine follows first-order kinetics, which means drug metabolism and elimination will occur concurrently with drug distribution at a rate proportionate to the plasma drug concentration (Onetto & Sharif, 2021). In other words, as the process of drug elimination commences from the CC, the plasma concentration of the drug will decline, which will cause the drug to redistribute

from the PC back into the CC to maintain the state of equilibrium. As soon as the process of drug elimination commences, both the plasma and overall concentration of the drug in the body declines (Mansoor & Mahabadi, 2020).

At any given time, the amount of drug in the plasma relative to the overall drug concentration in the body can be measured. This is expressed as a proportionality constant, also known as the drug's volume of distribution (Vd) (Mansoor & Mahabadi, 2020). Phentermine's basic and lipophilic characteristics allow for it to leave the plasma and be extensively taken up by tissue, and the drug, therefore, exhibits a high Vd of 348 L/h (Claire, 2020; Onetto & Sharif, 2021). However, since phentermine's metabolism and elimination process occur concurrently with its distribution process, the drug will have multiple Vd values, which are all time-dependent (Onetto & Sharif, 2021).

2.4.4 Metabolism and elimination

Drug elimination describes the process where drugs are removed from the body, and this is accomplished by either excreting the unmetabolised and unchanged form of the drug or by metabolically transforming the drug prior to the excretion thereof (Garza *et al.*, 2020; Le, 2020d; Routes, 2004:28; Sakai, 2009:35). The kidneys are the primary organs responsible for removing drugs from the body fluids and mainly does so by forming and excreting urine (Garza *et al.*, 2020; Lawrence *et al.*, 2018:249). However, some drugs are too lipophilic and must thus be metabolically modified in the liver to more hydrophilic compounds, so they can readily be excreted by the kidneys (Garza *et al.*, 2020).

Most of phentermine, approximately 70-80% of a therapeutically administered dose, is excreted unmetabolised and unchanged in the urine. The remaining 20-30% of the drug undergo hepatic metabolism before the metabolites are excreted in the urine (Choi *et al.*, 2016:22; iNova Pharmaceuticals, 2007:1; Vivus, Inc, 2012). As mentioned above, the kidneys are incapable of excreting unionised, lipophilic molecules, as they are reabsorbed into the bloodstream and transported out of the kidneys into the circulation (Lawrence *et al.*, 2018:249; Pharma Professional Services, 2016; Routes, 2004:28).

These drug molecules will eventually be distributed to the liver, where they will be metabolised to detoxify the drug and increase its hydrophilicity (Garza *et al.*, 2020). Take into consideration that the liver also receives 25-27% of cardiac output, and the unionised lipophilic drug molecules in the plasma will also be metabolised and made more hydrophilic for excretion (Comparative pharmacokinetics lectures, 2017; Garza *et al.*, 2020). Thus, when the unionised lipophilic drug

molecules passively diffuse across the membrane and enter the liver tissue, the drug molecules will be converted from one biochemical moiety to another via metabolic pathways (Almazroo *et al.*, 2017:1).

Two metabolic pathways exist for drug metabolism, including phase I and phase II reactions (Garza *et al.*, 2020). During phase I reactions, drugs are made more hydrophilic by altering their chemical structures, which occurs through oxidation, hydrolysis and reduction reactions (Henriques *et al.*, 2020:2; Susa & Preuss, 2021). During phase II reactions, on the other hand, drugs are made more hydrophilic for excretion by coupling the drug molecule with another molecule, occurring through conjugation reactions (Henriques *et al.*, 2020:9; Susa & Preuss, 2021). Phentermine is metabolically transformed during phase I reactions, where the drug undergoes *p*-hydroxylation and N-oxidation (Henriques *et al.*, 2020:2; Susa & Preuss, 2021; Vivus, Inc, 2012).

These reactions are achieved by enzymes that reside in the liver cells (also known as hepatocytes), where they catalyse the mechanism of phase I and phase II reactions. The two most important enzymes responsible for drug metabolism is monoamine oxidase (MAO) and cytochrome (CYP) P450 (Susa & Preuss, 2021). Phentermine is mainly but not extensively metabolised by CYP 3A4, a subfamily of CYP P450 (Choe & Garnett, 2010:3). The drug thus undergoes *p*-hydroxylation on the aromatic ring to produce *p*-hydroxyphentermine, and N-hydroxylation on the side chain to produce N-hydroxyphentermine (Choe & Garnett, 2010:3; Choi *et al.*, 2016:22). Thereafter, N-hydroxyphentermine can either reduce back to phentermine or undergo further N-oxidation and produce α -nitrophentermine (Choe & Garnett, 2010:3; Choi *et al.*, 2016:22). However, the main metabolites of phentermine found in the urine are *p*-hydroxyphentermine and N-hydroxyphentermine (Choi *et al.*, 2016:22).

Urine is formed in the functional unit of the kidneys (also known as (aka) the nephron), using three processes known as glomerular filtration, tubular reabsorption and, lastly, tubular secretion (Garza *et al.*, 2020; Rolfe, 2018). Glomerular filtration is the first step in forming urine and thus the first step in the process of excreting drugs from the body (Libretexts, 2020a).

Every minute the kidneys receive 22 - 24% of blood that is pumped out by the heart (Comparative pharmacokinetic lectures, 2017). The blood plasma, containing the drug molecules and their metabolites (subsequent to hepatic metabolism), is carried via the afferent arteriole into the glomerulus (filtering component of the kidney), where approximately 20% of the plasma is filtered via pores, in the glomerular endothelium, to the inside of the glomerulus (glomerular capsule) (Libretexts, 2020a; Rolfe, 2018). The kidneys can only eliminate drugs if they are polar or

completely ionised at physiological pH or if the drug has a low molecular weight (Hopkins *et al.*, 2020; Routes, 2004:28). Here only the unbound, hydrophilic (ionised) fraction of phentermine, along with water and other filterable components, are filtered into the glomerular capsule, also known as Bowman's capsule, to form the glomerular filtrate (hereinafter referred to as the filtrate) (Le, 2020e). The lipophilic bound fraction of the drug, along with other components that cannot be filtered, will exit the glomerular capillaries through the efferent arteriole, where it will be distributed to the peritubular capillaries (capillaries supplying the nephron) (Lawrence *et al.*, 2018:249; Rolfe, 2018).

The filtrate, on the other hand, has now been filtered into Bowman's capsule and will move through the remainder of the nephron (Libretexts, 2020a). Some of the filtrate is reabsorbed back into the bloodstream via the peritubular capillaries and will not be excreted as urine (Le, 2020e). Here the pH of the environment will determine whether phentermine will be reabsorbed or whether it will be excreted in the urine. This process of reabsorption occurs via passive diffusion to maintain homeostasis, an internal environment that is relatively stable and constant (Editors of Encyclopaedia Britannica, 2020; Libretexts, 2020a). For example, if there is a disturbance in the normal physiological pH of this environment (i.e., the homeostasis of the environment), the kidneys may need to restore the unbalanced pH by reabsorbing bicarbonate and excreting acid into the urine, which will result in an increase in the pH of the urine (alkalinisation); or reabsorption may not be necessary and the urine will become more acidic (pH decreases) (Hopkins *et al.*, 2020).

If acidification of the urine does occur, the excretion of phentermine will increase and the elimination half-life ($t_{1/2}$) of the drug will reduce by approximately 7-8 hours (Le, 2020e; iNova Pharmaceuticals, 2007:2). The elimination $t_{1/2}$ of a drug can be defined as the length of time needed to reduce its concentration by 50% of the initial concentration in the body (Hallare & Gerriets, 2020). However, if urine alkalinisation occurs, the unionised fraction of the drug will be reabsorbed via the peritubular capillaries and the $t_{1/2}$ of the drug will increase, which may potentially cause drug toxicity (i.e., the drug concentration in the blood may potentially cause harm to the individual) (Pharma Professional Services, 2016; Routes, 2004:28).

It is clear that the urine pH is of utmost importance as it influences the $t_{1/2}$ of the drug and determines the concentration of phentermine which will be excreted via the urine (Akula & Lakshmi, 2018:3; Le, 2020a). Under normal physiological circumstances, the urine has a pH of 4.5-8, which will cause the ionised form of phentermine to be predominant, and thus excreted; and the unionised fraction will be reabsorbed into the peritubular capillaries (Le, 2020e). Phentermine (under normal physiological circumstances) has a $t_{1/2}$ of approximately 25 hours,

i.e., the drug concentration in the plasma will reduce by 50% after 25 hours (Hallare & Gerriets, 2020; iNova Pharmaceuticals, 2007:2).

Furthermore, in the last stage of urine formation (aka tubular secretion), those drug molecules that were too large to enter the kidney via glomerular filtration are eliminated from the peritubular capillaries and carried against a beneficial chemical gradient into the proximal tubule of the nephron (Lawrence *et al.*, 2018:249; Libretexts, 2020a). This process is called tubular secretion and differs from reabsorption in the sense that secretion is about cleaning the blood or removing substances from the blood rather than absorbing them (Libretexts, 2020a). Tubular secretion is done via two transport systems known as basic carriers and acid carriers, which carry basic and acidic drug molecules, respectively, into the proximal tubule (Rolfe, 2018). Certain substances such as hydrogen ions and potassium ions are also transported out of the blood and into the urine (Le, 2020e). Finally, the formation of urine is complete, and it moves down the collecting duct (the last part of the nephron) where it drains into the renal pelvis (upper part of the ureter) (Lawrence *et al.*, 2018:249). The ureter carries the urine into the bladder, where it is kept until it is eliminated from the body, via the urethra, during a process known as micturition (the process of urinating) (Libretexts, 2020a). Figure 2-4 roughly illustrates the process of phentermine's drug elimination from the body (adapted from Karki (2017) and Mayo Clinic (2020d)).

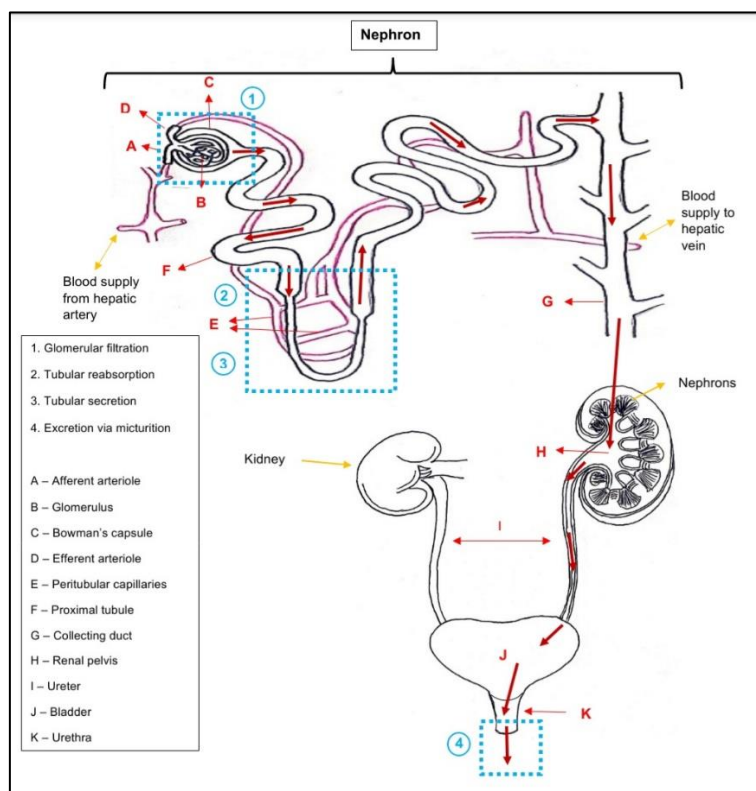


Figure 2-4: The process of phentermine's drug elimination from the body

Certain other systems and routes also share the responsibility of excreting drugs from the body and include the biliary system, saliva, breastmilk, sweat, tears, lungs and faeces (Garza *et al.*, 2020; Le, 2020d). Evidently, this is not of clinical importance for phentermine, as the drug gets excreted via the kidneys.

2.5 Pharmacodynamic properties

Pharmacodynamics describes what the drug delivery system does to the body (Glassman & Muzykantov, 2019:576). It focuses on the drug's biochemical, physiological and molecular effects on the body, from where the drug is taken up by tissue right to where it causes a therapeutic effect in the body (Glassman & Muzykantov, 2019:576; Yartsev, 2018b). Phentermine's PD properties will be discussed under the sub-headings: "Mechanism of action" and "Side effects".

2.5.1 Mechanism of action

Phentermine is a central-acting sympathomimetic amine with CNS stimulating properties resulting in appetite suppression (Rossiter, 2016:70). Before the mechanism of action of phentermine can be understood, the reader first needs an overview of the relevant anatomy and physiology of the CNS.

The CNS consist of both the brain and the spinal cord, where the brain transmits signals to the rest of the body via the spinal cord (Kennedy Shriver, 2018; Sheffler *et al.*, 2021). Nerve cells, also called neurons, are the fundamental units of the nervous system, and there are approximately 100 billion of them located in the brain (Kennedy Shriver, 2018). The neurons consist of a cell body with a nucleus and unique extensions, known as axons and dendrites (Aggarwal & Mortensen, 2018:1; Kennedy Shriver, 2018). Numerous axons (bundled together) are known as nerves, and they make up the peripheral nervous system (PNS) (Kennedy Shriver, 2018). The PNS branches off the spinal cord and spreads throughout the body, which explains how the brain transmits its signals to the rest of the body (Kennedy Shriver, 2018). Figure 2-5 provides a simplified representation of the composition of the CNS and the anatomy of a neuron, synaptic cleft and nerve as adapted from Alvites *et al.* (2017) and Caire *et al.* (2021).

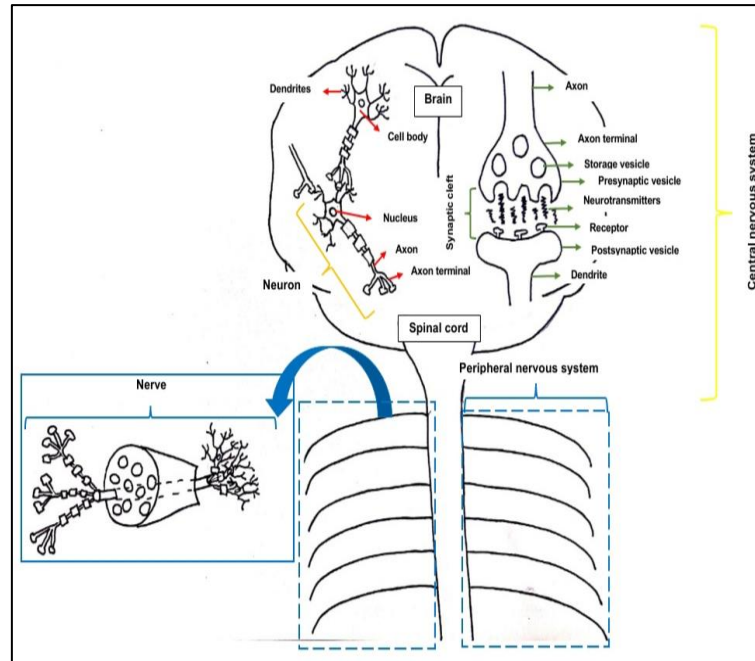


Figure 2-5: A simplified composition of the CNS and anatomy of a neuron, synaptic clefts and nerve

Axons and dendrites allow for neurons to communicate with one another throughout the body. For example, one neuron can send a message to the next neuron with an electrical signal, which will be carried down the length of the axon to the axon terminal (end of the axon) (Sheffler *et al.*, 2021). As a result thereof, a chemical signal will be released from the presynaptic vesicle (where neurotransmitters are stored) into the synapses or the synaptic cleft; the area between the axon of one neuron and the dendrites of an adjacent neuron (Hussain *et al.*, 2021; Kennedy Shriver, 2018). These dendrites, which receive the chemical messages, convert the signal back to an electrical signal that will, again, be carried via the length of the axon to the next neuron (Kennedy Shriver, 2018). Additionally, the neurotransmitters will be released from the presynaptic vesicle into the synaptic cleft, where they will bind to postsynaptic receptors and cause a physiological response (Kennedy Shriver, 2018; Sheffler *et al.*, 2021).

The CNS has monoamine-containing neurons that release the monoamine neurotransmitters DA, NE and 5-HT into the synaptic cleft so they can bind to receptors and cause their physiological effect in the body (Aggarwal & Mortensen, 2018:1, Rothman & Baumann, 2000:53; Sheffler *et al.*, 2021). Dopamine binds to dopamine-1 (D_1), D_2 , D_3 , D_4 and D_5 receptors in the CNS, PNS, kidneys and vasculature (Bathia *et al.*, 2020). Dopamine₁ and D_5 receptors are highly expressed in the striatum, olfactory bulb, substantia nigra and nucleus accumbens of the brain, as well as in the

kidneys, where stimulation of these receptors regulates the reward system, attention, memory, motor activity, impulse control, locomotion, decision-making, learning, cognition and renal function (Bathia *et al.*, 2020). Dopamine₂ to D₄ receptors are predominantly expressed in the striatum, centre of the nucleus accumbens, hippocampus, cerebral cortex, amygdala, external globus pallidus and hippocampus, where binding to these receptors regulate locomotion, attention, memory, sleep, learning, impulse control, cognition and the upkeep and development of DA neurons (Bathia *et al.*, 2020).

Moreover, DA also binds to β_1 receptors mainly located in the cerebral cortex, heart, adipose cells and kidneys (Alhayek & Preuss, 2021; Bathia *et al.*, 2020). Stimulating these receptors will accelerate the heart rate, increase the breakdown of fat cells (lipolysis) and increase the blood volume through the contraction of smooth muscle cells in the kidneys (Alhayek & Preuss, 2021). Norepinephrine also binds to β_1 receptors, together with α_1 , α_2 and β_2 receptors, where stimulation of NE on β_1 receptors will have the same effects as those that occur when DA stimulates β_1 receptors (Alhayek & Preuss, 2021; Bathia *et al.*, 2020). These α and β receptors are known as the adrenergic receptors, and they are mainly responsible for transmitting signals to the SNS (Alshak & Das, 2020).

The SNS is responsible for the involuntary or unconscious functioning of various organ systems (Alshak & Das, 2020). Beta₂₋₃ receptors can be found in the cerebral cortex and fat cells, respectively (Alshak & Das, 2020; Hussain *et al.*, 2021). Stimulation of NE on β_2 receptors will cause the ciliary muscle in the eye to relax, which will, in turn, improve far vision, increase the heart rate as well as cardiac output, dilate the bronchioles of the lungs and reduce pulmonary secretions, decrease the motility of the GIT and gallbladder contraction, relax the detrusor muscle of the bladder and contract the urethral sphincter to inhibit urination, poorly constrict the arteries supplying the skeletal muscles, and elevate the blood glucose levels via the liver (Alshak & Das, 2020; Hussain *et al.*, 2021).

Norepinephrine also acts on α_1 receptors located in the locus coeruleus, cerebral cortex, amygdala, olfactory bulb, dentate gyrus and the thalamus of the brain. Stimulation of these receptors will affect the eyes, lungs, stomach, intestine, pancreas, salivary glands, arteries, liver and spleen (Alshak & Das, 2020; Hussain *et al.*, 2021). Thus, stimulation of α_1 receptors will cause the pupils and lungs to dilate, decrease the peristalsis and thus motility of the GIT, decrease pancreatic and insulin secretion, cause vasoconstriction of the arteries, cause weak constriction of the arteries in the skeletal muscles, increase glucose levels in the blood and cause contraction of the spleen (Alshak & Das, 2020; Hussain *et al.*, 2021).

Furthermore, α_2 receptors are also stimulated by NE, and they are expressed in the locus coeruleus, hypothalamus and amygdala (Hussain *et al.*, 2021). When NE stimulate these receptors in the brain, it will result in inhibitory effects of cells with a decline in the secretion of pancreatic enzymes and insulin (Alshak & Das, 2020; Hussain *et al.*, 2021). Thus, the overall responsibility of NE in the body is to regulate heart rate and blood pressure, to provide blood flow to skeletal muscles and to increase blood glucose levels for energy (Alhayek & Preuss, 2021; Alshak & Das, 2020; Bathia *et al.*, 2020; Hussain *et al.*, 2021).

Serotonin in the brain mainly binds to 5-HT_{1A} and 5-HT_{2A} receptors, which are expressed in the hippocampus, amygdala, neocortex, hypothalamus, septum, and in the frontal cortex, claustrum and olfactory nuclei, respectively (Carhart-Harris & Nutt, 2017:1091; Frazer & Hensler, 1999). Serotonin_{1A} receptors (when stimulated) are responsible for regulating emotions, cognition and serotonergic neurons, whereas 5-HT_{2A} is responsible for regulating memory and learning (Carhart-Harris & Nutt, 2017:1091; Frazer & Hensler, 1999; Zhang & Stackman, 2015). Other 5-HT receptors in the body include 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2C}, 5-HT₃, 5-HT₄ and 5-HT₇ receptors, where 5-HT_{1B} and 5-HT_{1D} receptors are expressed in the globus pallidus and the substantia nigra, and they are responsible for regulating the release of 5-HT and acetylcholine (a neurotransmitter) (Frazer & Hensler, 1999). Moreover, 5-HT_{2C} is predominantly expressed in the choroid plexus, hypothalamus, hippocampus, globus pallidus, neocortex, septum and substantia nigra, where they modulate, amongst other unknown functions, motor activity and the volume of the cerebrospinal fluid (Frazer & Hensler, 1999). Lastly, 5-HT₃ and 5-HT₄ receptors are found in the spinal cord, medulla, and in the substantia nigra, striatum, hippocampus, olfactory tubercle and on neurons in the alimentary tract, respectively, where 5-HT₃ regulate neurotransmitter and substance P release, as well as nociceptive mechanisms, and 5-HT₄ enhance the release of DA in the striatal, induce alimentary tract secretions and peristaltic reflexes (Frazer & Hensler, 1999). Table 2-2 present the monoamine neurotransmitters and the respective receptors to which they bind.

Table 2-2: The monoamine neurotransmitters and the different receptors they bind to

Monoamine neurotransmitters	Receptors							
Dopamine	β ₁	D ₁	D ₂	D ₃	D ₄	D ₅		
Norepinephrine	α ₁	α ₂	β ₁	β ₂				
Serotonin	5-HT _{1A}	5-HT _{2A}	5-HT _{1B}	5-HT _{1D}	5-HT _{2C}	5-HT ₃	5-HT ₄	5-HT ₇

The neurotransmitters DA, NE and 5-HT will thus bind to their respective receptors and cause their individual physiological effects in the body (Sheffler *et al.*, 2021). Eventually, these neurotransmitters are pumped back, from the synaptic cleft (extracellular space), into the presynaptic neural terminal via monoamine neurotransmitter transporters (MATs) (Aggarwal & Mortensen, 2018:1). Dopamine transporters (DAT), NE transporters (NET) and 5-HT transporters (5-HTT) are responsible for transporting DA, NE and 5-HT, respectively (Aggarwal & Mortensen, 2018:1; Sheffler *et al.*, 2021). Monoamine neurotransmitter transporters determine how long monoamine neurotransmission will occur (i.e., how long the stimulatory effect will last), emphasising the absolute importance of their role in reuptake (Aggarwal & Mortensen, 2018:1).

Reuptake is the primary mechanism through which monoaminergic transmission in the brain can be terminated, and it is also essential in maintaining homeostasis of these neurotransmitters (Aggarwal & Mortensen, 2018:1; Rothman & Baumann, 2000:53). Evidently, alterations in these MATs will drastically disrupt the regulation of neuronal activity, which may, in turn, disrupt the normal internal homeostatic environment of the body (Aggarwal & Mortensen, 2018:2). Here, drugs such as phentermine are deliberately administered to disrupt the functioning of the MATs, which, in turn, disrupts the modulation of neural activity (Aggarwal & Mortensen, 2018:2; Perez *et al.*, 2019:2).

However, before any drug, including phentermine, can access the brain, and thus the CNS, it needs to cross a special membrane called the blood-brain barrier (BBB) (Kennedy Shriver, 2018; Pardridge, 2012:1959). The BBB is a selectively permeable membrane of capillary endothelium between the blood and the brain, preventing certain drugs from entering the brain (Pardridge,

2012:1959). However, drugs such as phentermine can, via lipid-mediated diffusion, readily cross the BBB to enter the interstitial fluid of the brain (Pardridge, 2012:1959).

As per discussion, the brain has approximately 100 billion neurons, including monoamine-containing neurons possessing MATs (Kennedy Shriver, 2018; Rothman & Baumann, 2000:53). Phentermine is a substrate for NET, DAT, and to a lesser extent, 5-HT, which means that once the drug enters the CNS, it will bind to these MATs, which are positioned on neural cell bodies and nerve fibres (Aggarwal & Mortensen, 2018:1; Rothman & Baumann, 2000:53). Once phentermine is bound, the MAT will pump the drug into the neuron, taking it for storage in the storage vesicles via vesicular monoamine transporters (VMAT) (Aggarwal & Mortensen, 2018:1; Sanchez-Ramos, 2015:137). Phentermine displaces the neurotransmitter from the storage vesicle, and in return, the monoamine neurotransmitters bind to the VMAT, where it is transported out of the cell to the cytoplasm via the same route with which phentermine was transported into the cell (Sanchez-Ramos, 2015:137).

It is clear that phentermine stimulates the release of these neurotransmitters by displacing them from their storage vesicle, which results in an increase in the synaptic concentration of NE, DA, and to a lesser extent, 5-HT (Kalyanasundar *et al.*, 2020:2; Sanchez-Ramos, 2015:137). Additionally, the binding of phentermine to these MATs also inhibits the reuptake of the extracellular neurotransmitters back into the neuron, resulting in a further increase in the extracellular neurotransmitter concentration (Kalyanasundar *et al.*, 2020:2; Marais, 2016:18; Rothman & Baumann, 2000:55; Sanchez-Ramos, 2015:137). Inhibition of the reuptake of these neurotransmitters will result in prolonged monoaminergic neurotransmission and prolonged stimulatory effects (Aggarwal & Mortensen, 2018:1; Rothman & Baumann, 2000:53). The stimulation of release, and thus the increase in extracellular concentrations of these neurotransmitters, will result in an increase in the intensity of the stimulatory effects (Kalyanasundar *et al.*, 2020:2; Sanchez-Ramos, 2015:137).

