THE OCCURRENCE OF DRUG RELATED PROBLEMS IN A PRIMARY HEALTH CARE SETTING: A PHARMACEUTICAL CARE APPROACH

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ABSTRACT

Title: The occurrence of drug related problems in a primary health care setting: a pharmaceutical care approach.

Keywords: Pharmaceutical care, health care provider, drug therapy problems, drug interactions.

The worldwide trend in the pharmacy profession is towards pharmaceutical care. According to the latest views the provision of pharmaceutical care by pharmacists is the way forward for the profession in South Africa.

Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve patients quality of life (Hepler & Strand, 1990:539). The provision of pharmaceutical care is the responsibility of health care providers (e.g. a pharmacist, nurse and physician). The roles and functions of the pharmacist in the provision of pharmaceutical care are stipulated in the activities specially pertaining to the Pharmacy Profession and the scope of practice of the pharmacist (Pharmacy Act, 53/1974).

The patient's quality of life can be harmed by a drug therapy problem (e.g. adverse effects of a drug, drug interactions, etc.). A drug therapy problem can be defined as any undesirable event experienced by a patient that involves or is suspected to involve drug therapy and that actually or potentially interferes with a desired patient outcome (Cipolle *et al.,* 1998:75). Drug interactions are classified as a drug therapy problem and are a serious problem to consider. Drug interactions can be defined as an altered or modified action of a drug as a result of interaction with another drug.

The aim of this study was to investigate the occurrence of drug interactions in a primary health care setting and make recommendations for the identification of drug interactions in health care facilities. Philani Prime Cure® provided the data of primary health care setting used in this study. The data from the seven medi centres were analysed in this study. Ten of the most prescribed drugs [i.e. diphenhydramine, tetracycline (doxycycline and oxytetracycline), co-trimoxazole, hyoscine, theophylline, loperamide, glibenclamide, multivitamin, diclofenac and reserpine] of Philani Prime Cure® medi centres were studied for the identification of drug interactions.

A study population of 24991 patients in the seven medi centres were used. There were 131081 medicine items prescribed during the research period (1 January 2000 to 30 June 2000). The ten selected drugs represented 31409 (23.96%) of the total number of medicine items prescribed.

The interactions that occurred were drug-drug and drug-age interactions. A total number of 14449 possible drug-drug interactions and a total number of 3604 drug-age interactions occurred with the ten drugs. Interactions were classified according to the significance levels formulated by Tatro (2001:xiv). Level 1 interactions are classified as severe and well documented interactions. Level 2 and 3 interactions are less severe and are also well documented. Level 4 and 5 interactions are classified as minor and unlikely interactions (Tatro, 2001:xiv). For the drug-drug interactions were significance levels are indicated in the literature, level 5 drug-drug interactions occurred the most with the ten selected drugs (n = 1869, 12.94% of all drug-drug interactions). Level 4 interactions (n = 411, 0.31%) did not occur as much as level 5 interactions. Level 1 to 3 drug-drug interactions represented 2017 (10.43%) of all drug-drug interactions. Level 1 interactions occurred the most frequent with doxycycline (1.62% of all drug-drug interactions), viz., interaction between doxycyline and antacids. The most frequent level 2 interactions occurred with theophylline (1.32% of all drug-drug interactions), viz., interaction between theophylline and macrolide antibiotics, and diclofenac (1.94% of all drug-drug interactions), viz., diclofenac and thiazide diuretics. Level 3 interactions occurred the most frequent with multivitamin (3.22% of all drug-drug interactions), viz., interaction between multivitamin and salicylate. During this study another level of significance was created, namely level 6. This level was created to accommodate the identified drug-drug interactions that were not well documented in the literature and needed further investigation.

The most drug-age interactions occurred with children and the elderly patients. The most frequent drug interactions occurred with diphenhydramine (19.48% of all drug-age interactions) which were prescribed to patient younger than two years and patients older than 50 years.