Phentermine is said to suppress appetite, produce its weight-reducing effects and modulate neuronal activity through the nucleus accumbens shell (NAcSh) of the brain (Kalyanasundar *et al.*, 2015:594). The NAcSh of the brain plays an essential role in the mechanism of reward associated with eating, with DA and 5-HT being the primary neurotransmitters responsible for the functioning of this part of the brain (Kalyanasundar *et al.*, 2015:585). The NAcSh directly projects DA-containing neurons that express D₁ receptors via the mesolimbic pathway to the ventral tegmental area of the brain, and those that express D₂ receptors to the lateral hypothalamus (LH) and the ventral pallidum (VP) of the brain (Castro *et al.*, 2015:10). Increased stimulation of D₁ receptors in the mesolimbic reward pathway

correlates with phentermine's DA-induced reward mechanism resulting in appetite suppression (Poulton *et al.*, 2016:3; Rege, 2018). The increased and prolonged 5-HT neurotransmission in the NAcSh of the brain will also result in appetite suppression, although it was found that these effects are only achieved at high doses of phentermine and not within the normal therapeutic range (15 mg to 30 mg phentermine base) (Perez *et al.*, 2019:6; Rothman & Baumann, 2000:55).

Regardless of phentermine's weight-reducing effects in the NAcSh, the drug mainly produces its weight-reducing effects through stimulating the adrenergic nervous system (ANS) via the adrenergic receptors (Campbell & Young, 2017:20). The increased and prolonged stimulation of the adrenergic receptors (α_1 and α_2 receptors) indirectly caused by phentermine, in the amygdala of the brain, will result in increased and prolonged activation of the SNS (McCorry, 2007:3; Volkow *et al.*, 2011:39). The amygdala sends signals to the hypothalamus, which sends signals to the pituitary gland, and the pituitary gland sends signals to the adrenal glands via the hypothalamus-pituitary axis (HPA) (Sheng *et al.*, 2021:4). The adrenal glands are located on top of the kidneys, and stimulation thereof will result in the release of catecholamines DA, NE and epinephrine into the bloodstream (Dutt *et al.*, 2021). Dopamine, NE and epinephrine all act as hormones and neurotransmitters, hence the reason they are called catecholamines (Paravati *et al.*, 2020).

These catecholamines target α and β receptors in adipose tissue and multisystem smooth muscles (Paravati *et al.*, 2020). Once DA and NE are released into the bloodstream, the binding of these catecholamines to β_1 and β_3 receptors will increase the breakdown of adipose tissue, which will result in weight loss (Alhayek & Preuss, 2021; Bathia *et al.*, 2020; Paravati *et al.*, 2020). The release of epinephrine into the bloodstream and the binding thereof to α_1 , α_2 and β_2 receptors, will also cause blood glucose levels to rise, resulting in appetite suppression (Alhayek & Preuss, 2021; Bathia *et al.*, 2020). That is because appetite and feeding are physiologically initiated via hunger signals, which are sent to the brain when the stomach is empty, and the blood sugar levels are low (McCorry, 2007:5; Volkow *et al.*, 2011:41). When an individual's blood sugar or glucose levels drop, signals are sent to the lateral hypothalamic feeding centre, and the individual eats (Volkow *et al.*, 2011:42). Consequently, the blood glucose levels rise, signals are sent to the ventral hypothalamic feeding centre, and the individual feels full and discontinues eating (Volkow *et al.*, 2011:42). Thus, when phentermine indirectly increases the concentration of NE in the bloodstream, blood glucose levels will rise, signals will be sent to the feeding centre in the ventral hypothalamus, and the individual will feel satiated, consequently suppressing appetite.

It is clear that phentermine evokes responses imitating those that occur when the sympathetic nerves are stimulated (Campbell & Young, 2017:20). Therefore, the drug is labelled as an indirect-

acting sympathomimetic agent that increases the endogenous concentration of catecholamines within the synaptic cleft by prohibiting the reuptake thereof and stimulating the release of neurotransmitters (Coulter *et al.*, 2018:2; Farzam *et al.*, 2021; Marais, 2016:18). However, because these catecholamines bind to adrenergic receptors, which are widely distributed throughout various organ systems in the body, the drug will evoke responses known as side effects, which are not necessarily desired effects (Farzam *et al.*, 2021; Law & Martin, 2020).

2.5.2 Side effects

Phentermine's unwanted effects are caused by the drug's prompt and continuous activation of catecholamine release into the bloodstream (Sanchez-Ramos, 2015:137). These catecholamines continuously stimulate the adrenergic and dopaminergic receptors, prolonging and intensifying their physiological effects in the body, which results in side effects (Kalyanasundar *et al.*, 2020:2; Sanchez-Ramos, 2015:137). Each of the α , β and D receptors are situated in various organ systems, and Table 2-3 gives the location of each respective receptor as well as their physiological effects when stimulated (Alshak & Das, 2020; AMBOSS, 2020; Bhatia *et al.*, 2020; Farzam *et al.*, 2021; Hussain *et al.*, 2021; Lokhandwala & Barrett, 1983:300).

Table 2-3: Adrenergic and dopaminergic receptors and their physiological effects on various organ systems in the body

Receptor	Organ system	Physiological effect when stimulated
α_1	1. Eyes	- Dilating the pupil through increased pupillary muscle dilator contraction (mydriasis) - Improve far vision through increased ciliary muscle relaxation
	2. Blood vessels	- Increase in the vascular contraction of the smooth muscle of the arterioles, resulting in increased peripheral resistance and afterload* of the heart - Constriction of the veins, which results in increased venous return and preload** of the heart
	3. GIT	Contraction of the upper and lower oesophageal, anal and pyloric sphincter
	4. Liver	Increasing the process where glycogen is broken down to glucose (glycogenolysis)

	5. Bladder	• Contraction of the sphincter to retain urine
	6. Male reproductive organs	• Ejaculation via the vas deferens
α_2	1. Eyes	• Increase the production of aqueous humour (translucent fluid produced by the eye)
	2. Blood vessels	• Increase the aggregation of platelets
	3. Pancreas	• Decrease insulin secretion
	4. Adipose tissue	• Reduce lipolysis
β_1	1. Heart	• Increase the heart: rate, contractility, automaticity and rapidity of conduction
	2. Kidneys	• Increase the secretion of renin^{***}
	3. Adipose tissue	• Increase lipolysis
β_2	1. Eyes	• Decrease the production of aqueous humour
	2. Blood vessels	• Vasodilation of the periphery, resulting in decreased peripheral resistance and afterload of the heart
	3. Bronchi	• Dilation of the bronchioles
	4. GIT	• Decrease of peristalsis
	5. Liver	• Increase in glucose production (gluconeogenesis)
	6. Pancreas	• Increase insulin secretion
	7. Bladder	• Relax the detrusor muscle
	8. Female reproductive organs	• Decrease the tone of the uterus
	9. Skeletal muscle	• Increase contraction and glycogenolysis
	10. Adipose tissue	• Increase lipolysis
β_3	1. Skeletal muscles	• Increase the production of heat (thermogenesis)
	2. Adipose tissue	• Increase lipolysis
D_1 and D_5	1. Kidneys	• Increased excretion of electrolytes

		• Vasodilation of the efferent and afferent arterioles
	2. Smooth muscle of vasculature	• Vasodilation of the coronary and peripheral vessels resulting in a decrease in blood pressure
	3. Adrenal cortex	• Inhibits aldosterone release
* Afterload is the force at which the heart must contract in order for it to discharge blood therefrom (O'Keefe & Singh, 2020). **Preload is the stretching of the heart's muscle cells prior to heart contraction (i.e., after diastole) (O'Keefe & Singh, 2020). *** Renin is an enzyme that regulates blood pressure (Fountain & Lappin, 2020).		

Phentermine indirectly affects the eyes, blood vessels, GIT, liver, bladder, male reproductive organs, pancreas, adipose tissue, heart, kidneys, bronchi, female reproductive organs, skeletal muscles, smooth muscles of the vasculature and the adrenal cortex (Alshak & Das, 2020; AMBOSS, 2020; Bhatia *et al.*, 2020; Farzam *et al.*, 2021; Hussain *et al.*, 2021; Lokhandwala & Barrett, 1983:300). Overstimulation of these respective sites may result in unwanted effects; that is, any effect caused by the drug other than appetite suppression and weight loss (Kalyanasundar *et al.*, 2020:2; Sanchez-Ramos, 2015:137). Phentermine's effect on the blood vessels, heart and kidney secretion may, unfortunately, result in cardiovascular side effects such as tachycardia, palpitations, pericardial pain and hypertension (iNova Pharmaceuticals, 2000).

The prolonged and continuous stimulation of β_1 receptors in the heart will enhance the contractility, automaticity, rapidity of conduction and the rate at which the heart beats (AMBOSS, 2020). These physiological effects in the body are responsible for the potential manifestation of tachycardia (abnormal fast heartbeat, usually > 100 beats per minute), palpitations (abnormally fast or unusual heartbeat usually characterised as the heart skipping a beat or a feeling of fluttering, pounding or flip-flopping in the chest and is sometimes the residual effect of tachycardia), pericardial pain, angina (chest pain) and myocardial infarction (MI) (also known as a heart attack) (Drugs.com, 2020a; Goyal *et al.*, 2020; Hermiz & Sedhai, 2020; iNova Pharmaceuticals, 2000; Ojha & Dhamoon, 2020). Other rare (apart from angina and MI) cerebrovascular side effects, which may occur, include heart failure, cardiac arrest and stroke (caused by a depletion of blood perfusion, oxygen and nutrients to specific area(s) of the brain) (iNova Pharmaceuticals, 2000; Tadi & Lui, 2021).

Hypertension (high blood pressure) is caused by peripheral vasoconstriction when α_1 receptors are stimulated, which results in increased venous return and preload (AMBOSS, 2020; World Health Organization (WHO), 2019a). Alpha₁ receptor stimulation also causes the vascular smooth

muscles of the arterioles to contract, which results in enhanced peripheral resistance and afterload (AMBOSS, 2020). The net result of these physiological effects in the body is the force exerted against the arterial walls in the body being too high, a medical condition known as hypertension (WHO, 2019a). Also, β_1 receptor stimulation of the juxtaglomerular cells of the kidneys causes renin to be released into the bloodstream with the over-activation of renin secretion, causing the body to preserve too much water, which will consequently result in an increase in the volume of the blood and thus an increase in the blood pressure (AMBOSS, 2020; Trerattanavong & Chen, 2021).

Even though phentermine is expected to induce these amphetamine-like side effects such as increased heart rate and blood pressure, Hendricks *et al.* (2011:2358) reported the opposite (Jordan *et al.*, 2014:1181). Phentermine neither induce adverse increases in the heart rate, nor does the drug adversely increase blood pressure. In fact, pharmacotherapy with phentermine would be beneficial to treat pre-hypertensive and hypertensive obese patients since weight loss assists in lowering LT blood pressure values (Hendricks *et al.*, 2011:2358).

Moreover, apart from phentermine's ability to cause cardiovascular side effects, the drug also influences the GI system, possibly causing side effects such as nausea, abdominal cramps, constipation, vomiting, diarrhoea, xerostomia and a unpleasant taste in the oral cavity (iNova Pharmaceuticals, 2000). Stimulation of α_1 , α_2 and β_2 receptors are responsible for the manifestation of these side effects (AMBOSS, 2020; iNova Pharmaceuticals, 2000). Alpha₁ receptor stimulation in the GIT will cause the oesophageal, pyloric and anal sphincters to contract (AMBOSS, 2020). Contraction of the oesophageal sphincter may cause food to get stuck in the oesophagus (prevent food from entering the stomach), which may cause pain or vomiting (UNC School of Medicine, 2017:2). Contraction of the pyloric sphincter prevents the adequate passage of food through the opening (i.e., delays gastric emptying), consequently resulting in both nausea and vomiting (UNC School of Medicine, 2017:3). Alpha₁ induced contraction of the anal sphincter may induce constipation since contraction of this sphincter results in faeces not being able to be exerted through the anus (Libretexts, 2020b). Additionally, α_1 receptor stimulation also causes the smooth muscles in the GIT to contract, resulting in diarrhoea (Libretexts, 2020b; UNC School of Medicine, 2017:6).

Beta₂ receptor stimulation of the GIT decreases the peristaltic movement of the small intestine (mechanism through which muscles contract to move GI contents towards the rectum), and food cannot move down the small intestine, further resulting in nausea, vomiting, constipation and abdominal cramps or discomfort (AMBOSS, 2020; UNC School of Medicine, 2017:5). Lastly, the stimulation of α_2 receptors decreases the secretion of salivary glands, which results in xerostomia

(Takakura *et al.*, 2009:225). This side effect has been reported as one of the most common side effects, amongst two others (dizziness and insomnia) experienced with phentermine therapy (Hendricks *et al.*, 2011:2358; Tantrachoti *et al.*, 2016:73).

These side effects can be attributed to phentermine's CNS stimulatory effects (iNova Pharmaceuticals, 2000; Sahu *et al.*, 2014:659). Insomnia, along with other CNS side effects such as restlessness, tremor and nervousness, is the result of ongoing β_2 receptor stimulation (AMBOSS, 2020). The less frequent CNS side effects experienced with phentermine therapy include euphoria, episodes of psychosis and hallucinations, where these manifestations are caused by the increased DA concentration in the CNS (Bhatia *et al.*, 2020; iNova Pharmaceuticals, 2000).

Lastly, other than the CVS, GIT and the CNS side effects, phentermine also affects the eyes, liver, bladder, male and female reproductive organs, pancreas, bronchi, adrenal cortex, skeletal muscles and adipose tissue (Alshak & Das, 2020; AMBOSS, 2020; Bhatia *et al.*, 2020; Farzam *et al.*, 2021; Hussain *et al.*, 2021; Lokhandwala & Barrett, 1983:300). Alpha₁ and β_2 receptor stimulation of the bladder, along with β_2 receptor stimulation of the female reproductive organs, are responsible for the manifestation of micturition disturbances (AMBOSS, 2020; iNova Pharmaceuticals, 2000). Stimulation of these receptors will cause the urethral sphincter to contract and the detrusor muscle of the bladder to relax, subsequently resulting in urinary retention (Alshak & Das, 2020; AMBOSS, 2020; Hussain *et al.*, 2021). Phentermine may also cause blurred vision, which can be attributed to α_2 receptor stimulation in the eyes, resulting in an increase in the production of aqueous humour (AMBOSS, 2020; iNova Pharmaceuticals, 2000). Other side effects which can also be experienced whilst on phentermine therapy is rashes, difficulty attaining an erection (i.e., impotence), fluctuations in libido and facial oedema (iNova Pharmaceuticals, 2000).

The side effects experienced with phentermine therapy usually range from mild to moderate in severity, with insomnia and xerostomia, as previously mentioned, being the most prevailing occurring side effects (Hendricks *et al.*, 2011:2358; Kim *et al.*, 2006:619,623; Tantrachoti *et al.*, 2016:73). These side effects are easily managed by encouraging individuals who experience a dry mouth to increase their water intake, and those experiencing insomnia are encouraged to administer the drug in the morning (Kim *et al.*, 2006:623). Although severe adverse events associated with phentermine use is rare, individuals should still be closely monitored for the occurrence of these effects since they may impair their daily functioning or be life-threatening (Kim *et al.*, 2006:623; WebMD, 2021).

Prescribers should also take precautions and ensure that they avoid prescribing phentermine together with any drug that may exacerbate effects that may be life-threatening (iNova Pharmaceuticals, 2000). Phentermine should also not be prescribed if a patient has a disease or medical condition in which the administration of the drug could worsen the patient's wellbeing (MedlinePlus, 2019). The drug, therefore, has known contraindications since the administration of phentermine together with these contraindicated drugs could potentially harm or cause discomfort to an individual, which may result in poor medicine adherence and patient outcome (Carver *et al.*, 2020; Hansberry, 2017; MedlinePlus, 2019).

2.6 Contraindications

Based on phentermine's mechanism of action (see section 2.5.1) (more specifically, the drug's ability to increase the heart rate and blood pressure), the drug should not be prescribed, and is therefore contraindicated, in individuals who have cardiovascular disease, glaucoma and hyperthyroidism (Podar *et al.*, 2019:24). The drug should also not be used in certain CNS, urinary tract, GIT and endocrine conditions, during pregnancy and lactation, in patients who are prone to drug abuse, in children before the age of 12 years and in patients who are hypersensitive for phentermine or amphetamines (iNova Pharmaceuticals, 2000; Teva Pharmaceuticals, 2020). Phentermine is further contraindicated with MAOIs, weight loss medication, ergot-like preparations, SSRIs and clomipramine (iNova Pharmaceuticals, 2000). Table 2-4 summarises the contraindications of phentermine with different diseases, conditions and medications as specified by the patient information leaflet of Duromine®.

Table 2-4: Phentermine's contraindications

Contraindications	
Diseases and conditions	
Cardiovascular diseases:	
• Pulmonary arterial hypertension • Arterial hypertension • Cerebrovascular diseases • Cardiac arrhythmias • Progressive arteriosclerosis	
Eye diseases:	
• Glaucoma	
Thyroid diseases:	
• Hyperthyroidism	

Urinary tract conditions:
• Renal impairment • Obstructive uropathy
Central nervous system conditions:
• Seizure disturbances • Anxiety • Psychiatric conditions
Gastrointestinal conditions:
• Galactose intolerance • Lapp lactase deficiency • Glucose-galactose malabsorption
Endocrine conditions:
• Diabetes mellitus
Other:
• Individuals with a history of substance abuse • During pregnancy and lactation • Children under 12 years old (< 12 years) • Individuals with known hypersensitivity to phentermine and amphetamine
Medication
Monoamine oxidase inhibitors:
• Rasagiline • Selegiline hydrochloride • Moclobemide • Tranylcypromine
Weight-loss medication:
• Amfepramone • Phendimetrazine
Ergot-like preparations:
• Ergotamine
Selective serotonin reuptake inhibitors:
• Citalopram • Escitalopram • Fluoxetine • Fluvoxamine maleate • Paroxetine • Sertraline
Other:
• Clomipramine

The cardiovascular diseases contraindicated with phentermine include pulmonary arterial hypertension (PAH), arterial hypertension, cerebrovascular diseases, cardiac arrhythmias and progressive arteriosclerosis (iNova Pharmaceuticals, 2000; Jordan *et al.*, 2014:1179). Pulmonary arterial hypertension is a medical condition where vascular resistance increases and the blood vessels inside the pulmonary vasculature are narrowed (Oldroyd & Bhardwaj, 2020). The mechanism of medicine-induced, specifically fenfluramine-induced, pulmonary hypertension (as previously mentioned in section 2.1) suggests that the disease is caused by 5-HT activity on the pulmonary smooth muscle cells of arteries (Hendricks & Rothman, 2011:869). Several studies, along with supporting literature, suggest it is highly unlikely for phentermine to induce PAH (whether via serotonergic mechanism or not), and one can thus conclude that phentermine monotherapy does not increase the prevalence of PAH (Hendricks & Rothman, 2011:869). However, because the drug increases blood pressure and can, therefore, theoretically worsen PAH, the drug should, for safety reasons, be avoided in such patients (iNova Pharmaceuticals, 2000; Jordan *et al.*, 2014:1179; Podar *et al.*, 2019:24).

Arterial hypertension is diagnosed when a patient has a persistent blood pressure reading of $\geq 140/90$ mmHg (Jordan *et al.*, 2018:558). Due to the known effects of phentermine on α_1 receptors consequently resulting in an increase in blood pressure levels, the use of phentermine in patients with arterial hypertension could further increase the blood pressure reading (AMBOSS, 2020; WHO, 2019a). Such increases in blood pressure may result in a hypertensive crisis ($\geq 180/110$ mmHg), which may, in turn, result in organ damage (Hopkins, 2018; Stöppler, 2018; Suneja & Sanders, 2017:467).

It has previously been mentioned (see section 2.5.2) that therapy with phentermine may cause cerebrovascular side effects, one of which is strokes (iNova Pharmaceuticals, 2000; Jordan *et al.*, 2014:1179). A stroke is classified as a medical emergency, with the foremost causative agent being hypertension (Khaku & Tadi, 2021). Strokes are responsible for a high morbidity and mortality rate, with survivors often left disabled or with fractional neurological discrepancies, including impaired speech and unilateral paralysis of limbs (Khaku & Tadi, 2021). Phentermine's connotation with hypertension, and thus strokes, warrants why the drug should be avoided in patients likely to experience such cerebrovascular incidents (iNova Pharmaceuticals, 2000; Jordan *et al.*, 2014:1179; Khaku & Tadi, 2021).

Phentermine is also contraindicated in patients with irregular heart rhythms (i.e., cardiac disease arrhythmias) (iNova Pharmaceuticals, 2000; Jordan *et al.*, 2014:1179). Cardiac disease arrhythmias such as tachycardia are another factor responsible for a high morbidity and mortality rate worldwide (Desai & Hajouli, 2021). Phentermine's enhancement in the contractility,

automaticity, rapidity of conduction and heart rate resulting in irregular heartbeats may exacerbate the pathophysiology already causing the cardiac arrhythmias in individuals, and the drug should therefore be avoided in such cases (AMBOSS, 2020; iNova Pharmaceuticals, 2000; Teva Pharmaceuticals, 2020).

Arteriosclerosis manifests when the arteries that supply blood from the heart to the remainder of the body become thick and hard (Mayo Clinic, 2021a). In the advanced stages of arteriosclerosis, blood flow may be restricted to organs and tissue sites, which may, in turn, result in angina, heart failure or cardiac arrest (Mayo Clinic, 2021a). Therefore, because of phentermine's association with angina, cardiac failure and cardiac arrest, the drug should be avoided when a patient has advanced arteriosclerosis (Al-Sharea *et al.*, 2018:465; iNova Pharmaceuticals, 2000).

Moreover, phentermine is also contraindicated in glaucoma, specifically narrow-angle glaucoma or physically narrowed angles (Drugs.com, 2021c). Glaucoma is a set of eye conditions (caused by unusually high pressure in the eyes) that impair the optic nerve. If it is not treated, it will result in permanent vision loss (i.e., blindness) (Mayo Clinic, 2020a). Phentermine's ability to cause mydriasis (i.e., pupil dilation) (see section 2.5.2) can trigger an acute occurrence of narrow-angle glaucoma since mydriasis may sometimes amplify the intraocular pressure (Drugs.com, 2021c). It is therefore suggested that phentermine should not be used simultaneously in patients presenting with either narrow-angle glaucoma or physically narrowed angles since it may result in permanent damage to the optic nerve (Drugs.com, 2021c).

Phentermine is further contraindicated in patients with hyperthyroidism – a medical condition in which the thyroid gland produces an excessive amount of the hormone thyroxine (Mayo Clinic, 2020b; Podar *et al.*, 2019:24). This may speed up the body's metabolism, resulting in unintended effects such as weight loss, tachycardia, arrhythmias and palpitations (Mayo Clinic, 2020b). The thyroid gland works together with the adrenal glands (which are also responsible for producing and releasing NE into the bloodstream) to ensure that the body's metabolism works accurately (Dutt *et al.*, 2021; Teixeira *et al.*, 2020:21). Thus, when phentermine places excessive stress on the adrenal glands (to release catecholamines into the bloodstream), it will also cause excessive stress on the thyroid gland, which will consequently add to the effects of the already overactive thyroid gland (hyperthyroidism) (Mayo Clinic, 2020b; Teixeira *et al.*, 2020:21). As a result, the thyroid gland will produce too much thyroxine (in addition to the existing high concentrations) and exacerbate the weight loss effects, as well as the irregularities in the heart rhythms (Mayo Clinic, 2020b). Phentermine should, therefore, be avoided in hyperthyroidism since the combination may be harmful to the patient (Podar *et al.*, 2019:24).

Apart from phentermine's association with hypertension and increased heart rhythms, which causes the drug to be contraindicated in the circumstances mentioned above, the drug is also contraindicated in several other conditions such as renal impairment, obstructive uropathy, seizure disturbances, anxiety, psychiatric conditions, substance abuse, galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption, diabetes mellitus, in pregnant and lactating women, children < 12 years and in individuals who are allergic to phentermine or amphetamines (iNova Pharmaceuticals, 2000; Podar *et al.*, 2019:24).

Phentermine is contraindicated in patients with severe renal impairment since the drug is extensively excreted via the kidneys, and as a result thereof, renal impairment may result in toxic reactions (Akrimax Pharmaceuticals, 2013; iNova Pharmaceuticals, 2000; KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020; UCB, Inc, 2012). The use of phentermine amongst the elderly is, therefore, also not recommended since the geriatric population is expected to have diminished renal function, and administration of phentermine will cause the drug to be inadequately excreted from the body, consequently resulting in toxic concentrations and reactions (Akrimax Pharmaceuticals, 2013; iNova Pharmaceuticals, 2000; KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020; UCB, Inc, 2012).

Phentermine should also not be administered to patients with obstructive uropathy as this disease can be associated with phentermine's α_1 and β_2 receptor stimulation, resulting in urinary retention (AMBOSS, 2020; iNova Pharmaceuticals, 2000). Obstructive uropathy is a medical condition where the urinary outflow is obstructed, causing the urine to back up into the kidneys, which may result in swollen kidneys (hydronephrosis) or kidney damage (Rishor-Olney & Hinson, 2021). Phentermine's effect on urinary retention will add to the obstruction of urinary outflow in individuals with obstructive uropathy, which may exacerbate the damaging effects on the kidneys. The drug should, therefore, be avoided in such patients (AMBOSS, 2020; iNova Pharmaceuticals, 2000; Rishor-Olney & Hinson, 2021).

Phentermine should not be used in patients with poorly controlled epilepsy or seizure disturbances (Drugs.com, 2020b; iNova Pharmaceuticals, 2000). Seizures are caused by abrupt, unanticipated electrical disturbances in the brain, which may sometimes (depending on how long they last) become a medical emergency (Mayo Clinic, 2021b). Phentermine's ability to stimulate the CNS may consequently result in seizures. The drug may also lower the threshold for convulsions in patients who have previously had seizures or electroencephalography abnormalities (Drugs.com, 2020b). Using phentermine in patients with such medical history could potentially cause significant harm to individuals; therefore, the drug should be avoided (Drugs.com, 2020b; iNova Pharmaceuticals, 2000).

Phentermine's CNS-stimulating properties further warrant the drug's contraindication in individuals with agitation or anxiety, previous psychiatric disorders, and substance abuse (Drugs.com, 2020b; iNova Pharmaceuticals, 2000; Teva Pharmaceuticals, 2020). Central nervous system stimulants have the potential to aggravate symptoms of anxiety or agitation, cause suicidal thoughts, and aggravate behavioural instabilities and thinking disturbances in patients, especially children, with psychosis (Drugs.com, 2020b). Jo *et al.* (2019:132) reported that patients might be subjected to recurring psychotic outbreaks after the administration of phentermine. Therefore, it is of utmost importance for prescribers to ensure that patients do not have a history of psychiatric (depression and anorexia) or psychotic conditions prior to initiating phentermine therapy and that they thoroughly educate patients about potential psychiatric side effects (Jo *et al.*, 2019:132). Moreover, it is a well-known fact that phentermine can cause abuse or dependence, despite ample evidence suggesting otherwise. Therefore, the drug should be avoided in patients who had previously abused or developed a dependence on drugs or alcohol (Coulter *et al.*, 2018:7; Drugs.com, 2020b; Hendricks *et al.*, 2014:297; iNova Pharmaceuticals, 2000; SAHPRA, 2019:8).

As indicated in phentermine's patient information leaflet (PIL), the drug contains lactose monohydrate (iNova Pharmaceuticals, 2000). After consumption, lactose is typically hydrolysed into galactose and glucose (both sugars) via the lactase enzyme so it can be absorbed across the lining of the small intestine (Malik & Panuganti, 2021). Individuals with lactase deficiency will not be able to hydrolyse lactose, resulting in inadequate digestion in the small intestine, causing the lactose to proceed to the colon or the patient to become lactose intolerant (Bouchoucha *et al.*, 2021:258; Malik & Panuganti, 2021). Lactose will consequently be degraded in the colon, which may cause symptoms such as diarrhoea, bloating, pain and gas (Bouchoucha *et al.*, 2021:258). In situations where individuals are incapable of absorbing the sugars glucose and galactose (i.e., those that have glucose-galactose malabsorption or galactose intolerance), it will attract a significant amount of water into the intestines, which may result in severe or chronic diarrhoea, potentially causing life-threatening dehydration (Zuvarox & Belletieri, 2021). Because of the life-threatening consequence thereof, phentermine should be avoided in patients with lactase deficiency, glucose-galactose malabsorption or galactose intolerance (iNova Pharmaceuticals, 2000).

Moreover, the presence of lactose monohydrate in phentermine's medicinal product also warrants the drug's contraindication in patients with diabetes mellitus (iNova Pharmaceuticals, 2000). Patients with diabetes mellitus have too much glucose in their blood, which may cause disabilities or life-threatening complications over time, including, but not limited to,

cardiovascular conditions, damage to the nerves, kidneys and eyes, and depression (Mayo Clinic, 2020c). If a diabetic patient were to administer phentermine, glucose and galactose will be absorbed into the bloodstream, thereby disrupting the glycaemic control of diabetic patients (iNova Pharmaceuticals, 2000; Malik & Panuganti, 2021). Knowing the risks of high glycaemic levels in the blood, phentermine should rather be avoided in patients with diabetes mellitus (iNova Pharmaceuticals, 2000).

Phentermine is categorised as category C during pregnancy, i.e., the drug should not be consumed during gestation since there is no available data supporting that it has no adverse effects on the foetus (Marin *et al.*, 2009:589). One case reported that a woman was administering phentermine during the first and second trimester of pregnancy. The baby was born with a large cerebrovascular lesion possibly caused by a prenatal stroke (D'Adesky & Ghosh, 2019:3). However, given the lack of data on the possible foetal risks associated with the use of phentermine, no definite causative relationship between phentermine and prenatal stroke could be established (D'Adesky & Ghosh, 2019:3).

Animal studies with phentermine have indicated an increase in the occurrence of foetal damage (iNova Pharmaceuticals, 2000). However, rats administered in later stages of pregnancy with doses of phentermine seven times higher than the maximum human dose showed no evidence of adverse effects on either the mother or the descendant (Drugs.com, 2021d). Nevertheless, despite the contradictory results of phentermine in animal studies and the lack of data on teratogenicity, phentermine should not be used in humans during pregnancy as weight loss poses no probable benefits to gestational women, and it may cause harm to the foetus (Drugs.com, 2021d; Teva Pharmaceuticals, 2020).

The use of phentermine in breastfeeding should be avoided as it is unknown if the drug is excreted in breastmilk (Drugs.com, 2021d; Teva Pharmaceuticals, 2020). It is, however, known that amphetamines do get excreted into breastmilk in concentrations that may exceed maternal plasma levels (Oei *et al.*, 2012:743; Teva Pharmaceuticals, 2020). Therefore, nursing infants may potentially be associated with severe adverse effects, and it should be decided whether the drug use or the nursing should be terminated (Drugs.com, 2021d; Oei *et al.*, 2012:743; Teva Pharmaceuticals, 2020). Due to the lack of evidence supporting the safety of phentermine during breastfeeding, the drug should be avoided during lactation (iNova Pharmaceuticals, 2000).

In South Africa, phentermine is contraindicated in children younger than 12 years; however, the FDA has approved the drug to be used, in addition to lifestyle modifications, in children

that are < 18 but > 16 years of age (iNova Pharmaceuticals, 2000; Woodard *et al.*, 2020:2). The drug is contraindicated in children due to the lack of safety and efficacy data supporting their use (iNova Pharmaceuticals, 2000; Teva Pharmaceuticals, 2020). It should be kept in mind that obesity amongst paediatrics is a chronic disorder requiring LT therapy, and phentermine is restricted to ST use only (Teva Pharmaceuticals, 2020). The only studies investigating the use of phentermine in paediatric populations were those done in the 1960s, and they had insignificant data on the safety and efficacy of phentermine in such populations (Ryder *et al.*, 2017:91). In a more recent study, Ryder *et al.* (2017:93) concluded that phentermine, in addition to standard-of-care lifestyle modification treatment, caused meaningful weight loss in adolescents (aged at an average of 16.1 years) at months 1, 3 and 6 when compared to those that only received standard-of-care lifestyle modification treatment. These findings encourage further examination of the use of phentermine as an option for treating obesity in paediatric patients (Ryder *et al.*, 2017:93).

Hypersensitivity to phentermine commonly presents as urticaria, also known as hives, and it may differ in severity and duration, where it may last for a few minutes or days or weeks or even months, nevertheless, usually not longer than 24 hours (Drugs.com, 2021e; Drugs.com, 2020c). Depending on the severity, hives may indicate a life-threatening allergic reaction known as anaphylaxis (Drugs.com, 2021e). Anaphylaxis requires immediate medical attention and typically presents with a skin rash, obstructive breathing, hypotension, nausea and vomiting. If left unattended, it may be fatal (Mayo Clinic, 2019a). Patients who are known to be hypersensitive to phentermine or amphetamines should, therefore, avoid using these drugs (iNova Pharmaceuticals, 2000; Teva Pharmaceuticals, 2020).

Furthermore, the use of phentermine together with MAOIs (rasagiline, selegiline hydrochloride, moclobemide and tranylcypromine) is contraindicated since these drugs potentiate each other's effects, which may result in a hypertensive crisis (a medical emergency, which may result in end-organ damage) and hyperpyrexia (extremely high body temperatures of $\geq 41.5^{\circ}\text{C}$) (iNova Pharmaceuticals, 2000; Laban & Saadabadi, 2021; Mayo Clinic, 2019b; Rossiter, 2016:469-470,499; Stöppler, 2018). Monoamine oxidase is the enzyme responsible for breaking down the neurotransmitters NE, 5-HT, DA and tyramine in the brain, and inhibition thereof will increase the concentration, and thus the effects, of these neurotransmitters in the body (see section 2.5.1 and 2.5.2) (Laban & Saadabadi, 2021; Mayo Clinic, 2019b). Certain MAOIs, such as phenelzine, irreversibly inhibit MAO, and their physiological effects in the body can persist for as little as 14 days (Fiedorowicz & Swartz, 2004:241). Phentermine should,

therefore, also not be used within 14 days after therapy with MAOIs has been discontinued to allow for a washout period (Fiedorowicz & Swartz, 2004:242).

Phentermine is further contraindicated in other weight-loss medications, such as amfepramone and phendimetrazine, since combining these medications with phentermine may result in severe heart problems, such as valvular heart disease and pulmonary hypertension (Drugs.com., 2021a; iNova Pharmaceuticals, 2000). Both amfepramone and phendimetrazine are classified as centrally acting amphetamine derivatives that suppress appetite via the same mechanism as phentermine; that is, potentiating catecholamine release (NE and DA) (Kalyanasundar *et al.*, 2020:2; Rossiter, 2016:70; Sanchez-Ramos, 2015:137). The effects these drugs have on the CVS will add to those of phentermine, which may potentially cause serious cardiovascular problems, as previously mentioned, and therefore the contraindication (Drugs.com., 2021a; iNova Pharmaceuticals, 2000). The use of phentermine in combination with other medicine indicated for weight loss, other than those mentioned above, is contraindicated since the safety and efficacy of such combinations have not been established (iNova Pharmaceuticals, 2000; Teva Pharmaceuticals, 2020).

Moreover, the use of phentermine together with ergot-like preparations such as ergotamine is not recommended since both drugs can be associated with cardiac failure (iNova Pharmaceuticals, 2000; Page *et al.*, 2016:38). Ergotamine is indicated as an antimigraine preparation that acts on α receptors by directly stimulating the effects on peripheral smooth muscles and cranial blood vessels, and that possesses 5-HT opposing characteristics (Page *et al.*, 2016:51). Ergotamine's redundant 5-HT activity may explain the potential mechanism causing valvular fibrosis (Page *et al.*, 2016:38). Phentermine's potential to cause heart failure, together with ergotamine's potential to induce valvular fibrosis, evidently rationalises why these drugs should not be used simultaneously (iNova Pharmaceuticals, 2000; Page *et al.*, 2016:38).

Lastly, phentermine is contraindicated with certain classes of antidepressants, such as SSRIs and TCAs, such as clomipramine (iNova Pharmaceuticals, 2000). The use of phentermine with SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine maleate, paroxetine and sertraline), as previously discussed (see section 2.1), may cause the life-threatening 5-HT syndrome, induce a coma or become fatal; therefore, the use of phentermine together with these drugs is not recommended (Drugs.com., 2021a; iNova Pharmaceuticals, 2000; Rossiter, 2016:495; Teva Pharmaceuticals, 2020).

The simultaneous use of phentermine with clomipramine may exacerbate the cardiovascular effects caused by phentermine and thus increase the risk of hypertension, fever, tachycardia and arrhythmias (Drugs.com., 2021a). Clomipramine is a tricyclic antidepressant (TCA) that may prolong the QT interval of the heart (the length of the heart's ventricular depolarisation and repolarisation), which may result in Torsade de Pointes (polymorphic type of ventricular tachycardia) (Al-Akchar & Siddique, 2021; Cohagan & Brandis, 2020; Page *et al.*, 2016:51). Given each individual drug's potential to cause severe cardiovascular side effects, it goes without saying that these drugs should not be used together.

To conclude, despite phentermine's FDA-approved label, the drug still gets prescribed together with medication causing these contraindications (Hendricks *et al.*, 2017:225,227). Contraindications such as hypertension, strokes, cardiac arrhythmias, agitation and heart failure are explicitly listed. However, without structured data encouraging these contraindications, there is no explicit confirmation that these ailments are definite contraindications (Hendricks *et al.*, 2017:226; iNova Pharmaceuticals, 2000; Teva Pharmaceuticals, 2020). Using phentermine with the medication mentioned above adds to each other's effects in the body (i.e., causes a DDI), which may potentially cause harm to the patient. The benefit-to-risk ratio should thus be established before combining these agents (MedlinePlus, 2019).

2.7 Drug-drug interactions

Drug-drug interactions are a substantial challenge to clinical healthcare worldwide due to the harmful effects they may cause in individuals (Kahandeparker & Rataboli, 2017:180; Vilar *et al.*, 2018:863). It can be defined as the phenomenon that occurs when two or more drugs administered simultaneously affect one another's biological activity in such a manner that it may compromise either the drug's safety or efficacy profile (Vilar *et al.*, 2018:863). The potential for an individual to experience a DDI increases when multiple drugs are taken at the same time (i.e., polypharmacy) (Alomar, 2013:84). Polypharmacy is commonly seen amongst older and obese individuals and individuals with several conditions that each require medicinal therapy (National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 2015; Slater *et al.*, 2018:8).

Drug-drug interactions can be classified as either PK or PD interactions (Yartsev, 2018a). Pharmacokinetic interactions concentrate on how substances affect one another's absorption, distribution, metabolism and elimination processes. In contrast, PD interactions focus on how drugs affect one another's mechanisms of action and whether they contribute to or counteract

each other's effects on the body (Yartsev, 2018a; Yartsev, 2018b). The DDI between phentermine and fenfluramine was discussed in section 2.1, and it serves as a perfect example of a PD DDI (Wellman & Maher, 1999:730; Yartsev, 2018b). This DDI is graded as a major or severe DDI since it may cause a life-threatening ADR, and the combination of these agents should be avoided as the risks outweigh the benefits significantly (Drugs.com., 2021a; Farooqui *et al.*, 2018:145; Wellman & Maher, 1999:730).

More examples of drugs that may cause severe DDIs when co-administered with phentermine are given in Annexure C (Drugs.com., 2021a). It also provides the classification of the DDI and the potential ADR that may arise when these drugs are co-administered with phentermine (Drugs.com., 2021a; Rossiter, 2016:70-613). Drugs that may cause moderate DDIs, such as sympathomimetics, adrenergic and dopaminergic agonists, are also included in Annexure C. Those that cause minor DDIs, such as evening primrose, are also identified, even though the interaction is not necessarily regarded as being clinically significant (Drugs.com., 2021a).

Minor DDIs, as seen with phentermine and evening primrose, occur when these drugs increase the incidence and brutality of adverse effects; however, they are not so severe that the interaction necessitates adjustments in therapy regimens (Drugs.com., 2021a; Shahabudin *et al.*, 2012:1259). Moderate DDIs are rated as such when they exacerbate the patient's condition and/or necessitates alterations in treatment plans (Shahabudin *et al.*, 2012:1260). They are further avoided when phentermine is being administered (i.e., only used when particularly necessary) due to the clinical significance in the ADR that may result from co-administration (Drugs.com., 2021a). Moreover, severe DDIs necessitate medical attention, interventions to minimise or avoid life-threatening effects, and they may potentially lead to fatalities (Shahabudin *et al.*, 2012:1260).

Given the severity of the ADRs (5-HT syndrome, hypertension, cardiac complications, mortality, hypoglycaemia and psychosis) caused by severe and moderate DDIs, it is certainly not in the best interest of any patient to administer phentermine together with drugs that may potentiate these adverse effects in individuals (Hopkins, 2018; Kahandeparker & Rataboli, 2017:180; Mayo Clinic, 2021b; Simon & Keenaghan, 2021; Stöppler, 2018; Suneja & Sanders, 2017:467; Vilar *et al.*, 2018:863). On the contrary, it emphasises the absolute importance of adequate knowledge and expertise when more than one drug is administered simultaneously, as it undoubtedly will decrease the incidence of such ADRs resulting from DDIs (Shahabudin *et al.*, 2012:1260). Lastly, it further brings to one's attention that these lethal circumstances can be avoided by prescribing according to the FDA-approved indications and prescribing guidelines, as

it eliminates the ignorance commonly associated with irrational drug prescribing (Shahabudin *et al.*, 2012:1260).

2.8 International and national specific prescriber guidelines for phentermine and drug utilisation

Phentermine is available worldwide and may legally be sold in certain countries including, but not limited to, the USA, Korea, Mexico, Chile, Australia and South Africa (Cohen, 2021; Cohen, 2020). In certain other countries, including, but not limited to, Canada, the European Union, Spain, Sweden, Mauritius, Turkey and England, phentermine was withdrawn from the market due to safety concerns, and the drug may not legally be sold from these parts of the world (Cohen, 2021; Onakpoya *et al.*, 2016:194). Nevertheless, where phentermine may be sold, the drug has different trade names, product strengths and scheduling statuses. Table 2-5 summarises the different trade names and strengths for phentermine hydrochloride and phentermine resin, from where the product is available as well as the scheduling status (S) for the drug for each specific region (Cohen, 2022; Cohen, 2021; Cohen, 2020; iNova Pharmaceuticals, 2021; iNova Pharmaceuticals, 2000; KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020).

Table 2-5: Trade names and availability of products comprising phentermine

Trade name	Product formulation	Product strength(s)	Availability	Scheduling status (S)
Adipex-P®	Phentermine hydrochloride	37.5 mg	USA	S4
Lomaira®	Phentermine hydrochloride	8 mg	USA	S4
Dietamin®	Phentermine hydrochloride	37.5 mg	Korea	S4
Terfamex®	Phentermine resin	15 mg 30 mg	Mexico	S4
Sentis®	Phentermine hydrochloride	18.75 mg 37.5 mg	Chile	S4
Duromine®	Phentermine resin	15 mg 30 mg 40 mg	Australia New Zealand	S4
Duromine®	Phentermine resin	15 mg 30 mg	South Africa	S5

Each of these individual products has prescriber-specific guidelines that are provided in the PILs of each drug as it assists prescribers in the rational and safe prescribing of phentermine. The concept of rational prescribing involves maximising clinical efficiency and minimising harm (Maxwell, 2016:459). These guidelines, therefore, specify how therapy with each individual product should be initiated, how and when dosages should be adjusted and in which populations phentermine should be avoided. Evidently, the FDA has provided these international guidelines to ensure the drug is used appropriately, safely, rationally and effectively. The prescribing information provided in the PILs of products that are not available in South Africa, such as Adipex-P®, Lomaira®, Dietamin®, Terfamex®, Axcion®, Sentis® and Duromine® (Australia), serves as an international standard for the prescribing of phentermine.

In the USA, phentermine is available in its hydrochloride formulation (see Table 2-5), and the drug is scheduled as a schedule four (S4) controlled substance, i.e., it has a low risk of developing physical or physiological dependence (Cohen, 2021). Patients need a valid prescription from a primary healthcare doctor (specialist or non-specialist) that has a license from the Drug Enforcement Administration (DEA) to obtain phentermine (Cohen, 2021; Hendricks *et al.*, 2009:1730; Preuss *et al.*, 2022). Prescribers may initiate pharmacotherapy with the drug for the ST management of obesity (BMI ≥ 30 kg/m² or ≥ 27 kg/m²) in addition to lifestyle and behavioural adjustments (KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020). The dosage of Adipex-P® and Lomaira® should be individualised for each patient to ensure that a satisfactory response to therapy is achieved at the lowest effective dose (Teva Pharmaceuticals, 2020; UCB, Inc, 2012). Starting at the lowest effective dose decreases the risk of side effects and cessation of therapy (Lee & Dixon, 2017:473).

As seen from Table 2-5, Adipex-P® comprise 37.5 mg of phentermine hydrochloride, which is equivalent to 30 mg of phentermine base (Cohen, 2021; Kim *et al.*, 2006:624; Teva Pharmaceuticals, 2020). It is recommended that patients be started on 18.75 mg of Adipex-P® per day, i.e., half a tablet per day. Doses should be titrated up to 37.5 mg per day if the individual fails to lose at least 2 kg over four weeks (Lee & Dixon, 2017:473; Teva Pharmaceuticals, 2020). The standard adult dose, prescribed by authorised healthcare providers, is 37.5 mg of phentermine hydrochloride daily. In some cases, it might be necessary to adjust the dosage according to the patient's needs and 18.75 mg daily or 18.75 mg twice daily may be sufficient (Akrimax Pharmaceuticals, 2013; Du Toit *et al.*, 2012; Teva Pharmaceuticals, 2020). Because phentermine may cause insomnia in general, Adipex-P® should be taken 1-2 hours after breakfast has been consumed to control appetite (Teva Pharmaceuticals, 2020; WebMD, 2021). Insomnia that may result from phentermine consumption clarifies why the drug should not be administered

in the evening or to individuals younger than 16 years of age (phentermine hydrochloride) (Akrimax Pharmaceuticals, 2013; Teva Pharmaceuticals, 2020).

Lomaira® tablets contain 8 mg of phentermine hydrochloride (equivalent to 6.4 mg of phentermine base) (Akrimax Pharmaceuticals, 2013; KVK-Tech, Inc, 2018). Therapy should be initiated at one tablet (8 mg) three times a day; however, depending on the response to treatment, the dose might need to be reduced to half a tablet three times a day (KVK-Tech, 2018). Lomaira® should be administered at least half an hour before meals (KVK-Tech, Inc, 2018). Doses should be determined according to each patient's specific needs, recalling that the maximum daily dosage of phentermine may not exceed 37.5 mg of phentermine hydrochloride or 30 mg of phentermine resin (iNova Pharmaceuticals, 2000; Rossiter, 2016:71; Teva Pharmaceuticals, 2020). The recommended daily dose should not be surpassed to increase the effect of the agent nor be used in combination with other appetite suppressants to increase the effect thereof (iNova Pharmaceuticals, 2000; iNova Pharmaceuticals, 1991:2).

As previously mentioned, phentermine is also available in Korea, where the drug has been widely distributed by clinicians since its introduction in 2004 (Kim *et al.*, 2006:615). The drug is available as 37.5 mg of phentermine hydrochloride (equivalent to 30 mg phentermine base) and is also scheduled as an S4 controlled substance, as specified by the USA DEA (Kim *et al.*, 2006:624). Patients may, therefore, with a valid doctor's prescription, receive pharmacotherapy with Dietamin® provided that the drug is indicated for the ST management of obesity (Cohen, 2021; Hendricks *et al.*, 2009:1730; Preuss *et al.*, 2022; Teva Pharmaceuticals, 2020). In Korea, the Asia-specific guidelines define obesity as having a BMI of $\geq 25 \text{ kg/m}^2$ (Kim *et al.*, 2006:614; Woo & Jeong, 2018:290). Therefore, pharmacotherapy with Dietamin® may be considered in obese Korean patients, i.e., those with a BMI of $\geq 25 \text{ kg/m}^2$. However, the FDA specifies that the BMI should be $\geq 30 \text{ kg/m}^2$ or $\geq 27 \text{ kg/m}^2$ if the patient has adipose-related complications (Kim *et al.*, 2006:614; Teva Pharmaceuticals, 2020; Woo & Jeong, 2018:290). Dietamin® should be started at the lowest dosage, which is 18.75 mg of phentermine hydrochloride (half a tablet) daily. If weight loss is not sufficient after four weeks, i.e., the patient has not lost at least a standard of 2 kg of body weight, the dosage may be increased to 18.75 mg twice a day or 37.5 mg daily (Akrimax Pharmaceuticals, 2013; Du Toit *et al.*, 2012; Teva Pharmaceuticals, 2020). Dietamin® should be taken in the morning, approximately 1-2 hours after breakfast (Teva Pharmaceuticals, 2020; WebMD, 2021).

In Mexico, phentermine is available as 15 mg or 30 mg of phentermine resin and the drug trades as Terfamex® (DiBonaventura *et al.*, 2018:8; Márquez-Cruz *et al.*, 2021:540). The drug is also scheduled at S4 and requires a doctor's prescription to receive pharmacotherapy (Cohen, 2021).

Therapy with Terfamex® may be initiated in patients with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² if the patient has adipose-related complications (Kim *et al.*, 2006:614; Teva Pharmaceuticals, 2020; Woo & Jeong, 2018:290). Terfamex® should be initiated at the lowest effective dose, and patients should therefore be started on 15 mg of phentermine daily (15 mg twice daily may be required) (Cohen, 2022). If the patients fail to lose 2 kg over four weeks, the dose should be titrated up to 30 mg of phentermine, taken as a single daily dose (Cohen, 2022). Terfamex® should be taken before breakfast at approximately seven in the morning (i.e., on an empty stomach) with a full glass of water (Cohen, 2022; iNova Pharmaceuticals, 2021; iNova Pharmaceuticals, 2000). Patients are advised to administer the drug first thing in the morning as the drug may cause insomnia if taken later during the day (Cohen, 2022; iNova Pharmaceuticals, 2021; iNova Pharmaceuticals, 2000). Phentermine resin should generally not be administered to patients < 12 years, as there is no data to support the safety thereof (Cohen, 2022; iNova Pharmaceuticals, 2021; iNova Pharmaceuticals, 2000).

In Chile, phentermine trades as Sentis® with either 18.75 mg (equal to 15 mg of phentermine base) or 37.5 mg (equal to 30 mg of phentermine base) of phentermine hydrochloride as the active ingredient (Cohen, 2021). Medical doctors are authorised to prescribe this drug and do this by supplying patients with a valid “receta cheque” (translates to “check prescription”), which they hand in at local pharmacies and get their medicine supply in return (Cohen, 2021). Sentis® require a prescription as the drug is scheduled as an S4 controlled substance (Cohen, 2021). Pharmacotherapy may be initiated in obese individuals (BMI ≥ 30 kg/m² or ≥ 27 kg/m² if the patient has adipose-related complications) and should be started at 18.75 mg of Sentis® per day (Kim *et al.*, 2006:614; Teva Pharmaceuticals, 2020; Woo & Jeong, 2018:290). Patients will take one of the 18.75 mg phentermine hydrochloride tablets daily (see Table 2-5). Doses should be increased to either 18.75 mg twice a day or to the standard dose of 37.5 mg once a day if weight loss is insufficient after four weeks (i.e., < 2 kg) (Akrimax Pharmaceuticals, 2013; Du Toit *et al.*, 2012; Lee & Dixon, 2017:473; Teva Pharmaceuticals, 2020). It is recommended the drug be administered in the morning (1-2 hours after breakfast) as it may cause insomnia (see section 2.5.2) (Teva Pharmaceuticals, 2020; WebMD, 2021).

Phentermine is also available in Australia and trades as Duromine®, which is available as 15 mg, 30 mg and 40 mg of phentermine resin (Hocking *et al.*, 2017:5.3). The drug is scheduled as an S4 controlled substance, which means it can only be sold to patients provided they have a valid prescription from an authorised healthcare prescriber (iNova Pharmaceuticals, 2021). Both GPs and specialists are permitted to prescribe phentermine to patients with a BMI ≥ 30 kg/m² or patients with a BMI from 25 kg/m² to 29.9 kg/m² with adipose-related complications (Forgione *et*

al., 2018:195; iNova Pharmaceuticals, 2021). General practitioners are advised to refer patients for bariatric specialist treatment options, provided the patient has a BMI ≥ 40 kg/m² (Forgione *et al.*, 2018:195). In Australia, phentermine is indicated for the ST adjacent therapy of obesity, and the maximum daily dose may not exceed 40 mg of phentermine (iNova Pharmaceuticals, 2021). The recommended starting dose for Duromine® in Australia is 30 mg of phentermine daily; however, larger patients may require 40 mg of phentermine per day (iNova Pharmaceuticals, 2021). The drug should be administered before seven in the morning, on an empty stomach and with water (Cohen, 2022; iNova Pharmaceuticals, 2021).