This study supports the importance of the identification of drug therapy problems in pharmacy practice. Drug interactions were discussed according to the effects of the drugs on each other and the patient quality of life is markedly reduced.

The results of this study provide information to the Philani Prime Cure® database to incorporate drug interactions in their protocols. This incorporation of interactions can assist their health care team to identify potential interactions and improve their patient therapeutic outcomes.

OPSOMMING

Titel: Die voorkoms van probleme met geneesmiddelgebruik in 'n primêregesonheidsorgopset: 'n benadering vanuit farmaseutiese sorg.

Sleutelwoorde: Farmaseutiese sorg, gesondheidsorgverskaffer, probleme met geneesmiddelbehandeling, geneesmiddelinteraksies.

Wêreldwyd is die neiging in die aptekersprofessie na farmaseutiese sorg. Volgens die jongste sienings lê die toekoms van die professie in Suid-Afrika in die voorsiening van farmaseuties sorg deur die apteker.

Farmaseutiese sorg is die verantwoordelike verskaffing van behandeling met geneesmiddels om besliste uitkomste ter verbetering van die kwaliteit van lewe van pasiënte te bereik (Hepler & Strand, 1990:539). Die verskaffing van farmaseutiese sorg is die verantwoordelikheid van die gesondheidsorgverskaffer (bv. apteker, verpleegster en dokter). Die rol en funksie van die apteker in die verskaffing van farmaseutiese sorg word bepaal deur die aktiwiteite wat spesifiek met die aptekersprofessie en die bestek van die praktyk van die apteker verband hou (Wet op Aptekers, 53/1974).

Die kwaliteit van lewe van die pasiënt kan benadeel word deur probleme vanweë behandeling met geneesmiddels (bv. nadelige effekte van die geneesmiddel, geneesmiddelinteraksies, ens.). 'n Probleem vanweë behandeling met geneesmiddels kan gedefieer word as enige ongewensde effek wat die pasiënt ervaar wat werklik of vermoedelik aan die geneesmiddel toeskryfbaar is en wat die verlangde uitkoms werklik of moontlik beïnvloed (Cipolle *et al.,* 1998:75). Geneesmiddelinteraksies word geklassifiseer as 'n probleem vanweë behandeling met geneesmiddels en is 'n ernstige kwessie wat in gedagte gehou moet word. 'n Geneesmiddelinteraksie kan gedefineer word as 'n ongewensde werking van 'n geneesmiddel as gevolg van interaksie met 'n ander geneesmiddel.

Die doel van die studie was om die voorkoms van geneesmiddelinterakises in 'n primêregesondheid-sorgopset te bestudeer en om aanbevelings te maak vir die identifisering van geneesmiddelinteraksies in gesondheidsorgsentrums. Philani Prime Cure® het die data verskaf van 'n primêregesondheidsorg-opset wat in hierdie studie gebruik is. Die data van sewe mediese sentrums is in hierdie studie ontleed. Tien van die middels [d.i. difenhidramien, tetrasiklien (doksisiklien en oksitetrasiklien), kotrimoksasool, hiossien, teofillien, loperamied, glibenklamied, multivitamiene, diklofenak en reserpien] wat die meeste by die mediese sentrums van Philani Prime Cure® voorgeskryf word, is vir die identifikasie van geneesmiddelinteraksies bestudeer.

'n Studiepopulasie van 24991 pasiënte van die sewe mediese sentrums is gebruik. 'n Totaal van 131081 mediese items is voorgeskryf in die tydperk wat deur die navorsing gedek word (1 Januarie 2000 tot 30 Junie 2000). Die tien gekose middels het 31409 (23.96%) van die totale aantal mediese items beloop.

Geneesmiddel-geneesmiddel- en geneesmiddel-ouderdom-interaksies het voorgekom. 'n Totaal van 14449 moontlike geneesmiddel-geneesmiddel- en 3604 geneesmiddel-ouderdom-interaksies is met die tien middels waargeneem. Interaksies is geklassifiseer volgens die vlakke van beduidenheid van Tatro (2001:xiv). Interaksies van vlak 1 word geklassifiseer as ernstige en goed gedokumenteerde interaksies. Interaksies van vlakke 2 en 3 is minder ernstig, maar ook goed gedokumenteer. Interaksies van vlakke 4 en 5 word beskou as geringe en onwaarskynlike interaksies (Tatro, 2001:xiv). Geneesmiddel-geneesmiddel-interaksies van vlak 5 het die meeste onder die tien geselekteerde middels voorgekom (n = 1869, 12.94%). Interaksies van vlak 4 (n = 411, 0.31%) het nie soveel as dié van vlak 5 voorgekom nie. Interaksies van vlakke 2 en 3 het 2017 (10.43%) van alle geneesmiddel-geneesmiddel-interaksies uitgemaak. Interaksies van vlak 1 het die meeste met doksisiklien voorgekom (1.62%), nl. interaksie tussen doksisiklien en teensuurmiddels. Die mees algemene interaksies van vlak 1 het met teofillien voorgekom (1.32%), nl. interaksie tussen teofillien en die makroliedantibiotika, en met diklofenak (1.94%), nl. interaksie tussen diklofenak en tiasieddiuretika. Interaksies van vlak 3 het die meeste met multivitamine voorgekom (3.22%), nl. interaksie tussen multivitamine en salisilaat. Tydens hierdie studie is 'n nuwe vlak interaksies geskep, naamlik vlak 6, om geïdentifiseerde geneesmiddel-geneesmiddel-interaksies wat nie goed in die literatuur gedokumenteer is nie en verdere ondersoek vereis, te akkommodeer.

Die meeste interaksies van geneesmiddels met ouderdom het in kinders en in bejaarde pasiënte voorgekom. Die meeste hiervan was met difenhidramien (19.48% van alle geneesmiddel-ouderdom-interaksies) wat aan pasiënte jonger as twee jaar of ouer as 50 jaar voorgeskryf was.

Die studie beklemtoon die belang van die identifikasie van probleme vanweë behandeling met geneesmiddels in die aptekersbedryf. Geneesmiddelinteraksies is beskryf volgens die effekte van die middels op mekaar wat die pasiënt se kwalitieit van lewe benadeel.

Die resultate van hierdie studie verskaf inligting oor geneesmiddelinteraksies aan Philani Prime Cure® wat by hulle protokolle ingesluit kan word. Die insluiting van data oor interaksies kan hulle gesondheidsorgspan help om moontlike interaksies te identifiseer en om die terapeutiese uitkoms van hulle pasiënte te verbeter.

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CHAPTER 1: INTRODUCTION

This dissertation focuses on the occurrence of drug therapy problems in a primary health care setting. A pharmaceutical care approach will be taken and this study will specially focus on the prevalence of drug interactions (drug-drug, drug-disease, etc.) with medication prescribed in clinics of a private primary health care group.

1.1 PROBLEM STATEMENT

Health care systems around the world are in a state of flux. Change is everywhere, and each day different priorities and expectations are presented (Cipolle *et al.*, 1998:1). The worldwide trend in the pharmacy profession is towards pharmaceutical care. Also in South Africa pharmaceutical care has been recognised as the key to the future of pharmacy in health care, because potentially the pharmacist's interventions lead to cost savings and improved health care for the patient (Stiglingh *et al.*, 1999:67).

Drug-related mortality and morbidity have reached such a magnitude in society that it has become necessary for a specific professional to be designated to address this issue openly and comprehensively, since only then can a specific individual be held accountable for its management (Cipolle *et al.*, 1998:18).

The pharmacist is the most likely professional to face these drug-related needs of the patients. According to WHO (1988:10) community pharmacists are the health professionals that are most accessible to the public. In addition to ensuring an accurate supply of appropriate products, their professional activities also cover counselling of patients at the time of dispensing of prescription and non-prescription drugs. They maintain links with other health care professionals in primary health care (WHO, 1988:10).