As seen from Table 2-5, Duromine® is also available in South Africa; however, the drug is only available as 15 mg and 30 mg phentermine resin (iNova Pharmaceuticals, 2000). The PIL of Duromine® (South Africa), together with the South African Medicine Formulary (SAMF) and the Essential Medical (EM) Guidance, serves as the national prescribing standard for prescribing phentermine in South Africa. The SAMF and EM Guidance are respected resources that provide South African healthcare professionals with unbiased material to inform them on the reasonable selection and utilisation of medication (EM Guidance, 2021a; Rossiter, 2016:1). As such, these resources serve as adequate national guidelines for prescribing phentermine.

Lastly, phentermine is also available in South Africa, where the drug trades as Duromine®, which is available in 15 mg and 30 mg phentermine resin (iNova Pharmaceuticals, 2000). In South Africa, the drug is scheduled as an S5 controlled substance, i.e., there is a low to moderate possibility that the drug might cause abuse and dependence (iNova Pharmaceuticals, 2000; SAHPRA, 2019:8). As such, authorised prescribers, including GPs and specialists, may prescribe phentermine to patients who are medically diagnosed with obesity (see section 2.3). The supply of S5 substances is controlled, and phentermine may, therefore, only be dispensed to patients if they have a valid prescription from an authorised prescriber (SAHPRA, 2019). Schedule five substances may be prescribed for a period not exceeding six consecutive months; however, the PIL of Duromine®, South Africa, specifies that the DOT with the drug should not exceed 12 consecutive weeks or three months (Hendricks, 2017:226; iNova Pharmaceuticals, 2000; SAHPRA, 2019:8).

Therapy may be initiated in obese or overweight individuals (see section 2.3) and should be started at 15 mg of phentermine per day (Cohen, 2022; iNova Pharmaceuticals, 2000). If weight loss is < 2 kg after a four-week treatment period, the dosage should be increased to 30 mg of phentermine, administered before breakfast or seven in the morning (Cohen, 2022; iNova Pharmaceuticals, 2000). Duromine® is contraindicated in children < 12 years, as there is insufficient evidence to support the safety thereof (Cohen, 2022; iNova Pharmaceuticals, 2021;

iNova Pharmaceuticals, 2000). Should the prescriber initiate pharmacotherapy with phentermine in patients with renal impairment and the elderly, despite the use thereof not being recommended, the dosage of phentermine resin, and hydrochloride, should be adjusted accordingly (EM Guidance., 2021b; Teva Pharmaceuticals, 2020).

The phentermine dosage should be adjusted in patients with impaired renal function since insufficient drug excretion may result in toxic drug concentrations in the body (see section 2.6). Patients with a glomerular filtration rate (GFR) of ≥ 30 mL/min do not need any adjustments in their therapeutic doses (EM Guidance., 2021b; Teva Pharmaceuticals, 2020). In contrast, patients with a GFR ranging between 29 and 15 mL/min may only receive a maximum daily dose of 15 mg phentermine base, and those patients with a GFR < 15 mL/min and with end-stage renal conditions should avoid using phentermine (EM Guidance., 2021b; Teva Pharmaceuticals, 2020). Phentermine is, for this reason, not recommended to be used amongst the elderly as they are often associated with reduced renal function (Akrimax Pharmaceuticals, 2013; iNova Pharmaceuticals, 2000; KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020; UCB, Inc, 2012;).

If the prescriber chooses to prescribe phentermine in patients with renal impairment, the patient's renal function should be monitored to avoid further loss of function and toxic effects (Akrimax Pharmaceuticals, 2013; KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020). The blood pressure and glycaemic levels should also be monitored in patients with hypertension and diabetes mellitus, respectively, as phentermine influences the blood pressure and the glycaemic levels in the blood (EM Guidance., 2021b). After a defined course of therapy, ideally not longer than 12 consecutive weeks, a patient should be medically reviewed by an authorised healthcare provider. Therapy should only be continued if the patient reaches and upholds 5% of weight loss (in addition to the weight loss prior to phentermine being initiated) (iNova Pharmaceuticals, 2000; Rossiter, 2016:70). If the patient does not lose at least 2 kg over a four-week treatment period, the patient's devotion to their diet, exercise and medicine should be evaluated (Rossiter, 2016:70). The prescriber might increase the dose, discontinue the current agent or change therapy with phentermine to another drug (Rossiter, 2016:70).

Furthermore, prescribers are encouraged to adhere to these guidelines of phentermine as it eliminates potential irrational drug prescribing and associated ADRs. However, available literature shows that prescribers in the USA often prescribe phentermine off-label and expose patients to the risk associated with off-label drug prescribing. Results from the following studies support this statement.

In 1996 and 1997, Connolly *et al.* (1997:582) did a study in Rochester, Minnesota (USA), and these authors investigated the cardiovascular effects that may result from the concomitant use of phentermine with fenfluramine. As discussed in section 2.1, the phentermine/fenfluramine duo was a well-known approach to treat obesity in the 1990s, which fortunately became extinct (Li *et al.*, 2000:448). The study population consisted of 24 female participants (average BMI 35 kg/m²), which were included in the study as they, during routine evaluation, presented with several clinical problems while taking the phentermine/fenfluramine duo (Connolly *et al.*, 1997:581). The patients were aged 30-56 years and received phentermine (together with fenfluramine) in maximum doses varying from 15 mg, 30 mg, 48 mg and 60 mg per day (Connolly *et al.*, 1997:582). The minimum DOT with phentermine/fenfluramine was one month, the maximum duration was 28 months, and the average was 11 months (Connolly *et al.*, 1997:581). Regardless of the dose of fenfluramine, all 24 patients receiving phentermine/fenfluramine presented with unusual valvular diseases, a phenomenon which is not likely to be coincidental (Connolly *et al.*, 1997:588). The prescribing guidelines for phentermine in the USA specify that the drug should not be used in doses exceeding 37.5 mg phentermine hydrochloride daily and that the DOT should not exceed 12 consecutive weeks. Results from this study indicate that prescribers prescribed phentermine LT in doses exceeding 30 mg phentermine base, despite the guidelines suggesting not to do so, thereby potentially exposing these individuals to the manifestation of cardiac heart disease.

In 2009, Hendricks *et al.* (2009:1730) did a study to outline the utilisation patterns of medication used to treat obesity amongst American Bariatricians in practice. An online questionnaire was sent to the 757 members of the American Society of Bariatric Physicians (ASBP), of which only 266 (35.14%) bariatricians responded, and approximately 95% (n = 253) of the respondents indicated they use phentermine for the treatment of obesity. Of the respondents, 62% indicated they do not adhere to the BMI specifications when prescribing obesity drugs, including phentermine (Hendricks *et al.*, 2009:1732). Of those bariatricians that use phentermine, 56% do not restrict the duration of use with the drug to ST periods, but they use the drug for as long as they and the patients, seek it to be effective in achieving weight loss goals (Hendricks *et al.*, 2009:1733). These specialists prescribe phentermine in doses exceeding the maximum daily dose, which is 37.5 mg phentermine hydrochloride, with the highest average dose of phentermine being 56 mg/d (Hendricks *et al.*, 2009:1730).

Further results from this study indicated that the bariatricians commonly combine phentermine with L-5-hydroxytryptophan (5-HTP)/carbidopa to treat obesity. The FDA does not approve this drug combination; however, prescribers in the USA use it off-label LT and to treat obesity as it

causes a more significant amount of weight loss than monotherapy with phentermine (Drugs.com., 2021a; Hendricks *et al.*, 2009:1733). Retrospective chart reviews revealed that after six months of therapy with phentermine, average (SD) weight loss was approximately 16% (6.50%) of their initial body weight, and the average for those receiving phentermine with 5-HTP/carbidopa was 17% (6.6%). Regardless of its efficiency, what should cultivate concern and discomfort in such prescribers is the fact that phentermine and 5-HTP may potentially cause severe DDIs, which may result in life-threatening 5-HT syndrome (Maffei, 2021; Perez *et al.*, 2019:6; Sanchez-Ramos, 2015:137). This is because 5-HTP increases the concentration of 5-HT and phentermine may be associated with increased serotonergic activity, thereby adding to each other's effects in the body if administered simultaneously (Maffei, 2021; Perez *et al.*, 2019:6; Sanchez-Ramos, 2015:137; WebMD, 2021). Results from this study indicate that USA physicians prescribe phentermine off-label LT and together with drugs that may potentially cause DDIs, thereby exposing individuals to PDDIs, and thus, also ADRs.

Several studies have, whether purposely or as a result of their specific research objective, studied and reflected on the utilisation patterns of phentermine in practice in Korea, Mexico, Chile and Australia (Alexander *et al.*, 2011:684; Haddock *et al.*, 2000:262; Kim *et al.*, 2006:615; Márquez-Cruz *et al.*, 2021:540). These can be compared to the prescribing guidelines (see discussion above), and it can be established whether irrational drug prescribing occurs amongst prescribers in practice.

A study done by Kim *et al.* (2013:298) from 2006 to 2007 investigated the efficacy of phentermine amongst obese Korean individuals. Individuals with a BMI ≥ 25 kg/m² were included and consisted of 837 individuals who consulted 30 primary care physicians in Korea over the study period. Patients received a daily dose of 37.5 mg phentermine hydrochloride per day, and follow-up examinations were implemented after 12 weeks of pharmacotherapy with the drug (Kim *et al.*, 2013:299). There were 795 case report forms collected, i.e., study participants, of which 735 and 711 were analysed for safety and efficacy, respectively. The study participants mainly consisted of female patients aged approximately 36 years. The average BMI for women were 26.8 kg/m², and for men, it was 31.5 kg/m² (Kim *et al.*, 2013:300). Of the 711 patients that were selected for the analysis of efficacy with phentermine, 411 patients completed the 12-week treatment course with the residual of the patients discontinuing therapy with the drug. The average weight loss for the 711 patients was 5.2% of the initial body weight, thereby reducing the average BMI by 5.4%. A total of 266 patients were analysed to determine the safety profile of phentermine (Kim *et al.*, 2013:303). Of the study participants, 30% experienced side effects, of which none were adverse or serious. The most common side effects reported by patients were insomnia,

xerostomia and dizziness (Kim *et al.*, 2013:304). These results suggest that Korean clinicians adhere to the prescribing guidelines of phentermine, thereby achieving satisfactory weight loss whilst minimising ADEs.

A study by Márquez-Cruz *et al.* (2018:540) reflected on the utilisation patterns of phentermine among Mexican prescribers, although it was not the aim of the study. The study aimed to investigate the efficacy and safety of 15 mg or 30 mg phentermine amongst obese Mexican patients. The study included 932 Mexicans, all of which had a BMI ≥ 30 kg/m² and were mostly treated with 30 mg phentermine (n = 532; 57.08%) (Márquez-Cruz *et al.*, 2018:540-541). The study participants mainly consisted of female patients (n = 720; 77.25%), and all patients included in the study were > 20 years (Márquez-Cruz *et al.*, 2018:541). The efficacy and safety of phentermine therapy were assessed after three and six months. The average weight loss with 15 mg phentermine was 4.5 kg and 6.9 kg after three and six months, respectively. The average weight loss with 30 mg phentermine was 5.8 kg and 8.4 kg after three and six months, respectively. Further results of the study suggest that pharmacotherapy with phentermine for up to six months amongst obese Mexican individuals do not augment the heart rate nor the blood pressure levels, i.e., are considered safe (Márquez-Cruz *et al.*, 2018:542). Although prescribers in Mexico prescribe phentermine off-label LT, adverse effects are not likely to surface; in fact, the LT therapy with phentermine for up to six months causes more weight loss amongst obese Mexican individuals than ST pharmacotherapy with the drug.

According to literature, prescribers in Chile prefer 37.5 mg phentermine as it is the most popular dosage strength provided to patients (Cohen, 2021). The reason for this may be that the prescriber started the patient on 18.75 mg phentermine hydrochloride, the dosage was insufficient in causing the desired appetite-suppressing effect, and the prescriber upped the dosage to 37.5 mg phentermine hydrochloride daily (Cohen, 2021). No English literature is available that reflects the utilisation patterns of phentermine in Chile.

A quantitative analysis done by Haddock *et al.* (2000:262) analysed published randomised clinical trials of medication indicated for obesity and reflected on the utilisation patterns of phentermine in Australian practice. A total of nine clinical trials involving phentermine were published from 1969 to 1992 and were included for analysis (Haddock *et al.*, 2002:263). Monotherapy with phentermine versus (vs) placebo was evaluated in post-treatment outcomes. These studies revealed that a total of 32 (52.46%) patients received pharmacotherapy with phentermine, and approximately 29 (47.45%) received a placebo. Lifestyle treatment was given to 8.3% (n = 50.81) of patients (Haddock *et al.*, 2002:265). Of the 32 patients that received phentermine, 86.5% (n = 28) were female and receiving either 15 mg or 30 mg of phentermine. The average dose of

phentermine per day was 27.5 mg and did not exceed the recommended maximum daily dose of 30 mg phentermine base (Haddock *et al.*, 2002:265; iNova Pharmaceuticals, 2021). The DOT with the drug ranged from 2-24 weeks, with the average duration being 13.2 weeks. The average weight loss was 6.3 kg for the group receiving pharmacotherapy with phentermine and 2.8 kg for the placebo group (Haddock *et al.*, 2002:265). Although the DOT with phentermine exceeded 12 consecutive weeks, no systemic reports of ADEs were reported. The use of phentermine, adjacent to lifestyle treatment, resulted in significantly more weight loss when compared to the placebo group (Haddock *et al.*, 2002:265; Zhaoping *et al.*, 2005).

As previously mentioned, the use of phentermine in Australia requires a prescription from an authorised prescriber (iNova Pharmaceuticals, 2021). Literature reported that although it is not legal, phentermine can be obtained without a prescription by buying it “off the street” (Alexander *et al.*, 2011:684). As such, a 52-year-old man self-medicated with 30 mg phentermine (which he bought off the street) whilst on therapy with methadone. A DDI occurred and the patient suffered from auditory hallucinations and delusions (Alexander *et al.*, 2011:684). A casual relation between phentermine and the ADE could not be established (Zhaoping *et al.*, 2005).

To the researcher’s knowledge, the utilisation patterns of phentermine have not been studied in South Africa. Truter (2014:33), however, studied prescription appetite suppressants’ prescription patterns in South Africa for 2010 and 2011 and partially reflected on the utilisation of phentermine amongst South Africans. A total of 86 appetite suppressants were dispensed to the study population, which consisted of 58 patients receiving one or more appetite suppressants during the study period (see section 2.2 for different appetite suppressants in South Africa) (Truter, 2014:33-34). The study population mainly comprised female participants (80.03%, n = 47), and the average age was 40.02 years, with female patients, on average, younger than male patients (female: 37.98 vs male: 48.73 years) (Truter, 2014:33). Phentermine was the most frequently used appetite suppressant for the study period with 33 and 34 patients receiving phentermine in 2010 and 2011, respectively (Truter, 2014:33-34). Patients either received 15 mg or 30 mg phentermine resin, and neither phentermine nor any other appetite suppressants were used on an LT continuous basis (Truter, 2014:33-34).

Truter (2016:140) further contributes to South African literature through a study done in 2013 investigating the dispensing patterns of prescription appetite suppressants in the private healthcare sector of South Africa. The study population consisted of 27 703 patients receiving 52 555 prescription appetite suppressants in 2013 (Truter, 2016:140,142). Patients were mostly female (72.19%, n = 20 000) and aged, on average, 41.71 years (Truter, 2016:140). The findings are similar to those of Truter (2014:33) since female patients were, on average, also younger than

male patients (female: 40.02 vs male: 46.09 years) (Truter, 2016:140). Phentermine accounted for 92.44% (n = 48 581) of the total number of prescriptions dispensed for the study period, of which approximately 70% were for female participants and 0.27% (n = 130) were for individuals aged < 18 years (Truter, 2016:142). The study population, on average, received 1.90 prescriptions for 2013, implicating that prescription appetite suppressants, including phentermine, were generally not used LT (Truter, 2016:141). Since these results are not phentermine specific, it is not possible to establish whether the utilisation of phentermine in South Africa adheres to the recommended treatment guidelines provided in the PIL of Duromine® (see section 2.3). A retrospective DUR should therefore be conducted to evaluate the utilisation patterns of phentermine so irrational drug prescribing can be detected, and it can be established where a change in treatment regimens is needed to ensure optimal patient outcome (Carver *et al.*, 2020; Fanikos *et al.*, 2014:6).

2.9 Drug utilisation review

Drug utilisation reviews are the continuous, detailed, systematic approach to evaluating medication use using typical, observational standard quality-improvement techniques (Carver *et al.*, 2020; Jacob *et al.*, 2020:4095). The purpose of DURs is to improve the quality of medicine usage by evaluating and improving medicine-use procedures, as the incorrect use of medication may result in increased medical costs, ADRs and mortality among patients (Carver *et al.*, 2020; Jacob *et al.*, 2020:4095). Drug utilisation reviews further propose establishing rules for appropriate drug use, evaluating the efficacy of drug treatment, promoting the management of drug use methods, avoiding drug-associated problems and identifying the area which requires more knowledge for those who practice medicine (Jacob *et al.*, 2020:4096). Drug utilisation reviews are essential to ensure that medication is used appropriately so maximum patient outcome and adherence can be ensured (Jacob *et al.*, 2020:4095).

The main objectives of DURs are to offer the best patient care by ensuring patients receive the best medical treatment according to national and international treatment guidelines (Jacob *et al.*, 2020:4096; Scriptpharm, 2021). Traditionally, evidence-based criteria are used and applied retrospectively to establish to what degree a specific medication's use and prescribing do not adhere to the treatment guidelines (Carver *et al.*, 2020). Retrospective DURs evaluate and review the prescribing and dispensing of a particular medication after the therapy has been initiated (Carver *et al.*, 2020; Jacob *et al.*, 2020:4095). Such reviews aim to develop and execute procedures to progress medicine use, evaluate the procedure implemented, record the outcome and report the outcome to other healthcare workers (Jacob *et al.*, 2020:4096).

2.10 Chapter summary

Phentermine has been the most popular prescribed anorectic indicated for obesity since its development in 1959. The drug's relation to amphetamine and thus potential drug abuse, dependence and serious cardiovascular side effects, restricts the recommended DOT to a period not exceeding 12 consecutive weeks. Despite phentermine being an amphetamine derivative, the drug's catecholamine-releasing mechanism of action enables it not just to suppress appetite but also to cause some unwanted effects, known as side effects. Although most of these side effects are not considered severe, the combination of phentermine with other drugs that may exacerbate certain effects may become life-threatening and should therefore be avoided. Because of the drug's PK and PD properties, phentermine has many interactions and contraindications, whether with certain diseases or other medications, and they differ in severity. Prescribing guidelines are therefore included to minimise such interactions or DDIs that may lead to ADRs. Drug utilisation studies are performed to ensure that patients receive the best patient care according to the guidelines, so maximum patient adherence and outcomes can be ensured. The following chapter (chapter 3) will feature the research manuscripts and discuss the study results and findings.

CHAPTER 3: RESULTS

3.1 Introduction

This chapter presents the results and discussion of the empirical investigation objectives, which have been prepared and discussed in the format of two manuscripts. The objectives were to: 1) investigate the duration of phentermine therapy (for patients receiving 15 mg or 30 mg phentermine, respectively) on the PBM company's database for the specific study period, stratified by gender, age and prescriber, and 2) determine the prevalence of the co-prescribing of different strengths of phentermine with the top 20 drugs most frequently prescribed to long-term (LT) phentermine consumers that may potentially cause mild, moderate or severe DDIs (classified by a drug interaction checker). Manuscript one addresses the first objective, and the title is: "The duration of phentermine therapy in the private healthcare sector of South Africa: A retrospective analysis." Manuscript two presents the results and discussion of the second objective of the empirical investigation and is titled: "Potential drug-drug interactions with phentermine amongst long-term phentermine consumers: A retrospective analysis." Both manuscripts were submitted to the same peer-reviewed journal, as they complement and follow up on one another, namely the *South African Medical Journal* (SAMJ). The manuscripts were written and adhered to the requirements according to the SAMJ author guidelines. The author guidelines for the SAMJ are given in Annexure D and can be accessed via this link: <https://www.samj.org.za/index.php/samj/about/submissions>

3.2 Manuscripts

The section below provides the manuscripts that were submitted to the SAMJ. Figure 3-1 provides proof that both manuscripts were submitted to the SAMJ for peer review for possible publication and that both manuscripts were sent out to reviewers already (awaiting final journal feedback).

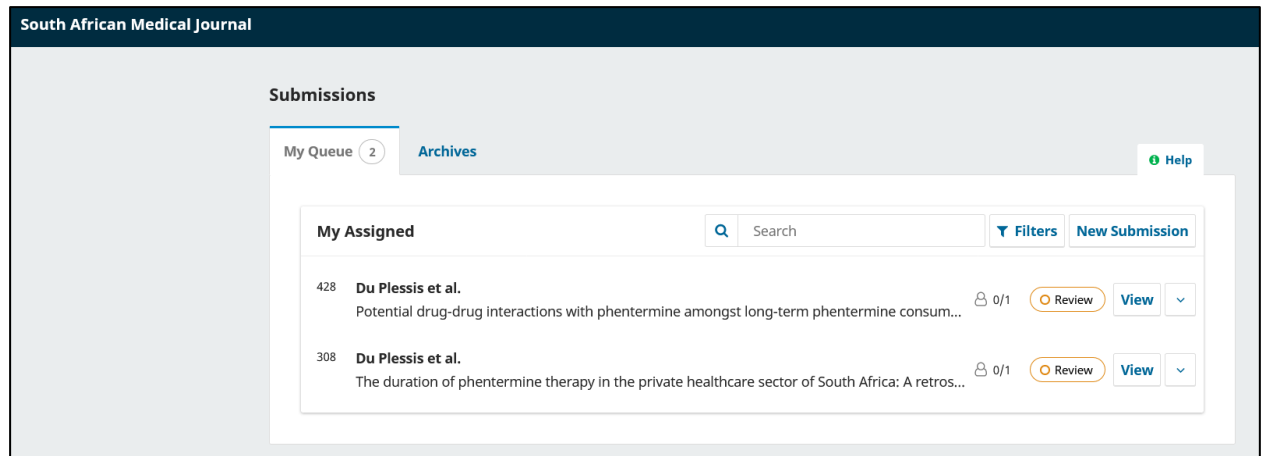


Figure 3-1: Proof of submission for manuscripts one and two

Manuscripts one and two will be discussed hereinafter.

3.2.1 Manuscript one

In this section, manuscript one is provided in the format it was submitted to the SAMJ.

The duration of phentermine therapy in the private healthcare sector of South Africa: A retrospective analysis

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Background. Phentermine is a remarkable amphetamine derivative and is globally the most frequently used appetite suppressant for the indication of obesity. The long-term (LT) use thereof (i.e., a period exceeding 12 consecutive weeks) may potentially be associated with amphetamine-like adverse effects. The Food and Drug Administration (FDA) therefore restricted the drug use to short-term (ST) use only (i.e., not longer than 12 consecutive weeks), specifically stated in the patient information leaflet (PIL). This serves as a prescribing guideline that is provided to assist both general and specialist practitioners in drug prescribing that is rational and safe, and to maximise patient outcomes and adherence. Since there were, to the researchers' knowledge, no studies done previously in South Africa that specifically provide data on the duration of phentermine use, this study was needed to determine whether the recommendations for the ST use of phentermine are reflected in the actual patterns of the duration of this drug's use.

Objective. To analyse the duration of phentermine therapy in the private healthcare sector of South Africa.

Method. A retrospective, cross-sectional drug utilisation review (DUR) was conducted by using longitudinal data from a South African pharmacy benefit management (PBM) company's medicine claims database. Paid claims for phentermine as of 1 January 2015 to 31 December 2019 were extracted for analysis. The information of the duration of the patients' phentermine therapy, their age and gender, as well as the prescriber's speciality of those patients receiving 15 mg or 30 mg phentermine, respectively, were considered and evaluated. Statistical analyses were done by using the Statistical Analysis System[®] (SAS[®]) 9.4 (SAS[®] Institute, Cary, NC).

Results. Records of 3 361 patients (paid claims for phentermine) were found on the claims database during the study period. The duration of therapy (DOT) with phentermine was analysed and results indicate that 2 472 (73.55%) patients received the drug ST, whereas the residual of the patients received the drug LT. The average (standard deviation [SD]) DOT with 15 mg and 30 mg phentermine were 57.26 (58.72) days and 67.10 (52.01) days, respectively.

Conclusion. Apart from the overall positive results of the study, indicating that phentermine is generally used ST, LT use of the drug was nevertheless detected. In the private healthcare sector of South Africa, the DOT with phentermine is therefore not restricted to ST use and some individuals may be exposed to the potentially harmful consequences accompanying LT therapy with phentermine.