The pharmacist plays an important role in the health of a nation. It is of such importance that the Government documented the role of the pharmacist in the National Drug Policy. According to the Government the role can be described as follows (Department of Health, 1996:18):
"Although all health care providers and the public are involved in the rational use of drugs, WHO has recommended a special role of pharmacists, particularly in quality assurance and in the safe and effective administration of drugs. Pharmacists will be in a strong position to promote the rational use of drugs through their extensive knowledge".

According to the relevant literature, pharmaceutical care is seen to be a way of dealing with patients and their medication. It is a concept that deals with the way people should receive and use medication and should receive instructions on the use of medicines (Foppe van Mil *et al.*, 1999:202).

Pharmaceutical care is a philosophy of practice in which the patient is the primary beneficiary of the pharmaceutical care practitioners' actions. Pharmaceutical care focuses on the attitudes, behaviours, commitments, concerns, ethics, functions, knowledge, responsibilities, and skills of the pharmacist in the provision of drug therapy with the goal of achieving definite therapeutic outcomes toward patient health and quality of life (WHO, 1993:7).

Health means different things to different people and many attempts have been made to define it. Health is:

- *"A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"* (WHO, 1947 quoted by Blenkinsopp & Panton, 1991:1).

- *"A relative state that represents the degree to which an individual can operate effectively within the circumstances of his heredity and his physical and cultural environment"* (McDermott 1977 quoted by Blenkinsopp & Panton, 1991:2).

The broader spectrum of this study is about drug therapy problems with special attention paid to drug interactions. There are various drug interactions, such as drug-drug, drug-disease, and drug-nutrient interactions. Ten of the top twenty drugs that were prescribed by Philani Prime Cure®, will be used to identify potential drug interactions.

There are various kinds of definitions for drug interactions. The following are a few of the possibilities to establish a broad picture of drug interactions:

- *'An interaction is said to occur when the effects of one drug are changed by the presence of another drug, food, drink or by some environmental chemical agent'* (Stockley, 1991:1).
- *'Most drug interactions are special kinds of adverse drug interactions in which the effects of a drug are altered by the effects of another drug'* (Grahame-Smith & Aronson, 1985:158).
- *'A drug interaction has been defined as the modification of the effect of a drug by prior or concomitant administration of another drug'* (Lee & Stockley, 2000:21-22).

It is important to understand the necessity of identifying interactions. According to Grahame-Smith and Aronson (1985:158) in the USA, for example, the number of drugs being taken by patients on admission to hospital is nearly twice that in the United Kingdom. It is clear that polypharmacy is an important factor – the more drugs a patient is taking the greater the chance of an interaction.

A study conducted by Saley (1999:203), on psychiatric outpatients in the North Wet Province in South Africa, showed that there were as many as 1123 out of 5674 prescriptions (19.79%) on which possible drug-drug interactions between prescribed psychiatric medicine were identified. Of these, 13.09% were severe and suspected or well-documented interactions. A study done (90 patients included in the study) in a community pharmacy in Windhoek, Namibië, has shown that 426 drug-related problems were identified in 83% of the chronic patients (Van Staden *et al.*, 2001:1).

A study done in a hospital found that the rate of interactions in patients taking 6 to 10 drugs was 7%, but 40% in those patients taking 16 to 20 drugs simultaneously (Stockley, 1991:1). According to Levin-Epstein (1998) adverse drug reactions and interactions are commonly believed to cost the United States about $25 billion per year. According to Lee and Stockley (2000:22) estimates range from 2.2 to 30% in studies carried out on hospital patients, and from 9.2 to 70.3% on patients in the community.

Combinations of drugs are used for many reasons. They may be necessary if a patient has more than one disease or if different aspects of the same disease require different treatments (Wade & Beely, 1976:39). Nies and Spielberg (1996:51) mentioned that when physicians use several drugs concurrently, they face the problem of not knowing whether a specific combination in a given patient has the potential to result in an interaction. They must know how to take advantage of the interaction if it leads to improvement in therapy or how to avoid the consequences of an interaction if it is an adverse drug reaction.