INTRODUCTION

Phentermine, an exceptional amphetamine derivative, has been the most prominent appetite suppressant indicated for weight loss since its development and the Food and Drug Administration's (FDA) approval in 1959.^[1-2] Amphetamine, which has highly addictive and mood-altering properties,^[2-3] is a well-known drug of abuse. Phentermine is classified as an amphetamine derivative, since these constituents share a similar chemical structure and therefore have a similar mechanism of action.^[2,4-6] In fact, their chemical structures would have been identical, hadn't it been for the additional methyl group on the α -carbon of phentermine's chemical structure.^[7] This visually distinguishable characteristic of phentermine causes the drug to be less potent than amphetamine.^[4,7] Nevertheless, it is phentermine's connotation with amphetamine in general that raised concern that the drug might, just like amphetamine, cause severe cardiovascular effects, abuse and dependence if used long-term (LT).^[8] In this instance, long-term use describes periods exceeding 12 consecutive weeks.^[9] The reason for this is because amphetamine's addictive characteristics, potentially contributing to the LT use thereof, may correspond with elevated sympathetic nervous system (SNS) stimulation.^[2,10] Although indirectly, phentermine also stimulates the SNS and thereby causes responses typical of sympathetic nerve stimulation to arise.^[11] Substantial evidence exonerating the LT use of phentermine from such effects has not been found; thus, the duration of therapy (DOT) was restricted in 1977 and remains to be restricted to a period not exceeding 12 consecutive weeks.^[1-2] As such, the LT use of phentermine is not recommended, as specified in the patient information leaflet (PIL) provided by the FDA.^[12]

This PIL serves as a guideline for prescribing practitioners, including general practitioners (GPs) and specialists, to assist them in the rationale and safe prescribing of phentermine.^[13-14] General practitioners are the predominant prescribers, as they are the foremost point of contact for most patients requiring healthcare.^[15] As such, GPs are often the first healthcare providers to diagnose and treat obesity.^[16] They are required to refer patients with severe, complex obesity, that is, those with a body mass index (BMI) > 40 kg/m², for specialist treatment recommendations.^[16] Irrespective of whether phentermine is prescribed through a GP or a specialist, prescribing according to the guidelines will ensure that patients receive optimal medicine treatment.^[17] However, as this is only a guideline, prescribers cannot be forced to adhere to the specifications therewithin, thereby creating room for potentially irrational drug prescribing.^[18-19]

The occurrence of irrational drug prescribing may manifest in different ways, one of which is over-prescribing medication, that is, prescribing medication for a longer period than it is intended to be used for.^[20] Unfortunately, this is not an uncommon phenomenon for therapy with phentermine and the drug is often prescribed LT.^[2] Over the past few decades, many studies have reflected on the utilisation patterns of phentermine in practice.^[12,14,21-26] In countries such as the USA, Mexico and Australia, where phentermine may legally be sold, prescribers often prescribe phentermine for off-label LT use.^[12,14,25-26] These prescribers deliberately prescribe phentermine LT, thereby exposing patients to the potentially harmful consequences accompanying LT use.^[11] In other countries such as Korea, phentermine may legally be sold, but prescribers adhere to the prescribing guidelines and do, to our knowledge, not prescribe phentermine LT.^[23] Prescribing according to the prescribing guidelines eradicates obliviousness accompanying irrational drug prescribing, and maximum patient outcomes and adherence can therefore be achieved.^[18]

Truter investigated the prescribing patterns of anti-obesity preparations in South Africa.^[21-22] The results indicated that appetite suppressants in South Africa, including phentermine, are generally used ST, and it is unclear whether the DOT with phentermine exceeds 12 consecutive weeks.^[21-22] It can, therefore, not be established whether the actual DOT with phentermine reflects the

suggested ST period. Due to the lack of scientific evidence supporting its use, the South African Health Regulatory Authority (SAHPRA) does not support the off-label use of medication.^[19] Without clinical data undeniably exempting the LT use of phentermine with potentially adverse effects, it is in the best interest of the patient not to use the drug LT. Additionally, the use of phentermine amongst the elderly (i.e., those ≥ 60 years) and children (i.e., those ≤ 12 years) is also not recommended due to the lack of data supporting its use.^[22]

There are, to the researcher's knowledge, no studies done in South Africa that specifically investigate the DOT with phentermine. This study, therefore, aimed to investigate the DOT with phentermine (both the 15 mg and 30 mg preparations) in the private healthcare sector of South Africa, from 1 January 2015 to 31 December 2019, stratifying the results by gender, specific age groups, and the prescriber's speciality.

METHODS

Study design

A retrospective, cross-sectional drug utilisation review (DUR) was performed by using data from a South African pharmacy benefit management (PBM) company's database of approved and paid claims for phentermine for the study period.

Study setting and data source

The study was done in the private healthcare sector of South Africa, using longitudinal data of patient medicine claims from the PBM company's database (the company's name is protected under a confidentiality agreement). The PBM is linked to all South African pharmacies and 98% of dispensing practitioners; the data, therefore, consisted of dispensing information from all participating pharmacies across all nine provinces of South Africa. For each medication record, the following were used: data fields such as the date the prescription was filled, the number of days the drug was supplied for, the strength of the active ingredient (phentermine), the National Pharmaceutical Product Index (NAPPI) code, the age and gender of the patient (each patient had a unique number to mask their identity), and information on the prescriber's speciality.

Study population

The study population consisted of all patients on the PBM company's database who had approved and paid claims for phentermine as from 1 January 2015 to 31 December 2019. Data containing the NAPPI code 721786-006 (15 mg phentermine) and 721794-009 (30 mg phentermine) were therefore extracted for analysis. For each patient, the DOT with 15 mg or 30 mg phentermine was assessed separately and the results were stratified by gender, age, and prescriber. Patients were categorised according to gender (female or male), age in either group 1 (≤ 18 years), 2 (19-34 years), 3 (35-59 years), or 4 (≥ 60 years), and as either receiving the drug from a GP or a specialist.

Interpretation of results

Since the drug requires once-daily administration, the DOT was parallel with the total number of days the drug was supplied for within the study period (thus also taken as such for the purpose of this study).^[5] In other words, if a patient received 30 capsules containing phentermine on 20 December 2019, the DOT with the drug was only 11 days, as all dates beyond 31 December 2019 and before 1 January 2015 were considered exclusion criteria for this study.

Statistical analysis

Extracted data were imported into the Statistical Analysis System®, SAS® 9.4 (SAS® Institute Inc., 2002-2012), for analysis. A statistician from the NWU's Potchefstroom Campus assisted with the interpretation of the statistical analysis. Descriptive statistics included means and were calculated and utilised to explain data with standard deviations that were used to establish the variability within a group. Inferential statistics included the two-sample *t*-test and analysis of variance (ANOVA); these were used to compare the average of two and two or more categorical variables, respectively. Cohen's *d*-value was used to specify the effect size of the results that were statistically significant, computed as a two-sided *p*-value of 0.05, with results > 0.05 of statistical significance. A *d*-value of 0.2 indicates a small effect, 0.8 a medium effect and ≥ 0.8 a large effect of the *p*-value.

Ethical considerations

There is a formal contractual agreement between the research entity MUSA and the PBM company's board of directors, based on the fact that the research entity may utilise the company's data if used for research purposes. The permitted researchers and the Director of MUSA, as well as the statistician, signed a confidentiality agreement prior to accessing the data. Permission and informed consent were granted to use the data obtained from the database. Confidentiality and anonymity were kept throughout the study, since patient records had "dummy" member numbers depersonalising all patient information so that neither the patient nor the prescriber could be identified. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Health Sciences of the NWU, Potchefstroom Campus (NWU-00179-14-A1-11).

RESULTS

There were 3 361 patients on the PBM company's database who had approved and paid claims for phentermine over the study period. For most patients, the DOT with phentermine did not exceed 12 consecutive weeks (*n* = 2 472; 73.55%); however, there were 889 (26.45%) patients who received the drug LT (for longer than 12 consecutive weeks or 89 days).

Demographic information of the study population

Of the 3 361 patients included in the study population, most were female (*n* = 2 848; 84.74%), aged 35-59 years (*n* = 1 952; 58.08%). There were 1 419 (42.22%) patients who received pharmacotherapy with 15 mg phentermine, and the remaining 57.78% (*n* = 1 942) received 30 mg phentermine. The demographic information of the study population receiving 15 mg and 30 mg, respectively, is summarised in Table 1.

Table 1. Percentage gender and age distribution of 15 mg and 30 mg phentermine, <i>n</i> (%)			
Gender, age group	Total <i>N</i> = 3 361 (100%)	15 mg Phentermine <i>n</i> = 1 419 (42.22%)	30 mg Phentermine <i>n</i> = 1 942 (57.78%)
Female, age group (years):	2 848 (84.74)	1 224 (36.42)	1 624 (48.32)
1 (≤ 18)	43 (1.28)	32 (0.95)	11 (0.33)
2 (19-34)	1 004 (29.87)	490 (14.58)	514 (15.29)
3 (35-59)	1 636 (48.68)	627 (18.66)	1 009 (30.02)
4 (≥ 60)	165 (4.91)	75 (2.23)	90 (2.68)

Male, age group (years):			
1 (≤ 18)	513 (15.26)	195 (5.80)	318 (9.46)
2 (19-34)	14 (0.42)	8 (0.24)	6 (0.18)
3 (35-59)	156 (4.64)	70 (2.08)	86 (2.56)
4 (≥ 60)	316 (9.40)	107 (3.18)	209 (6.22)
	27 (0.80)	10 (0.30)	17 (0.50)

In this study, two groups of authorised healthcare prescribers were used for analyses according to each prescriber's speciality. Prescribers were either identified as a GP or a specialist. Results indicated that the majority of patients ($n = 3\ 000$; 89.26%) received phentermine through a GP, as opposed to the 361 (10.74%) patients who received the drug through a specialist.

Analysis of the duration of therapy with 15 mg and 30 mg phentermine, respectively

The mean (SD) DOT with 15 mg phentermine was 57.26 (58.72) days and with 30 mg phentermine, 67.10 (52.01). The two-sample *t*-test was used to detect differences in the average DOT between patients receiving 15 mg and 30 mg phentermine, respectively. Differences were detected, with a statistically longer DOT for patients receiving 30 mg phentermine compared to those receiving 15 mg phentermine ($p < 0.001$; *d*-value = 0.17). The minimum and maximum number of days for 15 mg and 30 mg phentermine, respectively, were 5-720 days for 15 mg phentermine and 1-360 days for 30 mg phentermine. The average, minimum and maximum DOT with 15 mg and 30 mg phentermine for female and male patients, the different age groups, and the prescribers are illustrated in Table 2.

Analysis of the duration of therapy with 15 mg and 30 mg phentermine according to gender

The mean (SD) DOT for female patients receiving 15 mg phentermine was 58.55 (61.29) days and for male patients 49.15 (38.08) days. The two-sample *t*-test detected differences in the average DOT between female and male patients, with a statistically longer DOT for female patients compared to male patients receiving 15 mg phentermine ($p < 0.04$; *d*-value = 0.15). Both female and male patients had a minimum DOT of five days with 15 mg phentermine, and the maximum DOT was observed amongst female patients (720 days).

Female patients receiving 30 mg phentermine (mean [SD] 68.16 [52.74] days) also had a statistically longer DOT when compared to male patients (61.64 [49.79] days) ($p < 0.03$; *d*-value = 0.12). The minimum duration with 30 mg phentermine (one day) was observed amongst male patient(s), whereas the maximum DOT of 360 days was detected amongst female patient(s).

Analysis of the duration of therapy with 15 mg and 30 mg phentermine according to different age groups

In the analysis of the DOT with 15 mg and 30 mg phentermine, patients were categorised according to their age in either age group 1 (≤ 18 years), age group 2 (19-34 years), age group 3 (35-59 years), or age group 4 (≥ 60 years). The total number of patients in each age group and receiving 15 mg or 30 mg phentermine, respectively, is given in Table 1. The average, minimum and maximum DOT with 15 mg phentermine for different age groups are presented in Table 2, and the one-way analysis of variance (ANOVA) test was used to identify differences in the average DOT between different age groups. Results indicated that there were statistically significant differences in the average DOT with 15 mg phentermine for patients in age groups 2 (49.06 [43.78] days) and 3 (62.70 [67.99] days) ($p < 0.0004$; *d*-value = 0.2). The shortest DOT with 15 mg phentermine was

five days, which was observed amongst patients in age group 2, whereas the maximum DOT was detected amongst patients in age groups 2 and 3 (720 days).

The DOT with 30 mg phentermine for patients in different age groups is also given in Table 2; the ANOVA test was also used to report differences in the average DOT amongst different age groups receiving 30 mg phentermine. The average DOT was significantly longer for patients in age group 3 (71.46 [55.37] days) when compared to patients in age group 2 (57.35 [40.00] days) ($p < 0.0001$; d -value = 0.25). There was also a statistically longer DOT therapy for patients in age group 4 (73.18 [60.03] days) when compared to patients in age group 2 ($p < 0.0001$; d -value = 0.26) (see Table 2). The minimum DOT with 30 mg phentermine was detected amongst patients in age group 3 (one day). Patients in age group 2 had a minimum DOT of 14 days, followed by those in age groups 1 and 4 (30 days). Patients in age group 3 had the longest DOT with 30 mg phentermine, which was 360 days.

Analysis of the duration of therapy with 15 mg and 30 mg phentermine according to prescribers

The average DOT for GPs prescribing 15 mg phentermine was 57.07 (55.35) days; for specialists, it was 58.31 (75.18) days. There was no significant difference in the average DOT with 15 mg phentermine for GPs and specialists ($p = 0.8$). The minimum DOT with 15 mg phentermine (five days) was detected amongst GPs, whereas specialists prescribed the drug for a minimum of seven days. General practitioners and specialists prescribed 15 mg phentermine LT with a maximum DOT of 720 days.

When the DOT with 30 mg phentermine was analysed according to the different prescribers, the average DOT for GPs was significantly longer than that of specialists ($p < 0.04$; d -value = 0.18). A specialist was responsible for the minimum DOT with 30 mg phentermine (one day). General practitioners and specialists prescribed 30 mg phentermine for longer than 12 consecutive weeks, with the maximum DOT being 360 and 330 days, respectively.

Table 2. Average, minimum and maximum duration of therapy with phentermine for male and female patients in different age groups and as prescribed by prescribers

Variable	Average duration of therapy (days), mean $\pm$ SD	Minimum duration of therapy (days)	Maximum duration of therapy (days)
15 mg Phentermine	57.26 (58.72)	5	720
Gender			
Female	58.55 (61.29)	5	720
Male	49.15 (38.08)	5	330
Age group (years)			
1 (≤ 18)	62.25 (51.01)	30	210
2 (19-34)	49.06 (43.78)	5	720
3 (35-59)	62.70 (67.99)	7	720
4 (≥ 60)	61.95 (56.30)	7	330
Prescriber's speciality			
General practitioner	57.07 (55.35)	5	720
Specialist	58.31 (75.18)	7	720
30 mg Phentermine	67.10 (52.01)	1	360
Gender			

Female	68.16 (52.74)	14	360
Male	61.64 (47.79)	1	270
Age group (years)			
1 (≤ 18)	60.00 (76.49)	30	330
2 (19-34)	57.35 (40.00)	14	240
3 (35-59)	71.46 (55.37)	1	360
4 (≥ 60)	73.18 (60.03)	30	300
Prescriber's speciality			
General practitioner	67.80 (52.08)	10	360
Specialist	58.59 (50.50)	1	330

Duration of therapy with phentermine amongst individuals younger than 12 years

Ten (0.30%) patients were 12 years old or younger and had paid claims for phentermine for the study period. Of these, seven (0.21%) patients received 15 mg phentermine, with the average DOT with the drug being 55.71 (43.92) days. The minimum DOT for patients in this category was 30 days and the maximum 120 days. The remaining three (0.09%) patients received 30 mg of phentermine and the average DOT, as well as the minimum and maximum DOT, was 30 days.

DISCUSSION

This is the first South African study to investigate the DOT with phentermine in the private healthcare sector of South Africa. The demographic information of the study population ($n = 3361$) is given in Table 1. Phentermine is available in South Africa as 15 mg and 30 mg phentermine resin and, therefore, patients on the database received either one of these product strengths.^[5] There were slightly more patients receiving 30 mg than 15 mg phentermine, with the distribution closer to 60/40 than 50/50. The average DOT for the patients who received 15 mg phentermine was 57.26 (58.72) days and for the remaining patients who received 30 mg phentermine, the average was 67.10 (52.74) days. These results indicate that the DOT with phentermine was generally ST, which is a positive finding for the authors, since the LT use of phentermine may potentially be associated with adverse effects and is therefore not advised.^[1-2] However, as previously mentioned, approximately 30% ($n = 889$; 26.45%) of the study population received phentermine LT and were therefore exposed to the potential risks associated with the LT use of phentermine.^[1-2]

For both 15 mg and 30 mg phentermine, respectively, female patients had a longer DOT compared to male patients. This might be because there were considerably more female patients in the study population (see Table 1), with the distribution of female to male patients approximately 85/15. For 15 mg phentermine, the shortest DOT (five days) could be observed amongst both female and male patients receiving the drug in this strength. For 30 mg phentermine, the shortest number of day(s) the drug was supplied for was observed amongst male patient(s). The longest DOT with 15 mg and 30 mg phentermine, respectively, was observed amongst female patients.

The study population consisted mostly of patients between 35 and 59 years (58.08%), with more than 80% of the study population between the ages of 19 and 59 years. For those patients receiving 15 mg phentermine, patients in age group 3 generally had the longest DOT, followed by those in age groups 1, 4 and 2. Patients in age group 3 had a significantly longer DOT compared to patients in age group 2. There were no significant differences in the DOT amongst other age groups receiving 15 mg phentermine. For those patients receiving 30 mg phentermine, patients in age group 4 had the longest average DOT, followed by those in age groups 3 and 1. Patients in age

groups 3 and 4 had significantly longer DOT with 30 mg phentermine compared to patients in age group 2.

Moreover, despite the fact that the use of phentermine is not recommended for children ≤ 12 years and the elderly (≥ 60 years), there were patients in these categories receiving therapy, both ST and LT, with the drug.^[5] The use of phentermine amongst such individuals is not recommended, as there are no data supporting the safety thereof.^[5] Additionally, elderly individuals are often associated with renal impairment, which suggests that phentermine might not be excreted from the body adequately; this may possibly result in toxic side effects.^[5,27-31] Children ≤ 12 years received LT therapy with 15 mg phentermine for a maximum of 120 days, whereas the LT use of both 15 mg and 30 mg phentermine was detected amongst the elderly. Not only is the use of phentermine amongst such individuals classified as risky, but they were also exposed to the potentially severe consequences accompanying the LT use of phentermine.^[1-2,19]

Two groups of prescribing practitioners were used to analyse the DOT with phentermine according to the prescriber's speciality. There was no statistically significant difference in the DOT with phentermine as prescribed by a GP or a specialist. Notably, our analyses indicated that prescribers in both these categories prescribed phentermine for periods exceeding 12 consecutive weeks and had a maximum DOT of 720 days. This can be considered as irrational drug prescribing, since the safety of the LT use of phentermine has not yet been established.^[4,20,30] There were 817 and 72 patients who received LT therapy with phentermine from a GP and a specialist, respectively. It can be expected that the majority of the patients would receive therapy with phentermine through a GP, since prescribing practitioners in general practice are typically the first prescribers to diagnose and initiate pharmacotherapy for the treatment of obesity.^[15-16] As such, it can also be expected that GPs would mostly be responsible for LT therapy with phentermine when compared to specialists.

Lastly, the general ST use of phentermine, as well as the fluctuations in the number of days it was supplied for, deserves discussion. As seen from the results in Table 2, the patient(s) received 30 mg phentermine for one day. Some patient(s) received phentermine for five, seven, ten or 14 days. The reason for this relatively short DOT with the drug is not known. Prescribers are advised to evaluate response to therapy only after a four-week course of treatment.^[4] However, as these numbers are only a reflection of the quantities dispensed and not the actual quantities prescribed, it is impossible to establish whether irrational drug prescribing occurred.

Study limitations

There were certain limitations to this study. First, the study population included patients who had approved and paid claims for phentermine and excluded patients who had paid cash for the drug. Therefore, the number of patients receiving phentermine for the study period could not be precise. Second, inaccuracy regarding the actual DOT with phentermine may have surfaced, since the dispensing information of the drug was analysed and not the actual consumption patterns. Finally, the DOT with the drug may have been miscalculated further, since the data were limited to the patients on the database for the specific study period, and clinical history and follow-up data were not available.

CONCLUSION

Phentermine is South Africa's number one appetite suppressant indicated and used for the management of obesity.^[5,14,21] It is recommended that the DOT with the drug be limited to a period not longer than 12 consecutive weeks.^[5] The reason for this is that the LT use of the drug might,

theoretically, cause severe side effects.^[1-2] Therefore, the drug is indicated for the ST management of obesity, as ST use has been proven safe, effective and without severe side effects.^[4-5,23] Fortunately, these results indicate that prescribing practitioners in the private healthcare sector of South Africa generally prescribed phentermine for ST use (ST:LT - 3:1). Unfortunately, the LT use of the drug was also detected amongst these individuals, thereby exposing them to the potential risks associated with LT use. Results also indicate that phentermine was used amongst individuals ≤ 12 years, as well as the elderly, despite the use thereof not being recommended for them.^[5] Additionally, some of these individuals were also exposed to the potential adverse effects associated with LT therapy of phentermine. This causes concerns as to why prescribing practitioners would put these individuals at risk of possibly experiencing adverse effects associated with the LT use of phentermine. It also constructs the question of whether the benefit of using the drug LT in such individuals outweighed the risk and whether the prescribing practitioner did a benefit-to-risk analysis before initiating phentermine. These are factors that require further investigation.

It can thus be concluded that individuals in the private healthcare sector of South Africa generally receive pharmacotherapy with phentermine on an ST basis. However, some patients receive LT phentermine therapy and are therefore exposed to the potentially adverse effects accompanying it. Pharmacotherapy with phentermine for individuals in the private healthcare sector of South Africa is, therefore, not restricted to ST periods only. Additionally, phentermine therapy is not restricted to a specific age group and can even be seen amongst individuals ≤ 12 years. Prescribing practitioners should be reminded of the potentially harmful effect of LT therapy with phentermine and the use of the drug amongst certain age groups. They should also be reminded that a benefit-to-risk ratio should precede pharmacotherapy with phentermine (and any drug, for that matter), as it assists with rational and safe prescribing of a drug.

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Manuscript two will be discussed hereinafter.

3.2.2 Manuscript two

This section provides the SAMJ submitted version of manuscript two.

Potential drug-drug interactions with phentermine amongst long-term phentermine consumers: A retrospective analysis

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Background. Phentermine is an internationally recognised amphetamine derivative with significant appetite suppressing properties. The drug is indicated for the short-term management of obesity, as the long-term (LT) use of phentermine may potentially be associated with severe cardiovascular side effects, abuse and dependence. The LT use hereinafter describes periods exceeding 12 consecutive weeks. This use may also be associated with potential drug-drug interactions (PDDI), which may result in adverse drug reactions (ADRs). Literature reported that phentermine is often prescribed LT and for several other off-label indications, increasing the risk for individuals to experience adverse drug events (ADEs) and drug-drug interactions (DDIs). There is, to our knowledge, no South African studies investigating the prevalence of co-prescribing LT phentermine with drugs that may potentially cause DDIs.

Objective. To determine the prevalence of mild, moderate and severe DDIs with phentermine use when the duration of therapy in private healthcare exceeded 12 consecutive weeks

Methods. A cross-sectional drug utilisation review (DUR) was done by using data obtained from a South African pharmacy benefit management (PBM) company's database. Retrospective data of medicine claims for phentermine, from 1 January 2015 to 31 December 2019, were extracted for analysis. The number of days phentermine was supplied was used to identify the study population, in other words, those patients who received the drug LT. A drug interaction checker (Drugs.com) was used to identify potential mild, moderate and severe DDIs when using phentermine and co-prescribed drugs concurrently.

Results. A total of 889 patients received phentermine LT. The top 20 drugs identified as being frequently co-prescribed in this study population demonstrated no mild PDDI, 15 (75%) moderate PDDIs and five (25%) severe PDDIs. The most common co-prescribed drug in the moderate group was dextromethorphan (n = 282; 31.72%) and the least co-prescribed one was formoterol (n = 52; 5.85%). Amongst the drug group "severe PDDIs", tramadol (n = 416; 46.79%) was most frequently prescribed, whereas phenylpropanolamine (6.76%) was the least prescribed to patients in this group.

Conclusion. There are patients who receive LT phentermine therapy despite the potential severe consequences that may result. These patients may receive concomitant therapy with phentermine and other pharmaceutical constituents, which may potentially cause DDIs, more specifically, moderate and severe DDIs. As such, these patients are not only confronted with the consequences of DDIs, but are also at risk to experience ADRs as the residual effect of PDDIs.

INTRODUCTION

Phentermine, an extraordinary amphetamine derivate, is South Africa's most popular prescription-only anti-obesity medication used for its appetite suppressing properties.^[1-4] The drug stimulates the central nervous system (CNS), inhibiting the reuptake and stimulating the release of endogenous neurotransmitters, including dopamine (DA), serotonin (5-HT) and norepinephrine (NE).^[5-7] Consequently, there is an increase in the concentration of these neurotransmitters in the CNS and stimulatory effects.^[5-6] In the brain, the increased DA concentration will provide a constant DA-induced feeling/sensation of reward (associated with eating), which will result in appetite suppression.^[6,8] Persistent 5-HT neurotransmission in the brain may also result in appetite suppression; however, these effects are only achieved at doses higher than the recommended maximum daily dosage, that is, > 30 mg phentermine.^[9-10] Once NE is released, the hormone cascade of the hypothalamus-pituitary axis (HPA) is activated via the amygdala of the brain.^[11-13] Signals are transmitted from the amygdala to the hypothalamus, then to the pituitary gland, and finally to the adrenal cortex, positioned on top of the kidneys.^[13-14] As a result, DA, NE and epinephrine are released into the bloodstream, where they will bind to adrenergic receptors (α and β receptors) of fat tissue and smooth muscles.^[14-15]

The stimulatory effects of DA and NE will enhance the breakdown of fat tissue, consequently resulting in weight loss.^[15-17] Epinephrine will result in increased blood glucose concentrations, the individual will feel satiated and the appetite is suppressed.^[11,16-17] Unfortunately, the effects of these catecholamines are not limited to the above-mentioned desired effects, as these hormones bind to multiple adrenergic receptors located throughout the body.^[18] As such, an individual may experience some undesired effects, also known as side effects.^[18-19] Fortunately, the most common side effects of phentermine are dry mouth and insomnia,^[20,21] as phentermine is generally used short-term (ST),^[3,22] in other words, not longer than 12 consecutive weeks.^[23] It is recommended that phentermine not be used for longer than 12 consecutive weeks (hereinafter referred to as long-term [LT]), as the LT use (off-label indication for the drug) may be associated with severe cardiovascular side effects, abuse, and dependence.^[24-25] The increase in the blood concentration of DA and NE will also increase the stimulatory effects of the heart,^[16-17,26-27] kidneys,^[16-17] and blood vessels,^[26-27] which may result in heart rate irregularities (tachycardia, arrhythmias, and palpitations) and hypertension.^[24,28-32] The increase in the stimulatory effects of the CNS may also result in drug abuse, dependence^[24,29] and seizures,^[24] or trigger DA-induced hallucinations or episodes of psychosis.^[17-24] The LT use of phentermine may, theoretically, cause significant harm to patients; the United State's Food and Drug Administration (FDA), therefore, restricted the duration of this medicine's use to ST use.^[4,24]

The LT use of phentermine is permitted, provided the drug is administered as the FDA-approved, fixed-dose combination phentermine/topiramate.^[33] This is also the only instance in which phentermine may be combined with other pharmaceutical preparations for the treatment of obesity.^[33-34] The success of this drug combination can be attributed to a moderate drug-drug interaction (DDI) between phentermine and topiramate.^[29] Moderate DDIs are classified as such,

since they may cause distinctively infuriating, stressful or intolerable ADRs amongst individuals.^[35] Topiramate is an anti-epileptic that can, in its own capacity, induce weight loss and if administered together with phentermine, increase the plasma concentration thereof and thus also the efficacy.^[29,34,36] However, as it increases the plasma concentration of phentermine, it may also increase the adverse effects thereof, such as tachycardia, increased blood pressure levels, and palpitations.^[36] Evidently, no matter how successful this combination may be, there are risks associated with it that may potentially be harmful to individuals. This drug combination is not available in South Africa.

Not all DDIs are as beneficial as the use of phentermine/topiramate and some may, depending on the severity, cause significant harm to individuals.^[37] Consequently, not only is the LT use of phentermine not recommended, but also the simultaneous use of phentermine with drugs that may potentially cause mild, moderate or severe DDIs.^[24,36] The patient information leaflet (PIL) of the drug warns against the simultaneous use of phentermine with other pharmaceutical preparations, including sympathomimetics, selective serotonin reuptake inhibitors (SSRIs), oral hypoglycaemic preparations, and antihypertensive and epileptogenic agents, as the simultaneous use thereof may result in DDIs and thus ADRs.^[24,36] Unfortunately, it is not uncommon for phentermine to be administered concurrently with preparations intended to lower blood glucose and blood pressure levels, as the drug is indicated for the treatment of obesity, which is commonly associated with diabetes and/or cardiovascular diseases such as hypertension.^[24, 38] Additionally, it is likely for phentermine to be used LT and in combination with pharmaceutical preparations that may cause DDIs.^[25] There is, to our knowledge, no South African study investigating the prevalence of PDDIs amongst patients receiving LT therapy with phentermine. The objective of this study was, therefore, to determine the prevalence of potentially mild, moderate and severe DDIs with phentermine when the duration of therapy (DOT) in the private healthcare sector of South Africa exceeded 12 consecutive weeks.

METHODS

Study design

A descriptive, retrospective, quantitative drug utilisation review (DUR) study design was used, making use of longitudinal patient medicine claims data from a South African pharmacy benefit management (PBM) company's database.

Study setting and data source

The study was conducted in the private healthcare sector of South Africa, using approved and paid medicine claims data for phentermine from 1 January 2015 to 31 December 2019. The data comprised dispensing information from all South African pharmacies across all the provinces in South Africa, as the PBM is linked to all pharmacies in South Africa and 98% of dispensing practitioners. The data fields from all patient records used included the date the prescription was issued, the number of days the drug was provided for, the information on the dispensed product (including the active ingredient), the National Pharmaceutical Product Index (NAPPI) code, and the gender and age of the patient. Each patient medication record was assigned a random number to mask the identity of the patient.

Study population

The study population comprised all patients on the PBM company's database who received phentermine LT from 1 January 2015 to 31 December 2019. A grace period of five days was given for early/late collection of prescriptions. Data comprising the NAPPI codes 721786-006 (15 mg

phentermine) and 721794-009 (30 mg phentermine) were analysed. Information on the gender and age was used to interpret the demographic results of patients receiving LT therapy with phentermine. Based on their gender, patients were considered either female or male.

Data analysis

The data were analysed by the director of Medicine Usage in South Africa (MUSA), Faculty of Health Sciences of the North-West University (NWU), Potchefstroom Campus, South Africa. Descriptive statistics were used to explain and interpret the data spread and included frequencies and percentages. The frequency and percentage were used to numerise the demographic information of those patients receiving phentermine LT. A list of drugs co-prescribed to patients receiving phentermine LT was also extracted for analysis. A drug interaction checker from Drugs.com was used to identify the drugs that may potentially cause a mild, moderate or severe DDI when co-prescribed with phentermine.^[36] The top 20 drugs that may cause PDDIs and are most frequently prescribed to patients receiving phentermine LT were listed accordingly. The potential ADRs that may occur between such DDIs were also listed.

Ethical considerations

Through a contractual agreement, the PBM company's board of directors consented to the research entity MUSA to access and use their database if the data are intended for research purposes. As such, the researchers are permitted, through the PBM company's consent, to use the company's data for this study. A confidentiality agreement was signed by the researchers involved and the Director of MUSA prior to gaining access to the database. The PBM company's name was, therefore, not disclosed throughout the study in order to ensure that confidentiality and anonymity are maintained. All patient records were de-identified, that is, any personal information of the patients, medical schemes or prescribers were depersonalised prior to the researchers accessing the database. Each patient record was, therefore, assigned a random "dummy" member number; this ensured that confidentiality and anonymity were maintained throughout the study. The Health Research Ethics Committee of the Faculty of Health Sciences of the NWU, Potchefstroom Campus, granted ethical approval to conduct the study (NWU-00179-14-A1-11).

RESULTS

The study population consisted of 889 patients on the medicine claims database who received LT therapy with phentermine during the study period. Of these patients, most were female 775 (87.18%) and aged 35-59 years (n = 602; 67.72%). The top 20 drugs that were most commonly co-prescribed with phentermine, which may potentially have caused a DDI amongst these LT phentermine consumers, are summarised in Table 1. The drugs are listed in descending order according to the number of people who received the respective co-prescribed drugs. The table also gives the ADRs that may have resulted from a PDDI between phentermine and the relevant co-prescribed drugs.

Table 1. Frequency of potential drug-drug interactions between phentermine and co-prescribed drugs

Active ingredient	Frequency (n), %	Severity of drug-drug interaction	Adverse drug reaction
Tramadol	416 (46.79)	Severe	Seizures
Dextromethorphan	282 (31.72)	Moderate	Serotonin syndrome

Ephedrine	232 (26.10)	Moderate	Hypertension, tachycardia
Salbutamol	196 (22.05)	Moderate	Hypertension, heart rate irregularities
Metformin	185 (20.81)	Moderate	Hypoglycaemia
Amitriptyline	177 (19.91)	Moderate	Hypertension, arrhythmias, tachycardia
Phenylephrine	152 (17.10)	Moderate	Hypertension, tachycardia
Levothyroxine	132 (14.85)	Moderate	Cardiac insufficiency (tachycardia, arrhythmias, palpitations)
Pseudoephedrine	126 (14.17)	Moderate	Hypertension, tachycardia
Thyroxine	118 (13.27)	Moderate	Cardiac insufficiency (tachycardia, arrhythmias, palpitations)
Escitalopram	99 (11.14)	Severe	Serotonin syndrome
Promethazine	94 (10.57)	Moderate	Psychosis, arrhythmias
Preparations containing alcohol	94 (10.57)	Moderate	Cardiovascular side-effects, including tachycardia
Fluoxetine	81 (9.11)	Severe	Serotonin syndrome
Salmeterol	77 (8.66)	Moderate	Hypertension, heart rate irregularities
Sertraline	75 (8.44)	Severe	Serotonin syndrome
Prochlorperazine	71 (7.99)	Moderate	Psychosis, arrhythmias
Phenylpropanolamine	69 (7.76)	Severe	Life-threatening cardiac complications (pulmonary hypertension)
Topiramate	65 (7.31)	Moderate	Hypertension, tachycardia, palpitations

Formoterol	52 (5.85)	Moderate	Hypertension, heart rate irregularities
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As seen from the results in Table 1, there were 15 (75%) drugs which may potentially have caused a moderate DDI with phentermine. The remainder of the drugs (n = 5; 25%) may potentially have caused a severe DDI.

The prevalence of potential drug-drug interactions with phentermine amongst patients receiving the drug long-term

The data were analysed to determine the prevalence of co-prescribing of phentermine with drugs that may potentially cause mild, moderate, and severe DDIs amongst patients receiving phentermine LT.

Prevalence of potentially mild drug-drug interaction

According to the data, there were no PDDIs that were mild to severe amongst the patients receiving phentermine LT.

Prevalence of potentially moderate drug-drug interactions

Results indicated that dextromethorphan (n = 282; 31.72%) was the drug most frequently prescribed to patients receiving phentermine LT that may potentially have caused moderate DDIs. Thereafter, ephedrine (n = 232; 26.10%) was most frequently prescribed, followed by salbutamol (n = 196; 22.05%) and metformin (n = 185; 20.81%). The drug that was least prescribed to patients in this group was formoterol (n = 52; 5.85%). Other drugs co-prescribed with phentermine that may potentially have caused moderate DDIs are given in Table 1.

Prevalence of potentially severe drug-drug interactions

The most common drug prescribed together with phentermine was tramadol, which means that 46.79% (n = 416) of patients receiving phentermine LT potentially experienced severe DDIs with tramadol. The second drug was escitalopram (n = 99; 11.14%), followed by fluoxetine (n = 81; 9.11%) and sertraline (n = 75; 8.44%). Phenylpropanolamine was the drug least prescribed to patients (n = 69; 7.76%) in this category.

DISCUSSION

This is the first South African study to investigate the prevalence of PDDIs with phentermine when the recommended DOT exceeded 12 consecutive weeks. The study revealed that a total of 889 patients from the private healthcare sector in South Africa received phentermine LT. In other words, from 1 January 2015 to 31 December 2019, there were 889 patients on the database who received phentermine LT despite the use thereof not being recommended.^[24] The LT use of phentermine is not advised, since there are no data supporting its use and it may potentially be associated with severe cardiovascular side effects (including tachycardia and hypertension), abuse, and dependence.^[20-25] Drug-drug interactions may also occur amongst patients who receive the drug LT, thereby increasing the risk for ADRs to occur.^[25]

Analysis of the top 20 drugs that were co-prescribed with phentermine and may potentially have caused a DDI indicates that these drugs may potentially have caused moderate and severe DDIs. There were no drugs co-prescribed with phentermine that may potentially have caused mild DDIs (e.g., evening primrose). It may thus be deduced that patients receiving LT therapy with phentermine may potentially have experienced moderate and severe DDIs.

The drugs co-prescribed with phentermine that may possibly have caused moderate DDIs are listed in Table 1. There were 282 (31.72%) patients who received phentermine together with the opium alkaloid,^[4] dextromethorphan, which is used as a cough suppressant and is a weak 5-HT reuptake inhibitor.^[4,36] As previously discussed, phentermine may also increase 5-HT concentration in the CNS.^[9-10] Therefore, if administered together, phentermine may potentiate the effects of dextromethorphan, thereby potentially causing a moderate DDI.^[36] Consequently, excessive nerve cell activity and life-threatening symptoms (e.g., high blood pressure and temperature) may surface, a condition also known as serotonin syndrome (5-HT syndrome).^[7,9,20,39-40] As such, these patients receiving LT therapy with phentermine may potentially have experienced 5-HT syndrome as the residual effect of a moderate DDI between phentermine and dextromethorphan.

Phentermine may potentially cause a moderate DDI with ephedrine, pseudoephedrine and phenylephrine as well. Pseudoephedrine and phenylephrine are used as systemic decongestions, whereas ephedrine is used as a pressor agent for low blood pressure (hypotension).^[4] These agents, as with phentermine, stimulate adrenergic receptors in the body and, if administered together, phentermine can potentiate the adrenergic response to these agents.^[4,36] As such, these drugs will add to the stimulatory effects of the heart, kidneys and blood vessels, which will further increase the blood pressure levels and heart rate.^[36] Patients may, therefore, experience hypertension and tachycardia (increased heart rate) as the result of PDDIs between phentermine and these agents.^[36] Phentermine may also potentiate the adrenergic response to salbutamol, salmeterol and formoterol. These agents stimulate adrenergic receptors too and are indicated for the treatment of asthma and chronic obstructive pulmonary disease.^[4] Therefore, those patients who received phentermine together with salbutamol (n = 196; 22.05%), salmeterol (n = 77; 8.66%), or formoterol (n = 52; 5.85) may potentially have experienced hypertension and/or heart rate irregularities.^[16]

Approximately 21% of patients who received phentermine LT also received metformin, a biguanide designed to lower the blood glucose levels.^[4] Metformin is indicated for the treatment of obesity amongst diabetic individuals, as it provokes mild anorexia and, therefore, assists in controlling weight gain.^[4] As previously discussed, phentermine increases the concentration of NE in the bloodstream and consequently also the blood glucose levels.^[15,27] As such, these constituents oppose each other's mechanism of action, thereby potentially causing a moderate DDI. However, this is not the mechanism through which the ADR, hypoglycaemia, occurs.^[36] Phentermine initially causes an increase in the blood glucose levels, resulting in appetite suppression and consequently also weight loss.^[15-16,27] Weight loss may have an impact on glycaemic control, as it lowers blood glucose levels.^[36] Therefore, since metformin and phentermine lower the blood glucose levels and the last-mentioned medicine causes weight loss, administering these drugs together may have additive effects that may potentially result in hypoglycaemia.^[15] In this instance, hypoglycaemia may commonly present with adrenergic neurogenic signs and symptoms such as anxiety, tremors and palpitations.^[41]

Moreover, the use of phentermine together with amitriptyline, a tricyclic antidepressant, may cause moderate DDIs that may potentially result in hypertension, arrhythmias and/or tachycardia.^[4,36] Amitriptyline is indicated for the management of depressive disorders and the drug acts by inhibiting the reuptake of NE.^[4,36] Consequently, administering phentermine together with this pharmaceutical constituent may further increase the concentration and stimulatory effects of NE, because phentermine (as previously discussed) also increases NE concentration.^[10,36,42] Therefore, those patients who received these two agents simultaneously (n = 177; 19.91%) may potentially have experienced above-mentioned ADRs as the residual effect of potentially moderate DDIs.

The thyroid hormones, levothyroxine and thyroxine, are indicated for hypothyroidism, a medical disease in which the thyroid hormone produces insufficient amounts of the hormone thyroxine.^[4,43] The thyroid gland co-operates with the adrenal glands to release NE into the bloodstream in order to ensure that the body's metabolism works sufficiently.^[44-45] Administration of these thyroid hormones will stimulate the adrenal gland to release NE into the bloodstream and administering phentermine together with these hormones will have additive effects.^[46] The net result will be excessive concentrations of NE in the bloodstream, which may potentially result in cardiovascular side effects such as tachycardia, arrhythmias and palpitations.^[46] Phentermine may also cause a moderate DDI with preparations containing alcohol, as alcohol potentiates the central nervous system (CNS) and cardiovascular effects of phentermine.^[36]

There were 94 (10.57%) and 71 (7.99%) patients receiving phentermine together with promethazine and prochlorperazine, respectively. These pharmaceutical agents are indicated, amongst other indications, for the treatment of nausea and vomiting.^[4,36] Promethazine and prochlorperazine supposedly oppose the dopaminergic activity of phentermine, which may reduce the weight reducing properties of the drug.^[36] Phentermine is expected to reduce the neuroleptic efficacy and potentiate the arrhythmogenicity of these agents, which may cause psychosis and arrhythmias, respectively.^[36] Additionally, phentermine may also exacerbate pre-existing symptoms of psychosis.^[36] As such, the mechanism of the PDDI is based on the fact that these agents may oppose the pharmacological effects of phentermine and vice versa.

Lastly, 65 (7.31%) patients received phentermine together with the anti-epileptic, topiramate, and may, therefore, have experienced moderate DDIs. The combination phentermine/topiramate was approved by the FDA in 2012 for the LT management of obesity, as these constituents have proven to cause significantly more weight loss when combined than when each agent is used individually as monotherapy.^[33,47-48] The precise mechanism of interaction between phentermine and topiramate has not been determined yet; however, it is known that topiramate increases the plasma concentration of phentermine and, therefore, also its efficacy.^[15] It is also known that weight loss is a common side effect of topiramate, thereby adding to phentermine's weight reducing effects if the two are administered simultaneously.^[33] Individuals may also experience more intense adverse effects caused by the increased plasma concentration of phentermine, for example tachycardia, increased blood pressure levels and palpitations.^[36] Nevertheless, the FDA has approved this drug combination, phentermine/topiramate, as it has been proven to be safe and effective.^[48] Regrettably, this combination is not available in South Africa yet.^[34]

Furthermore, patients receiving LT therapy with phentermine also received drugs that may potentially have caused severe DDIs with phentermine (see Table 1). Approximately 50% (n = 416; 46.79%) of patients in the study population potentially experienced severe DDIs with phentermine and tramadol. Tramadol is indicated for the management of moderate and severe pain and acts by inhibiting the reuptake of 5-HT.^[4] The use of phentermine and tramadol is not recommended since phentermine can lower the threshold for convulsions and tramadol may sometimes cause seizures.^[34,36] The combination of these epileptogenic agents may have additive effects, potentially causing a medical emergency and causing significant harm to an individual.^[29-51]

The PIL of phentermine warns explicitly against the simultaneous use of the drug with SSRIs, as these drugs inhibit serotonin metabolism and may be associated with cardiac valvular disease.^[24] The drugs are mainly indicated for depressive disorders,^[4] and there were 99 (11.14%), 81 (9.11%) and 75 (8.44%) patients receiving phentermine together with escitalopram, fluoxetine, and

sertraline, respectively. The combination of phentermine with SSRIs may result in 5-HT syndrome and should be avoided, given the severity thereof.^[36,40]

As seen from Table 1, the simultaneous use of phentermine with phenylpropanolamine may result in life-threatening complications too.^[29,36] In a case-control epidemiological study, the use of anorexigenic agents such as phenylpropanolamine and phentermine may be correlated with a greater risk for pulmonary hypertension.^[36] Therefore, if these agents were to be used simultaneously, they would add to the effects of one another on the cardiovascular system, which may potentially cause life-threatening cardiac complications.^[36,52] Evidently, given the severity of the potential ADRs that may result from these PDDI, such interactions require instant medical attention and a change in therapeutical regimens.^[53]

CONCLUSION

Phentermine is the most frequently used anorexigenic appetite suppressant in South Africa and the drug's popularity can be owed to the judicious use thereof.^[20,22-23] The DOT with the drug was restricted in 1977 to short-term use only, as there were concerns that the LT use of phentermine may be associated with severe cardiovascular side effects.^[1,49] To this day, the DOT with phentermine remains to be restricted to periods not surpassing 12 consecutive weeks, as no evidence has been provided to support the safety and effectiveness of LT therapy.^[1,49] Nonetheless, the results from this study indicate that prescribers in the private healthcare sector of South Africa prescribe phentermine off-label LT despite the potentially severe consequences thereof. The results also indicate that these prescribers combine LT therapy with phentermine with other drugs such as SSRIs, despite the PIL advising against such.^[24] The PIL of phentermine specifically warns against such a drug combination, as these drugs may affect one another's effects in the body, thereby causing PDDIs and ADRs that may harm individuals.^[24,50] It is evident from the study results that the patients who received LT therapy with phentermine were also at risk to experience other potentially moderate and severe DDIs, and as one can see from Table 1, the potential ADRs that may have occurred from these PDDIs seem rather severe. This raises the following concern: Why would prescribers put their patients at risk to potentially experience such ADEs? It also raises the question of whether a proper benefit-to-risk analysis was done prior to initiating pharmacotherapy with phentermine. These aspects deserve further investigation.

To conclude, patients receiving LT therapy with phentermine in the private healthcare sector of South Africa are at risk to experience moderate to severe DDIs. The ADRs that may occur from these PDDIs are rather serious and may be harmful to the patients involved. Prescribers should be more vigilant in the co-prescribing of phentermine with other drugs that may potentially cause DDIs. These prescribers should also be made aware of the label indications of phentermine, as they are provided to assist in the rational and safe prescribing of the drug so that DDIs and ADRs can be prevented.

Study limitations

This study is not without limitations. Firstly, this study only included approved and paid claims for phentermine and excluded cash paid claims; therefore, the actual number of patients in the study population could not be accurate. Secondly, the total number of patients receiving phentermine LT could potentially be miscalculated, since the analysis of the duration of use was limited to the study period and the number of patients in the database. The above-mentioned is also applicable to the prevalence of PDDIs with phentermine. Only one drug interaction checker was used to identify drugs that may potentially cause DDIs with phentermine; therefore, other PDDIs could possibly have existed. The study investigated the prevalence of PDDIs, and it could,

therefore, not be known for sure if the patients actually experienced a DDI. Furthermore, the data reflected the dispensing information of phentermine; the actual consumption patterns of the drug could thus not be known for sure, as there was no evidence that these patients in fact consumed the phentermine. Lastly, the analyses were done with the understanding that the data obtained from the PBM company's database were precise and reliable.

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3.2.3 Statements

Both the manuscripts and dissertation were prepared by the researcher, Ms A Fourie. The dissertation's supervisor (Dr JM du Plessis) and co-supervisors (Dr M Julyan and Ms CS Mostert) assessed and reviewed the writing of the manuscripts as well as the dissertation. Prof MS Lubbe analysed the data according to the data analysis plan (see Annexure A: Data analysis plan). Ms M Cockeran assisted with the statistical analysis and interpretation.

3.3 Chapter summary

The results of the empirical investigation were provided and discussed in an article format in the manuscripts above. Chapter 4 will consist of the overall conclusion of the study and recommendations for potential future research. The limitations and strengths of the study will also be provided.

CHAPTER 4: CONCLUSIONS, RECOMMENDATIONS AND LIMITATIONS

4.1 Introduction

This study, retrospectively, analysed the prescribing patterns of phentermine in the private healthcare sector of South Africa. It specifically investigated the duration of therapy (DOT) with phentermine and quantified the prevalence of potential drug-drug interactions (PDDIs) amongst long-term (LT) phentermine consumers. Data obtained/derived/collected from a pharmacy benefit management (PBM) company's database was used and included paid and medicines claims for phentermine from 1 January 2015 to 31 December 2019. The conclusions and the recommendations regarding this study will be discussed hereafter.

4.2 Conclusions based on research objectives

The conclusions of the dissertation are construed based on the findings of the literature review objectives and the results of the empirical investigation objectives. These conclusions will be discussed in sections 4.2.1 and 4.2.2 respectively.

4.2.1 Literature review objectives

The literature review objectives are presented one at a time in bullet format, followed by the conclusions made from each individual objective.

- **To present an overview on the background, pharmacological classification, therapeutic indication, contraindications and drug-drug interactions of phentermine.**

Since the discovery of phentermine, the drug has been the most popular appetite suppressant prescribed for the indication of obesity (Bazmi *et al.*, 2017:32; Haslam, 2016:208; Hendricks, 2017:226). There were speculations back in 1962 that the drug, being related to amphetamine, has the potential to cause dependence and severe cardiovascular side effects, if it is used for longer than 12 consecutive weeks; however, that is unlikely (Hendricks *et al.*, 2014:297; Lewis *et al.*, 2019:601). Unfortunately, to date no sufficient evidence has been provided to undeniably exempt phentermine from the supposed severe side effects and the DOT with the drug remains to be restricted to short-term (ST) use (Haslam, 2016:209; Hendricks, 2017:226).

Over the past few decades, many attempts have been made to combine phentermine with other drugs to treat obesity. Some of these attempted combinations have put patients at great risk to experience adverse drug events (ADEs), such as the combination of phentermine with: fenfluramine, dexfenfluramine and lorcaserin (Food and Drug Administration (FDA), 2020; Giovanni *et al.*, 2020:1; Leroy, 2017; Roig, 2016; Li *et al.*, 2003:448; Wellman & Maher, 1999:730). According to Arrone *et al.* (2013:2170) (see section 2.1) only a single combination, phentermine with topiramate, has been successful and the FDA approved this combination in 2012, which is not available in South Africa.

Phentermine's chemical structure, more specifically the phenylethylamine core, plays an essential role in the pharmacological classification thereof (see Figure 2-1, Figure 2-2 and Figure 2-3). The drug can be classified as an amphetamine derivative, anorexigenic appetite suppressant and natural monoamine alkaloid derivative (Drugs.com, 2021b; iNova Pharmaceuticals, 2000; Reyes-Parada *et al.*, 2020:5; Rossiter, 2016:70; Sanchez-Ramos, 2015:133; Willard *et al.*, 2017:116). The only visual distinguishable characteristic between phentermine and amphetamine's chemical structures (as seen in Figure 2-1) is the additional methyl group on the α -carbon of phentermine's chemical structure, causing for it to be less potent than amphetamine (Coulter *et al.*, 2018:7). In addition, the structure also decreases the dependence potential of phentermine (Coulter *et al.*, 2018:7; Rossiter, 2016:71). Other anorexigenic appetite suppressants (cathine, amfepramone and phendimetrazine) are also classified as amphetamine derivatives; however, their chemical structures each differ from amphetamine's in their own unique way (see Figure 2-2) (Rossiter, 2016:70; Stăcescu *et al.*, 2020:77). The distinctive characteristics of their chemical structures (see Figure 2-2) causes for these drugs to have a higher potential to cause abuse and dependence compared to phentermine (schedule five (S5)) and, therefore, they have a higher scheduling status (schedule six (S6)) (Rossiter, 2016:70; Stăcescu *et al.*, 2020:77).

Phentermine is indicated for the ST management of obesity (iNova Pharmaceuticals, 2000; Rossiter, 2016:70). Obese and overweight individuals have excess body fat, which negatively impacts all physiological functions in the body, thereby increasing the risk for these individuals to acquire adipose-related complications (cardiovascular diseases, diabetes and cancers) (see section 1.1 and 2.3) (Chooi *et al.*, 2019:6; Dugdale, 2019; Wharton *et al.*, 2020:884). As such, phentermine is also indicated in overweight individuals who experience the complications mentioned above (Rossiter, 2016:70). It is recommended that before therapy with phentermine is considered for a patient, a 3-6-month weight reduction programme must have been followed and deemed unsuccessful, the subordinate organic causes of the obesity must have been considered and eliminated and the benefits of administering phentermine to patients should outweigh the risk

thereof (iNova Pharmaceuticals, 2000; Lee & Dixon, 2017:473; Prescribers' Digital Reference (PDR), 2020; Rossiter, 2016:70; Upadhyay *et al.*, 2017:3; Williamson *et al.*, 2015:2319). A list consisting of five, international, off-label indications was put together, using available literature and include using phentermine LT, in doses exceeding 30 mg per day, in patients with excess body fat with a body mass index (BMI) < 27 kg/m², for the treatment of attention-deficit/hyperactivity disorder (ADHD) in obese patients and concurrently or regardless of contraindications (Hendricks, 2017:226-227, 230).

The contraindication of phentermine in various diseases, conditions and medications are summarised in Table 2-4 (iNova Pharmaceuticals, 2000; Teva Pharmaceuticals, 2020). Contraindications such as uncontrolled hypertension, coronary artery disease, arrhythmias, stroke and congestive heart failure are explicitly listed (Hendricks, 2017:227). These diseases in themselves can cause life-threatening pathophysiological changes in the body (see discussion in section 2.6) (iNova Pharmaceuticals, 2000; Teva Pharmaceuticals, 2020). Therefore, if phentermine were to be administered to a patient who suffers from any one of the above-mentioned diseases or conditions, the drug may aggravate the pathophysiological changes caused by the respective disorders, consequently worsening the severity of the disease or condition and patient outcome. However, the lack of structured data supporting this information, explains why no definite contraindication could be confirmed and why phentermine is still prescribed together with these contraindications.