There are many drug interactions which result in beneficial rather than adverse effects, e.g. the administration of carbidopa, an extracerebral dopadecarboxylase inhibitor, together with levodopa to prevent its peripheral degradation to dopamine (Lee & Stockley, 2000:22). The following are a few examples of beneficial drug interactions (Venter, 1989:37):

- One drug may enhance the efficacy of another drug: Penicillin G promotes the entry of aminoglycosides into S. faecalis and thus facilitates the destruction of the organisms.
- Some drugs may reduce the side effects of others, for instance atropine blocks muscarinic receptors and thus inhibits muscarinic effects of neostigmine.
- Certain drugs are synergistically:
  - Beta-adrenergic agonists, aminophylline and ipratropium cause bronchodilation through different mechanisms.

Philani Prime Cure provided the database used in this study®. Philani Prime Cure® delivers services through an integrated network, consisting of 53 wholly owned Medi Centres, joint venture companies that provide specialised primary health care services in pathology, dentistry and optometry, and an

extended network of over 230 contracted general practitioners who provide services to Philani Prime Cure® patients who live beyond the reach of the existing Medi Centre network (Anon, 2001).

This study is the second of two studies to make use of the Philani Prime Cure® database with special reference to interactions between drugs with the highest prescription rates. Both studies focus on the top twenty drugs indicated on the Philani Prime Cure® database list. The other study, conducted by researcher H.E. Van der Walt, investigated the top ten drugs, and this study the interactions of the subsequent ten drugs on the ratio lists, will receive closer attention.

The following research questions can be formulated on the basis of the above discussion:

- What does pharmaceutical care entail?
- What is the role of the pharmacist and the other health care professionals in the prevention of drug therapy problems?
- What does a drug therapy problem entail?
- What does a drug interaction refer to and what different kinds of interactions can occur?
- Which factors can affect drug interactions?
- Which are the top twenty drugs most prescribed by Philani Prime Cure®?
- What are the possible interactions that can occur when the ten selected drugs are used?
- What is the occurrence of the more severe interactions that can be identified in the data obtained from Philani Prime Cure®?

1.2 RESEARCH OBJECTIVES

The **general research objective** of this study is to identify the drug therapy problems that can exist in a private primary health care setting. This entails the prevalence of drug interactions (e.g. drug-drug, drug-disease, drug-food interactions) that occur in connection with the drugs topping the list of prescriptions at Philani Prime Cure®.

The specific objectives of the study will be discussed under the research methodology.

1.3 RESEARCH METHODOLOGY

The research project consisted of the two phases, namely, the literature phase and the empirical phase.

1.3.1 Phase 1: Literature study

The literature study consisted of two chapters. The first chapter (Chapter 2) focused on the definitions and concepts related to pharmaceutical care and drug therapy problems. It presented an in-dept look at drug interactions and general information on different interactions. The second chapter (Chapter 3) focused on the ten selected drugs identified in the Philani Prime Cure® medi centres. The possible

drug interactions were indicated in a table and formed part of Chapter 3. The mechanism of action for the interactions was also discussed.

1.3.1.1 *Specific objectives*

The specific objectives of the literature study included the following:

- To define managed pharmaceutical care.
- To illustrate where pharmaceutical care fits into managed pharmaceutical care and define the areas of managed pharmaceutical care.
- To define and discuss pharmaceutical care in detail.
- To discuss the different elements of the pharmaceutical care practice (e.g. philosophy of practice, patient care process and practice management).
- To determine the role of the different health care providers in the prevention of drug therapy problems.
- To discuss primary health care.
- To define and discuss the different drug therapy problems.
- To define and discuss drug interactions by examining
  - the classification of drug interactions; and
  - the drugs involved in interactions.
- To discuss the different drug-drug interactions, such as
  - pharmaceutical interactions;
  - pharmacokinetic interactions; and
  - pharmacodynamic interactions.
- To discuss drug-food interactions by investigating
  - the effect of food and medication on each other;
  - factors affecting drug-food interactions; and
  - different types of drug-food interactions.
- To determine the factors affecting drug interactions.
- To discuss iatrogenic illness.
- To discuss the ten selected drugs by referring to
  - classification of the drug;
  - pharmacological properties of the specific drug;
  - mechanism of action;
  - therapeutic uses of each drug; and
  - deficiencies where possible.
- To construct a table with all the potential drug interactions and the adverse reactions of each drug.
- To discuss the mechanism of the drug interactions.