The use of phentermine is contraindicated concurrently with certain pharmaceutical preparations, as PDDIs may occur (see Table 2-4) (Kapp *et al.*, 2013:83). Drugs that may cause severe drug-drug interactions (DDIs) with phentermine (such as fluoxetine and phendimetrazine) should be avoided, as the simultaneous use thereof may result in life-threatening adverse drug reactions (ADRs) (see Annexure C) (Drugs.com, 2021b; Shahabudin *et al.*, 2012:1258). It is recommended that phentermine should also not be administered with drugs that may cause moderate (such as topiramate and metformin) and mild DDIs (evening primrose); however, if prescribers intend to do so, a proper benefit-to-risk analysis should precede the prescribing thereof. Nevertheless, given the potential adverse effects and severity of DDIs that may result from the simultaneous use of phentermine with certain diseases or drugs, it should be enough motivation for prescribers to rather avoid these combinations. Again, a benefit-to-risk analysis should always precede the consideration of the combination of two drugs which alludes to the absolute importance of sufficient knowledge and expertise which should accompany risk assessment. Therefore, understanding the pharmacokinetic (PK) and pharmacodynamic (PD) properties of phentermine will assist in doing proper risk assessment,

consequently reducing and preventing side effects and ADRs resulting from DDIs (Sahasrabudhe *et al.*, 2015:111).

- **To investigate the pharmacokinetic and pharmacodynamic characteristics of phentermine that may lead to potential drug-drug interactions and adverse drug reactions.**

The PK and PD properties of phentermine were discussed in section 2.4 and 2.5 of this document, respectively. The drug's chemical properties play an important role in the specific storage instructions thereof. Should phentermine not be stored in its original packaging and according to the specifications provided by the manufacturer, the drug may be exposed to factors such as heat and moisture which may influence the stability, absorption and efficacy of the drug (Alqurshi, 2020:1418; iNova Pharmaceuticals, 2000; Mansour *et al.*, 2018:36; Medsafe, 2014:36; Shafaat *et al.*, 2013:2500). Consequently, product degradation or formation of toxic by-products may develop which may, if administered, be harmful to individuals (Alqurshi, 2020:1418; iNova Pharmaceuticals, 2000; Mansour *et al.*, 2018:36; Medsafe, 2014:36; Shafaat *et al.*, 2013:2500).

Phentermine is administered via the oral route and will, therefore, be absorbed from the gastrointestinal tract (GIT) into the bloodstream (Alagga & Gupta, 2021; Lavielle, 2017). The product contains lactose monohydrate and may, therefore, cause ADRs in individuals with lactase deficiency, glucose-galactose malabsorption, glucose intolerance and diabetes mellitus. These individuals may experience chronic diarrhoea and thus severe dehydration, pain and gas which may result in bloating (Bouchoucha *et al.*, 2021:258; Zuvarox & Belletieri, 2021). In patients with diabetes mellitus, the absorption of glucose and galactose may increase the blood glucose levels and thus disrupt the glycaemic control of patients suffering from this disease (iNova Pharmaceuticals, 2000; Malik & Panuganti, 2021). Over time, this may result in ADRs such as cardiovascular disease, nerve damage, impairment of the kidneys and eyes and depressive disorders (Mayo Clinic, 2020c).

Phentermine follows a multi-compartment model of distribution kinetics and once absorbed, the unionised lipophilic configuration of the drug molecules distributes to organ tissue in both the central compartment (CC) and the peripheral compartment (PC) of the body (see section 2.3.4) (Akula & Lakshmi, 2018:3; Le, 2020a; Mansoor & Mahabadi, 2020). Phentermine may distribute to the foetus during pregnancy and may potentially have been the cause of a prenatal stroke in a previous case report (D'Adesky & Ghosh, 2019:3). However, this predicament has not been confirmed (D'Adesky & Ghosh, 2019:3; Marin *et al.*, 2009:589). Additionally, phentermine may, just like amphetamines, possibly be distributed into breastmilk and cause

ADRs in nursing infants (Drugs.com, 2021d; iNova Pharmaceuticals, 2000; Oei *et al.*, 2012:743; Teva Pharmaceuticals, 2020).

Once the concentration of phentermine reaches steady state during the distribution process, the process of drug metabolism and elimination commences (Mansoor & Mahabadi, 2020; Onetto & Sharif, 2021). A fraction of phentermine is subject to hepatic metabolism and will be made more hydrophilic during phase I reactions in the liver, ensuring that the drug can be readily excreted via the kidneys (Henriques *et al.*, 2020:2; Susa & Preuss, 2021; Vivus, Inc, 2012). Since phentermine is extensively excreted through the kidneys, patients with renal impairment may not be able to adequately excrete the drug, which may result in toxic blood levels and thus ADRs (see section 2.6) (Akrimax Pharmaceuticals, 2013; iNova Pharmaceuticals, 2000; KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020; UCB, Inc, 2012). As such, the dosage of phentermine should be adjusted accordingly in patients, including the elderly (≥ 60 years), with a glomerular filtration rate (GFR) ≤ 29 mL/min (EM Guidance., 2021b; Teva Pharmaceuticals, 2020). In fact, phentermine use should generally be avoided in the elderly and in children (< 12 years), as they may not be able to adequately excrete phentermine from the body which may also result in an ADR such as toxic blood concentrations (Akrimax Pharmaceuticals, 2013; iNova Pharmaceuticals, 2000; KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020; UCB, Inc, 2012).

The PD properties of phentermine were discussed in section 2.5.1 and 2.5.2 of this document. In short, phentermine acts on the central nervous system (CNS) and causes an increase in the concentration and stimulatory effects of dopamine (DA), serotonin (5-HT) and norepinephrine (NE) in the brain (Kalyanasundar *et al.*, 2020:2; Marais, 2016:18; Sanchez-Ramos, 2015:137). Dopamine induces the reward mechanism associated with eating which consequently results in appetite suppression (Kalyanasundar *et al.*, 2020:2; Rege, 2018). Constant serotonergic neurotransmission may also cause appetite suppression (Perez *et al.*, 2019:6; Rothman & Baumann, 2000:55). Norepinephrine indirectly stimulates the adrenal cortex, causing for DA, NE and epinephrine to be released into the bloodstream so these catecholamines can bind to various adrenergic receptors throughout the body (see Table 2-3) (Dutt *et al.*, 2021; McCorry, 2007:3; Paravati *et al.*, 2020; Sheng *et al.*, 2021:4; Volkow *et al.*, 2011:39). Dopamine and NE will break down stored fat tissue and epinephrine will increase the blood glucose levels, thereby causing feelings of satiation, consequently resulting in appetite suppressant (Alhayek & Preuss, 2021; Bathia *et al.*, 2020; Paravati *et al.*, 2020; Volkow *et al.*, 2011:42). Unfortunately, other receptors are also stimulated (see Table 2-3) thereby causing side effects in the body (Farzam *et al.*, 2021; Law & Martin, 2020). The different receptors and the respective effects they cause when stimulated, are summarised in Table 2-3 and discussed in section 2.5.2.

The most common side effects of phentermine are insomnia, xerostomia and dizziness, which differ from mild to moderate in severity (Hendricks *et al.*, 2011:2358; Kim *et al.*, 2006:619,623; Tantrachoti *et al.*, 2016:73). These side effects can easily be managed and prevented by initiating nonpharmacological approaches and advice such as increasing water intake (xerostomia) and administering phentermine early in the morning (insomnia). Other rare side effects of phentermine such as cardiovascular and cerebrovascular side effects, euphoria, episodes of hallucinations and psychosis may also surface (Bhatia *et al.*, 2020; iNova Pharmaceuticals, 2000; Tadi & Lui, 2021). These side effects are severe and nonpharmacological approaches may not necessarily be sufficient to overcome such adverse effects and alternative medical interventions may be required.

Phentermine has many interactions with diseases, conditions and other medication (see Table 2-4). The reason for this is because phentermine affects various organ systems throughout the body and may add to the underlying pathophysiological changes caused by certain diseases and conditions which may potentially aggravate the severity thereof (see section 2.6) (iNova Pharmaceuticals, 2000; Teva Pharmaceuticals, 2020). Administering phentermine together with drugs that may add to its physiological effects in the body and thus side effects, may potentially result in harmful consequences (see Annexure C). Prescribers are, therefore, advised to avoid prescribing drugs together with phentermine if the combination of the constituents may result harmful consequences (iNova Pharmaceuticals, 2000). Additionally, patients are encouraged to contact their prescriber or pharmacist or seek medical attention if they experience any adverse effects with phentermine that may influence their daily functioning. Healthcare workers should monitor patients for such adverse effects, report ADRs, initiate pharmacovigilance and continuous drug utilisations review (DURs) as they are essential in ensuring safe and effective medicine treatment, positive medicine experience and maximum patient outcomes and adherence.

- **To investigate both the international and national specific prescriber guidelines for prescribing phentermine.**

There are international and national prescribing guidelines with regards to the use of phentermine, which were compiled to assist with the rational and safe prescribing of the drug. International guidelines are available in the patient information leaflets (PILs) of Adipex-P®, Lomaira®, Dietamin®, Terfamex®, Sentis® and Duromine® (Australia and New Zealand) whereas national guidelines are available in the PIL of Duromine® (South Africa) and other academic resources, such as the South African Medicine Formulary (SAMF) and the Essential Medical (EM) Guidance

(Cohen, 2022; Cohen, 2021; Cohen, 2020; iNova Pharmaceuticals, 2021; iNova Pharmaceuticals, 2000; KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020). These prescribing guidelines are based on scientific information and provide unbiased reliable information on the rational prescribing of medication (EM Guidance, 2021a; Rossiter, 2016:1). When prescribers prescribe according to these guidelines, maximum clinical efficiency can be achieved whilst optimising patient outcomes (Maxwell, 2016:459).

Pharmacotherapy with phentermine (phentermine hydrochloride and resin) may be initiated in overweight and obese individuals (see section 2.8) and therapy should commence at the lowest available dose (Cohen, 2022; Cohen, 2021; iNova Pharmaceuticals, 2021; iNova Pharmaceuticals, 2000; KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020). The different dosage strengths of trading products are provided in Table 2-5. Starting at the lowest effective dose will ensure that the patient has an adequate response to therapy; that is, sufficient appetite control, whilst minimising side effects (Lee & Dixon, 2017:473).

Generally, it is recommended that phentermine be administered once daily in the morning (Adipex-P®, Dietamin®, Terfamex®, Sentis® and Duromine®) as it will reduce the risk for individuals to experience insomnia (iNova Pharmaceuticals, 2000). However, for some individuals once daily administration may not be adequate in achieving the desired appetite suppressing effects (KVK-Tech, 2018; Teva Pharmaceuticals, 2020). It is, therefore, recommended that each patient's response to therapy should be evaluated after 4 weeks (Rossiter, 2016:70). The target weight loss after a 4-week course of therapy with phentermine should be 2 kg and if the patients fail to reach this target, their dedication to their diet, physical exercise and medicine adherence should be assessed (Rossiter, 2016:70). Additionally, patients might require alterations in their daily dosage and prescribers should adjust the dosages in accordance with each individual patient's response to therapy (Cohen, 2022; Cohen, 2021; iNova Pharmaceuticals, 2021; iNova Pharmaceuticals, 2000; KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020). Some individuals may necessitate twice daily (Adipex-P®, Sentis®) or even three times daily (Lomaira®) doses of specific strengths, in order to achieve and maintain the desired therapeutic effect; which is appetite suppression (KVK-Tech, 2018; Teva Pharmaceuticals, 2020). Nevertheless, the recommended daily dose of phentermine (see section 2.8) in general should not be exceeded to increase the efficacy of the drug (iNova Pharmaceuticals, 1991:2; iNova Pharmaceuticals, 2000). The drug should also not be used together with other drugs that are indicated for appetite suppression, in order to increase the efficacy of phentermine (iNova Pharmaceuticals, 1991:2; iNova Pharmaceuticals, 2000).

The minimum target weight loss over the course of therapy, which is ideally not longer than 12 consecutive weeks, should at least be 5% of the patient's initial total body weight, prior to the initiation of pharmacotherapy with phentermine (Rossiter, 2016:70). Certain patient groups, such as those with hypertension and diabetes mellitus, should be monitored throughout the course of therapy as phentermine may increase the blood pressure levels and cause fluctuations in the blood glucose levels (AMBOSS, 2020; EM Guidance., 2021b; Haslam, 2016:209; Hendricks, 2017:226; PDR, 2020; Trerattanavong & Chen, 2021). Other groups, such as those with renal impairment should solely be dependent on their GFR. Patients with a GFR < 15 mL/min should not use phentermine, those with a GFR of 15-29 mL/min should not exceed doses of 15 mg phentermine base per day and ≥ 30 mL/min need no dosage adjustments (EM Guidance., 2021b; Teva Pharmaceuticals, 2020). However, all patients with renal impairment who receives phentermine therapy should be monitored throughout the course of therapy to ensure that no further loss of renal function or toxic effects occur (Akrimax Pharmaceuticals, 2013; KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020).

To conclude, these guidelines are merely a tool provided to assist prescribing physicians in the rational prescribing of the drug. These guidelines are based on scientific information and provide warnings, contraindications and interactions of phentermine (see section 2.6 and 2.7). Adherence to these guidelines would eliminate the potential of irrational drug prescribing; however, the adherence of consumers and prescribers are not enforceable. Continuous DURs are, therefore, necessary, as it provides retrospective information on the general prescribing patterns of a drug and how prescribing patterns differ from recommended treatment guidelines and it identifies where change is needed so that maximum patient outcomes can be achieved.

- **To investigate the utilisation patterns of phentermine both nationally and internationally.**

The utilisation patterns of phentermine in the United States of America (USA), Korea, Mexico, Chile, Australia and South Africa were discussed in section 2.8 this document (Alexander *et al.*, 2011:684; Connolly *et al.*, 1997:582; Haddock *et al.*, 2000:262; Hendricks *et al.*, 2009:1730; Kim *et al.*, 2006:615; Márquez-Cruz *et al.*, 2021:540; Truter, 2016:140; Truter, 2014:33). These utilisation patterns of phentermine can be compared to the recommended prescribing guidelines (see section 2.8) of the respective trading products to establish to what degree the use of phentermine differs from treatment guidelines. As such, any medicine-related problems can be identified and thus resolved and it can be established whether irrational drug prescribing occurs (Jacob *et al.*, 2020:4096; Melku *et al.*, 2021:1; Scriptpharm, 2021).

Hendricks *et al.* (2009:1730) and Connolly *et al.* (1997:582) reflected on the utilisation pattern of phentermine in the USA. From these results we can see that some prescribers adhere to the BMI specifications when prescribing phentermine and others do not. Patients received phentermine in doses up to 60 mg of phentermine per day and prescribers, therefore, prescribed phentermine in doses exceeding the maximum daily dose of 30 mg of phentermine (Connolly *et al.*, 1997:582; Hendricks *et al.*, 2009:1730; Teva Pharmaceuticals, 2020; UCB, Inc, 2012). The DOT with phentermine in the USA is not restricted to ST use as some individuals received pharmacotherapy with the drug for up to 28 months (Connolly *et al.*, 1997:581; Hendricks *et al.*, 2009:1730). The results from both studies indicated that prescribers prescribed phentermine together with drugs that may have potentially caused DDIs. Evidently, prescribers in the USA prescribe phentermine LT, in doses exceeding the recommendations and together with drugs that may cause DDIs (Connolly *et al.*, 1997:582; Hendricks *et al.*, 2009:1730; Teva Pharmaceuticals, 2020; UCB, Inc, 2012). Prescribers in the USA do not adhere to the prescribing guidelines when prescribing phentermine, and therefore, expose individuals to the potential risks associated with irrational drug prescribing (DDIs and ADRs) (Eguale *et al.*, 2016:61).

Although limited information was available on the use of phentermine among the Korean obese population, the results were compatible with the recommended prescribing guidelines of phentermine (Cohen, 2021; Kim *et al.*, 2013:300, 303-304). From these results one can clearly see that Korean prescribers adhere to the BMI specifications when prescribing phentermine ($\text{BMI} \geq 25 \text{ kg/m}^2$) (Kim *et al.*, 2013:298; Teva Pharmaceuticals, 2020; Woo & Jeong, 2018:290). The maximum daily dose of phentermine hydrochloride does not exceed recommended limits and the DOT does not exceed 12 consecutive weeks (Kim *et al.*, 2013:304). The use of phentermine amongst obese Korean individuals, therefore, to our knowledge, remain within the recommended guidelines (Cohen, 2021; Kim *et al.*, 2013:304). As such, individuals experienced satisfactory weight loss (5.2% of initial body weight) and did not experience any adverse effects (Kim *et al.*, 2013:304). Evidently, prescribing according to the specifications within the prescribing guidelines will minimise the risk for ADRs, which will maximise patient outcomes.

In Mexico, phentermine is generally used amongst individuals with a $\text{BMI} \geq 30 \text{ kg/m}^2$ and in doses of 15 mg and 30 mg phentermine per day (Márquez-Cruz *et al.*, 2018:540). Mexican prescribers, therefore, adhere to the BMI specifications when prescribing phentermine and the daily dose does not exceed the recommended maximum (Cohen, 2022; DiBonaventura *et al.*, 2018:8; Márquez-Cruz *et al.*, 2018:540-541). The DOT with the drug exceeded the recommended maximum and patients received pharmacotherapy with the drug for up to six months (Márquez-Cruz *et al.*, 2018:542). As such, prescribers do not adhere to the recommended DOT when prescribing

phentermine, thereby exposing individuals to the potential severe risk associated with LT phentermine prescribing (see section 2.1).

There is, to our knowledge, no English literature available on the utilisation patterns of phentermine in Chile and it could, therefore, not be established whether prescribers adhere to the recommended prescribing guidelines of Sentis®. As such, potential irrational drug prescribing could not be identified.

In Australia, patients receive pharmacotherapy with either 15 mg or 30 mg phentermine resin, despite doses of 40 mg phentermine resin being available (Haddock *et al.*, 2002:265; iNova Pharmaceuticals, 2021). The average daily dose amongst Australian consumers is 27.5 mg of phentermine resin, and therefore, do not exceed the recommended maximum in Australia (40 mg of phentermine resin) (Haddock *et al.*, 2002:265; iNova Pharmaceuticals, 2021). Prescribers prescribe phentermine LT for up to 24 weeks, and therefore, do not adhere to the prescribing guidelines when prescribing the drug (Haddock *et al.*, 2002:265). There is no controlled supervision over the distribution of phentermine in Australia, thereby, increasing the risk for individuals to experience DDIs and ADRs (Alexander *et al.*, 2011:684).

Although the use of phentermine in South Africa has, to our knowledge, not specifically been studied, Truter reflected on the utilisation pattern of prescription appetite suppressants in South Africa, including phentermine (Truter, 2016:140-142; Truter, 2014:33-34). The use of phentermine amongst consumers in South Africa have been consistent over the years. Patients remain to be treated with either 15 mg or 30 mg phentermine resin as it is the only dosage forms and strengths of the drug available in South Africa (iNova Pharmaceuticals, 2000; Truter, 2016:140-142; Truter, 2014:33-34). The DOT with the drug does not appear to be LT; however, these results are based on average values of all appetite suppressants in South Africa, and it can, therefore, not be guaranteed that the use of phentermine does not exceed 12 consecutive weeks (Truter, 2016:141). Evidently, the use of phentermine amongst South African consumers seems to be judicious and according to the prescribing guidelines of the drug (Truter, 2016:140-142; Truter, 2014:33-34). It is however, known that there is limited information available regarding the use of phentermine in such populations. Drug utilisation reviews are, therefore, needed to establish the utilisation patterns of phentermine in South Africa so patterns of potential irrational drug use can be detected, investigated and resolved. The DOT with the drug needs investigation so that where phentermine is being used LT and in high-risk individuals, physicians can be made aware of the potential lethal consequences thereof.

4.2.2 Empirical investigation objectives

The conclusions made from the empirical investigation objectives are discussed below.

- **To investigate the duration of phentermine therapy (for patients receiving 15 mg or 30 mg phentermine respectively) on the PBM company's database for the specific study period, stratified by gender, age and prescriber.**

Phentermine is indicated for the ST management of obesity, as the ST use (i.e., not longer than 89 days or 12 consecutive weeks) of the drug has been proven to be safe and effective and without severe side effects (iNova Pharmaceuticals, 2000; Kim *et al.*, 2006:614; Rossiter, 2016:70; WebMD, 2021). In fact, the most common side effects experienced with ST therapy is xerostomia and insomnia, which can easily be overcome by non-pharmacological approaches (WebMD, 2021). When the drug is used for longer than 12 consecutive weeks, i.e., LT, more severe effects may surface and include cardiovascular effects (hypertension), abuse and dependence (Kokkinos & Levine, 1993:310). Prescribers are, therefore, advised not to prescribe the drug LT as it may cause significant harm to individuals (Haslam, 2016:209; Hendricks, 2017:226). Despite these recommendations being readily available in the PIL of Duromine®, results from this study indicate that prescribers disregard this restriction, thereby unnecessarily putting their patients in harm's way.

This is, to our knowledge, the first South African study to investigate the DOT with phentermine in the private healthcare sector of South Africa. The DOT with 15 mg and 30 mg phentermine, respectively, stratified by gender, age and prescriber's speciality, were discussed in section 3.2. The study population consisted of 3 361 patients that had approved and paid claims for phentermine of which 1 419 (42.22%) were for 15 mg phentermine. The average (SD) DOT with both 15 mg (57.26 (58.72 days) and 30 mg (67.10 (52.01) days) phentermine was generally ST, i.e., it did not exceed 12 consecutive weeks. This is a positive discovery for the authors as the LT use of phentermine may possibly cause severe effects and are, as a result thereof, not recommended (Haslam, 2016:208; Hendricks, 2017:226).

There were however, 889 (26.45%) patients that received phentermine LT and patients were mostly, but not limited to, female patients ($n = 775$; 23.06%) and aged 35-59 years ($n = 602$; 17.91%). Female patients generally received pharmacotherapy with 15 mg ($p = 0.004$) and 30 mg ($p = 0.03$) phentermine for longer time periods compared to male patients. It might be because there were considerably more female patients in the study population compared to male patients. However, when a two sample t-test was conducted and Cohen's d-value was calculated,

a *d*-value of < 0.2 (see Annexure A) imply that the difference in the DOT between female and male patients receiving 15 mg (*d*-value = 0.15) and 30 mg (*d*-value = 0.12) phentermine respectively, is small.

The results of the DOT with phentermine were, as previously mentioned, also stratified according to different age groups. For 15 mg phentermine, patients in age group 3 (35-59 year) had the longest average DOT (62.70 (67.99) days) followed by those in age group 1 ($\leq$ 18 years) (62.25 (51.01) days), 4 ($\geq$ 60 years) (61.95 (56.30) days) and 2 (19-34 years) (49.06 (43.78) days), respectively. For 30 mg phentermine, patients in age group 4 had the longest average DOT (73.18 (60.03) days), followed by patients in age group 3 (71.46 (55.37) days), 1 (60.00 (76.49) days) and 2 (57.35 (40.00) days), respectively. Differences were detected in the DOT with 15 mg phentermine for patients in age group 2 and 3 ($p = 0.0004$); however, a *d*-value of 0.2 suggests that this difference is small. Differences in the DOT with 30 mg phentermine for patients in age group 2 and 3 ($p < 0.0001$; *d*-value = 0.26) and those in age group 2 and 4 ($p < 0.0001$; *d*-value = 0.26) were also detected; however, the *d*-value also suggests that the difference is small.

Moreover, from the results one can see that children < 12 years ($n = 10$; 0.30%) and the elderly ($\geq$ 60 years) ($n = 192$; 5.71%) received pharmacotherapy with phentermine. Prescribers are advised not to prescribe phentermine in the elderly and children (< 12 years) as there is no evidence that suggest that it is safe and effective to do so (iNova Pharmaceuticals, 2000). Additionally, some of these patients most likely have age-related and not disease-related underlying impaired or inadequate renal function and may, therefore, not be able to properly excrete the drug from the body, which may result in toxic effects (see section 2.6) (Akrimax Pharmaceuticals, 2013; iNova Pharmaceuticals, 2000; KVK-Tech, Inc, 2018; Teva Pharmaceuticals, 2020; UCB, Inc, 2012). It was noteworthy that these individuals also received LT therapy with phentermine, despite neither ST nor LT use being advised (iNova Pharmaceuticals, 2000). Prescribers took the additional risk to prescribe the drug LT to the elderly and children < 12 years and, therefore, exposed these individuals to the severe consequences associated therewith (Haslam, 2016:208; Hendricks, 2017:226).

In the analysis of the DOT with phentermine according to different prescribers, results were stratified according to general practitioner (GP) and specialist prescribing. The DOT with 15 mg phentermine, within the study period, as prescribed by GPs and specialist varied from 5-720 days and 7-720 days, respectively. For 30 mg phentermine, the DOT, as prescribed by GPs and specialist varied from 10-360 days and 1-330 days, respectively. There was no significant

difference in the DOT with 15 mg phentermine for different prescribers. The DOT with 30 mg phentermine was generally longer for GP prescribing (67.80 (52.08 days) compared to specialist prescribing (58.59 (50.50) days) ($p = 0.04$; d -value = 0.18) and the difference is small. Nevertheless, both groups of authorised prescribers prescribed phentermine LT (off label indication), and therefore, did not adhere to the prescribing guidelines of the drug (iNova Pharmaceuticals, 2000).

To conclude, prescribers in the private healthcare sector of South Africa do not adhere to the prescribing guidelines when prescribing phentermine, thereby creating room for irrational drug prescribing. The DOT with phentermine in private healthcare in South Africa is not restricted to ST use and some individuals ($n = 889$; 26.45%) may experience adverse cardiovascular effects, hypertension or even develop abuse and dependence as the residual effect of LT therapy with the drug. Prescribers also prescribe phentermine off-label in individuals ≥ 60 years and < 12 years, despite the use thereof not being recommended (iNova Pharmaceuticals, 2000). These obese individuals most likely have underlying co-morbid diseases (cardiovascular diseases, hypertension, diabetes and certain cancers), as obese individuals are often associated with such and the effects resulting from these off-label uses of phentermine may have had additive effects, causing significant harm to individuals (Chooi *et al.*, 2019:6; Dugdale, 2019). It is therefore, not in the patient's best interest to prescribe phentermine for indications other than the label indications and prescribers are, therefore, encouraged to adhere to the prescribing guidelines of the drug as it will maximise patient outcome and adherence. The DOT with phentermine should, therefore, remain to be restricted to ST use until sufficient evidence is provided to proof that LT therapy with the drug is safe and effective.

In addition to the potential toxic effects and the afore-mentioned adverse effects, the elderly and obese individuals are often associated with polypharmacy, thereby creating room for PDDIs to have occurred (National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 2015; Slater *et al.*, 2018:8).

- **To determine the prevalence of the co-prescribing of different strengths of phentermine with the top 20 drugs most frequently prescribed to long-term (LT) phentermine consumers that may potentially cause mild, moderate or severe DDIs (classified by a drug interaction checker).**

This section illustrated the prevalence of the co-prescribing of phentermine with drugs that may potentially cause mild, moderate and severe DDIs, when the DOT with the drug exceeded 12 consecutive weeks (hereinafter referred to as LT). The results are discussed in section 3.2.2.

It is a well-known fact that phentermine should not be used for the LT management of obesity as LT therapy may be correlated with severe cardiovascular effects, hypertension, abuse and dependence. Even so, prescribers, including prescribers in private healthcare of South Africa, prescribe phentermine LT despite the potential severe repercussions thereof. There were 889 (26.45%) patients on the medicines claims database that received LT therapy with phentermine during the study period of which the majority of the patients were female (n = 775; 87.18%) and aged 35-59 years (n = 602; 67.72%).

Moreover, we also know that the drug should not be used together with other drugs that may add or oppose to the effects thereof in the body, i.e., cause DDIs, as it may result in ADRs which may, depending on the severity thereof become life-threatening. Yet again, despite the PIL of phentermine warning against such uses, some prescribers prescribe phentermine together with drugs that may cause DDIs. Unfortunately, this is not the worst of the matter as some of these prescribers and those in private healthcare of South Africa, prescribe phentermine LT and in combination with drugs that may cause DDIs. As such, these patients are exposed to the potential severe effects accompanying LT phentermine as well as the ADRs that may result from PDDIs between phentermine and certain co-prescribed drugs.

Amongst the LT phentermine consumers in the private healthcare sector of South Africa, the top 20 drugs co-prescribed with phentermine, which may have caused PDDIs, were analysed and demonstrated no mild PDDIs. There were 15 (75%) pharmaceutical preparations that may have potentially caused moderate DDIs with phentermine and the residual of the constituents (n = 5; 25%) may have potentially caused severe DDIs amongst LT phentermine consumers. The most common drug prescribed to patients receiving phentermine LT, which may have caused potential moderate DDIs was dextromethorphan (n = 282; 31.72%), whereas formoterol (n = 52; 5.85%) was least prescribed to patients in this group. Results indicated that tramadol (n = 416; 46.79%) was the drug most frequently to patients and phenylpropanolamine (n = 69; 7.76%) was the drug least prescribed to patients which may have potentially experienced severe DDIs. Patients receiving LT therapy with phentermine may, therefore, have experienced moderate and/or severe PDDIs.

The potential ADRs that may have resulted from moderate PDDIs between phentermine and relevant co-prescribed drugs (see Annexure A) were discussed in section 3.2.2 and included serotonin syndrome (5-HT syndrome), hypertension, tachycardia, hypoglycaemia, palpitations, arrhythmias, psychosis and pulmonary hypertension. These ADRs may be irritating, worrying and even intolerable (Marsh, 2018). If the benefit of administering phentermine with these drugs, that may potentially have caused moderate DDIs, outweigh the risk thereof during a benefit-tot-risk

analysis, prescribers may prescribe such drug combinations; however, patients should be monitored for potential severe effects (see Annexure C) (Drugs.com., 2021a; MedlinePlus, 2019). Other drugs with moderate PDDIs that were frequently prescribed with phentermine, besides dextromethorphan, was ephedrine (n = 232; 26.10%), salbutamol (n = 196; 22.05%) and metformin (n = 185; 20.81%).

What is concerning is the fact that these patients also received LT therapy with phentermine and may, therefore, already have been experiencing certain cardiovascular adverse effects. As such, the effects of these ADRs, resulting from the PDDIs, may have added to the already present adverse effects resulting from LT therapy with phentermine which may have further worsened patient outcomes. These ADRs may potentially have additive effects on underlying pathophysiological changes commonly associated with obese individuals (Chooi *et al.*, 2019:6; Dugdale, 2019). As previously discussed, obese individuals are often associated with adipose-related diseases such as cardiovascular diseases, hypertension and diabetes mellitus (Chooi *et al.*, 2019:6; Dugdale, 2019). Therefore, the ADRs resulting from these PDDIs, together with the potential adverse effects of LT phentermine therapy, may have potentially worsened the patient's wellbeing and as such, some individuals may require a change in therapy (Shahabudin *et al.*, 2012:1258). If this is the case, prescribers are advised to not prescribe phentermine with any drug that may worsen the patient's wellbeing as it may cause poor medicine adherence, and therefore, also patient outcome (Carver *et al.*, 2020; Hansberry, 2017; MedlinePlus, 2019).

Prescribers should avoid prescribing phentermine with drugs that may potentially cause severe DDIs as the ADRs that may result from these interactions, may become life-threatening (see Annexure C) (iNova Pharmaceuticals, 2000). Other drugs with potentially severe DDIs commonly prescribed with phentermine, excluding tramadol, were the antidepressants escitalopram (n = 99; 11.14%), fluoxetine (n = 81; 9.11%) and sertraline (n = 75; 8.44%). Other potential severe DDIs with phentermine and certain co-prescribed drugs are further discussed in section 3.2.2 and patients may have potentially experienced severe ADRs including seizures, 5-HT syndrome and life-threatening cardiac complications (pulmonary hypertension). That is; in addition to the potential severe repercussions associated with LT phentermine therapy and (as previously discussed) potential underlying co-morbid diseases. Evidently, this is not the outcome healthcare workers aim to achieve whilst treating a patient with pharmaceutical preparations. On the contrary, the concept of rational drug prescribing requires prescribers to initiate pharmacotherapy that will be of maximum clinical efficacy and minimum patient harm (Maxwell, 2016:459). Given the severity of the ADRs that may result from the PDDIs discussed above, these DDIs may be life-threatening and surely do not minimise patient harm. In fact, these severe

DDIs would require immediate medical assistance or interventions to ensure that the outcomes do not result in fatalities (Shahabudin *et al.*, 2012:1258).

Prescribers should, therefore, apply their knowledge and expertise when co-prescribing two or more drugs as it will certainly reduce the incidence of ADRs that may result from PDDIs (Shahabudin *et al.*, 2012:1260). They should also consult the prescribing guidelines of phentermine when making a drug-related decision as it will further assist in avoiding brutalities that may result from DDIs and it eliminates the potential for irrational drug prescribing and thus ADEs (Shahabudin *et al.*, 2012:1260).

4.3 Recommendations

Based on the present study, the following recommendations are proposed for future studies:

- The short duration of use with phentermine deserves further investigation, more specifically the rational as to why prescribers prescribe the drug for 1 or 7 or 10 or 14 days.
- The utilisation patterns of phentermine amongst patients that are not on the medicine claims database, i.e., cash paid items, should be investigated.
- The outcome of patients receiving phentermine LT should be evaluated.
- The International Classification for Diseases and Related Health Problems (ICD) code should be used in future studies so the potential off-label indications of phentermine amongst South Africans can be determined.
- The possibility that patients might be abusing phentermine should be evaluated in the private healthcare of South Africa.
- Clinical trials are necessary to establish whether the LT use of phentermine can cause abuse, dependence and other severe cardiovascular side effects except for the cardiovascular conditions mentioned in the study.
- If phentermine is prescribed LT, it should be established whether prescribers follow up on the safety and effectiveness of treatment.
- To investigate and assess, by means of a questionnaire, the outcome of patients when potentially interacting drugs are prescribed together with phentermine.

4.4 Limitations

There are a few limitations that could have potentially influenced the applicability of the results and conclusions of this study. The following limitations were encountered through the study:

- The data obtained from the PBM company's database only included approved and paid claims for phentermine in the private healthcare sector of South Africa and thereby cash paid items were excluded. It was therefore difficult to generalise the results to the entire healthcare sector of South Africa as data from only a section of this sector were used.
- The PBM company holds reliable and accurate data; however, capturing errors could have occurred whilst the data analyses were conducted which may potentially have disrupted the accuracy of the results.
- The dispensing information of phentermine were analysed and not the actual consumption patterns of the drug, which may cause for the actual DOT with the drug to be inaccurate.
- Data were limited to the number of patients on the database for the study period; therefore, the number of patients in the study population, the DOT with the drug as well as the prevalence of PDDIs could have potentially been miscalculated.
- This study focused on potential, theoretical, DDIs with phentermine and it could therefore not be determined if patients actually experienced DDIs.
- Only one drug interaction checker was used to identify drugs that may potentially cause DDIs with phentermine, thus other potentially DDIs could have potentially existed.

4.5 Strengths

The PBM company records data of all pharmacies and 98% of dispensing practitioners nationwide, which enhances the estimates of the results with a rather high level of accuracy. All information needed on the demographic information of the study population and prescriber's speciality were accessible therefore no data were excluded as specified by the exclusion criteria (see section 1.4.6).

4.6 Chapter summary

In this final chapter of the study, the conclusions made from the literature review and empirical investigation objectives were discussed. Recommendations for future studies were discussed subsequently. The limitations and strengths of this study followed to conclude this chapter.

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ANNEXURE A: DATA ANALYSIS PLAN

The duration of therapy with 15 mg and 30 mg phentermine on the PBM company's database for the specific study period, stratified by gender, age and prescriber.	
Variable	Frequency (%)
Total number of patients receiving phentermine over the study period	3 361 (100)
Product strength	
15 mg Phentermine	1 419 (42.22)
30 mg Phentermine	1 942 (57.78)
Gender	
Female	2 848 (84.74)
Age groups	
1 (≤ 18 years)	43 (1.28)
2 (19-34 years)	1 004 (29.87)
3 (35-59 years)	1 636 (57.44)
4 (≥ 60 years)	165 (48.68)
Male	513 (15.26)
Age groups	
1 (≤ 18 years)	14 (0.42)
2 (19-34 years)	156 (4.64)
3 (35-59 years)	316 (9.40)
4 (≥ 60 years)	27 (0.80)
Age groups (years)	
1 (≤ 18 years)	57 (1.70)
2 (19-34 years)	1 160 (34.51)
3 (35-59 years)	1 952 (58.08)
4 (≥ 60 years)	192 (5.71)

Prescriber's speciality				
General practitioner		3 000 (89.26)		
Specialist		361 (10.74)		
Descriptive statistics according to product strength				
Variable	Frequency n (%)	Minimum duration of therapy (days)	Maximum duration of therapy (days)	Average duration of therapy (days), mean ± SD
15 mg Phentermine	1 419 (42.22)	5	720	57.26 (58.72)
Gender, age groups (years)				
Female	1 224 (36.42)	5	720	58.55 (61.29)
Male	195 (5.80)	5	330	49.15 (38.08)
Age groups (years)				
1 (≤ 18 years)	40 (1.19)	30	210	62.25 (51.01)
• < 12 years	7 (0.21)	5	720	49.06 (43.78)
2 (19-34 years)	560 (16.66)	7	720	62.70 (67.99)
3 (35-59 years)	734 (21.84)	7	330	61.95 (56.30)
4 (≥ 60 years)	85 (2.53)			
Prescriber's speciality				
General practitioner	1 206 (35.88)	5	720	57.07 (55.35)
Specialist	213 (6.34)	7	720	58.31 (75.18)
30 mg Phentermine	1 942 (57.78)	1	360	67.10 (52.01)
Gender, age groups (years)				
Female	1 624 (48.32)	14	360	68.16 (52.74)

Male	318 (9.46)	1	270	61.64 (47.79)	
Age groups (years)					
1 (≤ 18 years)	17 (0.51)	30	330	60.00 (76.49)	
• < 12 years	3 (0.09)	30	30	30 (0)	
2 (19-34 years)	600 (17.85)	14	240	57.35 (40.00)	
3 (35-59 years)	1 218 (36.24)	1	360	71.46 (55.37)	
4 (≥ 60 years)	107 (3.18)	30	300	73.18 (60.03)	
Prescriber's speciality					
General practitioner	1 794 (53.38)	10	360	67.80 (52.08)	
Specialist	148 (4.40)	1	330	58.59 (50.50)	
Inferential statistics					
Variable	Frequency n (%)	Average duration of therapy (days), mean ± SD	Test	p-value	d-value
15 mg Phentermine					
Gender			Two sample t-test	0.004 (<0.05)	0.15
Female	1 224 (36.42)	58.55 (61.29)			
Male	195 (5.80)	49.15 (38.08)			
Age groups			One-way ANOVA	0.0004 (<0.05)	0.2
2 (19-34 years)	560 (16.66)	49.06 (43.78)			
3 (35-59 years)	734 (21.84)	62.70 (67.99)			
Prescriber's speciality			Two sample t-test	0.8 (>0.05)	-
General practitioner	1 206 (35.88)	57.07 (55.35)			
Specialist	213 (6.34)	58.31 (75.18)			
30 mg Phentermine					
Gender			Two sample t-test	0.03 (<0.05)	0.12
Female		68.16 (52.74)			

Male	1 624 (48.32) 318 (9.46)	61.64 (47.79)			
Age groups 2 (19-34 years) 3 (35-59 years)	600 (17.85) 1 218 (36.24)	57.35 (40.00) 71.46 (55.37)	One-way ANOVA	<0.0001 (<0.05)	0.26
2 (19-34 years) 4 (35-59 years)	600 (17.85) 107 (3.18)	57.35 (40.00) 73.18 (60.03)	One-way ANOVA	<0.0001 (<0.05)	0.25
Prescriber's speciality General practitioner Specialist	1 794 (53.38) 148 (4.40)	67.80 (52.08) 58.59 (50.50)	Two sample t-test	0.04 (<0.05)	0.18
15 mg Phentermine vs 30 mg phentermine					
15 mg Phentermine 30 mg Phentermine	1 419 (42.22) 1 942 (57.78)	57.26, 58.72 67.09, 52.01	Two sample t-test	<0.001	0.17
The prevalence of the co-prescribing of phentermine with drugs that may cause mild, moderate and severe drug-drug interactions (classified by a drug interaction checker) when the recommended duration of therapy was exceeded.					
Variable			Frequency n (%)		
Total number of patients where the use of phentermine exceeded 12 consecutive weeks			889 (26.45)		
Gender					
Female			775 (23.06)		
Male			114 (3.39)		
Age groups					
1 (≤ 18 years)			14 (0.42)		
2 (19-34 years)			215 (6.40)		
3 (35-59 years)			602 (17.91)		
4 (≥ 60 years)			58 (1.73)		

Prescriber's speciality	
General practitioner	817 (24.31)
Specialist	72 (2.14)
Product strength	
Drugs co-prescribed to patients receiving phentermine long-term which may have caused a drug-drug interaction (N = 58)	
Active ingredient	Frequency (%)
Moderate drug-drug interactions	
1. Dextromethorphan	282 (31.72)
2. Ephedrine	232 (26.10)
3. Salbutamol	196 (22.05)
4. Metformin	185 (20.81)
5. Amitriptyline	177 (19.91)
6. Phenylephrine	152 (17.10)
7. Levothyroxine	132 (14.85)
8. Pseudoephedrine	126 (14.17)
9. Thyroxine	118 (13.27)
10. Promethazine	94 (10.57)
11. Preparations containing alcohol	94 (10.57)
12. Salmeterol	77 (8.66)
13. Prochlorperazine	71 (7.99)
14. Topiramate	65 (7.31)
15. Formoterol	52 (5.85)
Severe drug-drug interactions	
1. Tramadol	416 (46.79)
2. Escitalopram	99 (11.14)
3. Fluoxetine	81 (9.11)
4. Sertraline	75 (8.11)
5. Phenylpropanolamine	69 (7.76)

ANNEXURE B: ETHICS APPROVAL LETTER OF STUDY



Private Bag X1290, Potchefstroom
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Tel: 086 016 9698

Web: <http://www.nwu.ac.za/>

**North-West University Health Research Ethics
Committee (NWU-HREC)**

Tel: 018 299-1206

Email: Ethics-HRECAppl@nwu.ac.za (for human
studies)

30 June 2021

ETHICS APPROVAL LETTER OF STUDY

Based on approval by the North-West University Health Research Ethics Committee (NWU-HREC) on 30/06/2021, the NWU-HREC hereby approves your study as indicated below. This implies that the NWU-HREC grants its permission that, provided the general conditions specified below are met and pending any other authorisation that may be necessary, the study may be initiated, using the ethics number below.

Study title: A retrospective analysis of phentermine in the private healthcare sector of South Africa: duration and drug-drug interactions
Principal Investigator/Study Supervisor/Researcher: Dr JM du Plessis
Student: A Fourie - 27270033

Ethics number:

N	W	U	-	0	0	1	7	9	-	1	4	-	A	1	-	1	1
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Institution Study Number Year Status Sub-study
Status: S = Submission; R = Re-Submission; P = Provisional Authorisation;
A = Authorisation

Application Type: Sub-study

Commencement date: 30/06/2021

Expiry date: 30/06/2022

Risk:

Minimal

Approval of the study is provided for a year, after which continuation of the study is dependent on receipt and review of an annual monitoring report and the concomitant issuing of a letter of continuation. A monitoring report is due at the end of June annually until completion.

General conditions:

While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, the following general terms and conditions will apply:

- The principal investigator/study supervisor/researcher must report in the prescribed format to the NWU-HREC:
 - annually on the monitoring of the study, whereby a letter of continuation will be provided annually, and upon completion of the study; and
 - without any delay in case of any adverse event or incident (or any matter that interrupts sound ethical principles) during the course of the study.
- The approval applies strictly to the proposal as stipulated in the application form. Should any amendments to the proposal be deemed necessary during the course of the study, the principal investigator/study supervisor/researcher must apply for approval of these amendments at the NWU-HREC, prior to implementation. Should there be any deviations from the study proposal without the necessary approval of such amendments, the ethics approval is immediately and automatically forfeited.
- Annually a number of studies may be randomly selected for active monitoring.
- The date of approval indicates the first date that the study may be started.
- In the interest of ethical responsibility, the NWU-HREC reserves the right to:
 - request access to any information or data at any time during the course or after completion of the study;
 - to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process;

- *withdraw or postpone approval if:*
 - *any unethical principles or practices of the study are revealed or suspected;*
 - *it becomes apparent that any relevant information was withheld from the NWU-HREC or that information has been false or misrepresented;*
 - *submission of the annual monitoring report, the required amendments, or reporting of adverse events or incidents was not done in a timely manner and accurately; and/or*
 - *new institutional rules, national legislation or international conventions deem it necessary.*
- NWU-HREC can be contacted for further information via Ethics-HRECAppl@nwu.ac.za or 018 299 1206

Special conditions of the research approval due to the COVID-19 pandemic:

Please note: Due to the nature of the study i.e. (statistical analysis of previously collected medical claims data), this study will be able to proceed during the current alert level, following receipt of the approval letter. No additional COVID-19 restrictions have been placed on the study except that the researcher must ensure that before proceeding with the study that all research team members have reviewed the North-West University COVID-19 Occupational Health and Safety Standard Operating Procedure.

The NWU-HREC would like to remain at your service and wishes you well with your study. Please do not hesitate to contact the NWU-HREC for any further enquiries or requests for assistance.

Yours sincerely,



Digitally signed by Prof
Petra Bester
Date: 2021.06.30
18:54:42 +02'00'

Chairperson NWU-HREC

Current details:(23239522) G:\My Drive\9. Research and Postgraduate Education\9.1.5.4 Templates\9.1.5.4.2_NWU-HREC_EAL.docm
20 August 2019
File Reference: 9.1.5.4.2

ANNEXURE C: PHARMACOKINETIC AND PHARMACODYNAMIC DRUG-DRUG INTERACTIONS OF PHENTERMINE

Pharmacological class	Drugs	Pharmacokinetic drug-drug interaction	Pharmacodynamic drug-drug interaction	Adverse drug reactions
Severe interactions				
Centrally acting anti-obesity preparations	Amfepramone Phendimetrazine Diethylpropion		X	Life-threatening cardiac complications
DA reuptake inhibitor	Bupropion		X	Seizures
SSRIs	Citalopram Escitalopram Fluoxetine Fluvoxamine maleate Paroxetine Sertraline		X	5-HT syndrome
5-HT and NA reuptake inhibitors	Desvenlafaxine Duloxetine Venlafaxine		X	5-HT syndrome
Water-soluble, nephrotrophic, low osmolar X-ray contrast medium	Iohexol Iopamidol		X	Seizures
Oxazolidinone antibacterial	Linezolid		X	Hypertension Fatality
Antidote	Methylene blue		X	Hypertension Fatality
Sympathomimetics	Phenylpropanolamine		X	Life-threatening cardiac complications
Methylhydrazines	Procarbazine		X	Hypertension Fatality
MAOI	Selegiline Tranylcypromine		X	Hypertension Fatality

Opioids	Tramadol hydrochloride Tapentadol		X	Seizures
Antidepressant	Vortioxetine		X	5-HT syndrome
Moderate interactions				
α -glucosidase inhibitors	Acarbose		X	Hypoglycaemia
Selective β_2 agonists	Formoterol Indacaterol Salbutamol Salmeterol Terbutaline		X	Hypertension Heart rate irregularities
Alcohol	Preparations containing alcohol		X	Cardiovascular side effects such as tachycardia
Opioid anaesthetics	Alfentanil Fentanyl Pethidine Remifentanil Sufentanil		X	5-HT syndrome
Tricyclic antidepressants	Amitriptyline Clomipramine Dosulepin Imipramine Trimipramine		X	Hypertension Arrhythmias Tachycardia
D ₂ receptor antagonist	Amisulpride Chlorpromazine Flupentixol Fluphenazine Haloperidol Pimozide Sulpiride Trifluoperazine Zuclopenthixol		X	Psychosis Arrhythmias
Sulphonamides, urea derivatives	Chlorpropamide Glibenclamide		X	Hypoglycaemia

	Gliclazide Glipizide Glimepiride			
Opium alkaloids and derivatives	Dextromethorphan Methadone Noscapine Pholcodine Dihydrocodeine		X	5-HT syndrome
Adrenergic and dopaminergic agents	Adrenaline or epinephrine Dobutamine Dopamine		X	Hypertension Tachycardia
Sympathomimetics	Ephedrine sulphate Etilefrine hydrochloride Pseudoephedrine hydrochloride Phenylephrine		X	Hypertension Tachycardia
Disinfectants and antiseptics	Ethanol		X	Cardiovascular effects
GLP-1 agonists	Exenatide Liraglutide		X	Hypoglycaemia
Insulins and analogues	Insulin glulisine Insulin lispro Insulin aspart Insulin glargine Insulin detemir Insulin lispro protamine		X	Hypoglycaemia
General anaesthetics	Ketamine		X	Hypertension Heart rate irregularities
Thyroid hormones	Levothyroxine sodium Thyroxine Liothyronine sodium		X	Cardiac insufficiency

Biguanides	Metformin hydrochloride		X	Hypoglycaemia
Meglitinides	Nateglinide Repaglinide		X	Hypoglycaemia
Benzomorphan derivatives	Pentazocine		X	5-HT syndrome
Thiazolidinediones	Pioglitazone Rosiglitazone		X	Hypoglycaemia
Osmotically acting laxatives	Polyethylene glycol		X	Seizures
Anti-emetic	Prochlorperazine		X	Psychosis Arrhythmias
Phenothiazine derivatives	Promethazine hydrochloride		X	Psychosis Arrhythmias
Centrally acting antiadrenergic preparations	Reserpine Methyldopa		X	Decreased hypotensive effects
Dipeptidyl peptidase IV inhibitors	Saxagliptin Sitagliptin Vildagliptin		X	Hypoglycaemia
Antiepileptics	Topiramate	X		Hypertension Tachycardia Palpitations
Antihistamine	Trimeprazine		X	Psychosis Arrhythmias
Minor interactions				
Herbal medicine	Evening primrose		X	Lowers the seizure threshold

ANNEXURE D: SOUTH AFRICAN MEDICAL JOURNAL AUTHOR GUIDELINES

Author Guidelines

The SAMJ has launched a new submission and tracking system. Authors will be required to register a profile on the in order to submit a manuscript. To submit a manuscript, please proceed to: <https://samajournals.co.za/index.php/samj>

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Authorship

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conceptualisation, design, analysis and interpretation of data; (ii) drafting or critical revision of important scientific content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals). If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing. Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions. Author contributions should be listed/described in the manuscript.

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Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we

aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

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Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

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SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting.

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions. Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, **full** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and °C), e.g. '40 kg' and '20 cm' but '50%' and '19°C'.
- Please be sure to insert proper symbols e.g. μ not u for micro, α not a for alpha, β not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

Preparation of research articles

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are to fill a gap in the literature, a logical extension of previous work or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study. Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text. Do not replicate data in tables and in text.

Structured abstract

- This should be 250-400 words, with the following recommended headings:
 - o **Background:** why the study is being done and how it relates to other published work.
 - o **Objectives:** what the study intends to find out
 - o **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
 - o **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.

o **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g., primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g., smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.

- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the $\pm$ symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g., what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e., not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make ‘new rows’ as each row of data should have its own proper row.

Do not: use separate columns for *n* and % and rather combine into one column, *n* (%).

Do not: have overlapping categories, e.g., and rather use <> symbols or numbers that don’t overlap.

References

NB: Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must **not** be used.

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,^[2] and others.^[3,4-6]

- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
 - Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
 - Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
 - Volume and issue numbers should be given.
 - First and last page, in full, should be given e.g.: 1215-1217 not 1215-17.
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Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. <http://dx.doi.org/10.1000/hgjr.182>
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. <http://www.who.int/whr/2002> (accessed 16 January 2010).

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To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- The following are required for your submission to be complete:
 - o Anonymous manuscript (unless otherwise stated)
 - o Manuscript
 - o Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.
- Once the submission has been successfully processed, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Production process

Please note that there is a 6-month waiting time for publication, once an article has been sent to the production team.

The following process will follow:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g., by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.

5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.
7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

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- Research articles will appear *in abstract form only*, if selected for a print edition.

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We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish an erratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics.

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- Article title and authors
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