1.3.2 **Phase 2: Empirical study**

The specific objectives of the empirical study will be discussed.

1.3.2.1 *Specific objectives*

The specific objectives of the empirical study included the following:

- To determine the general information of the patient population during the research period by referring to
  - the total number of patients in the medi centres;
  - the gender distribution of the patients;
  - the age distribution of the patients; and
  - the average, minimum and maximum ages of the patients.
- To investigate the medicine usage patterns of the patients at the medi centres during the research period in order to determine
  - the total number of medicine items prescribed in each medi centre;
  - the average number of medicine items prescribed;
  - the total number and percentage of patient visits where one or more medicine items were prescribed; and
  - the occurrence of the ten selected drugs in the medi centres.
- To investigate the medical conditions or disease states in the medi centres according to
  - the total number of medical conditions or disease states diagnosed per medi centre;
  - the number of medical conditions or disease states diagnosed per patient visit;
  - the average number of medical conditions or disease states diagnosed per patient visit;
  - the ten most frequently diagnosed medical conditions or disease states diagnosed per patient visit; and
  - the top three medical conditions or disease states for which the ten selected drugs were prescribed in the medi centres.
- To identify and discuss the possible interactions that could occur when using the ten selected drugs by considering
  - the age groups interactions; and
  - the drug-drug interactions.
- To determine the medical conditions or disease states where the drug-drug interactions appeared.

1.3.2.2 *Steps of the empirical study*

The empirical study consisted of the following steps:

(i) Research design.

(ii). Selection of the study population.

(iii) Research instruments.

(iv) Drug interaction tables.

(v) Reliability and validity.

(vi) Discussion of the results of the empirical study.

(vii) Conclusions and recommendations.

(i) Research design

The aim of the research design was to ensure that the research is planned to provide satisfactory explanations to answer the formulated questions (Kerlinger, 1986:298; Mouton & Marais, 1992:35).

The research was an exploratory and descriptive study with contextual interest (Mouton & Marais, 1992:45-48). Exploratory research is applicable to the literature study where an overview of pharmaceutical care and drug interactions is given. Descriptive research applies to the empirical study, i.e. analysis of the database (Neuman, 1997:20).

The research can be classified as a non-experimental quantitative research (Huysamen, 1993:60). It shows an *Ex Post Facto* research design. *Ex Post Facto* research implies that the researcher analyses data that have already occurred and investigates the relationship of these varying data to subsequent behaviours. *Ex Post Facto* research does, therefore, not involve direct manipulation of the data (Leedy, 1997:226).

(ii) Selection of the study population

A retrospective study on the occurrence of drug interactions was investigated on the data of seven Philani Prime Cure® medi centres. The Philani Prime Cure® head office provided the database for the extraction of the data from all 53 medi centres. The seven medi centres were randomly chosen from the seven provinces where Philani Prime Cure® existed at the time. All the medi centres could not be used in the research because of the extent of the data. The seven medi centres used for the purposes of this study were:

- Brits (North West Province)
- Groblersdal (Mpumalanga Province)
- Kwanobuhle (Eastern Cape)
- Parow (Western Cape Province)
- Pietersburg (Northern Province)
- Rosslyn (Gauteng Province)
- Verulam (Kwazulu Natal Province)

Data for these medi centres were extracted for a six months period from 1 January 2000 to 30 June 2000. A total number of 29441 patient visits were recorded at the seven medi centres over the six month research period (refer to Chapter 5, Table 5.1).

(iii) Selection of the research instruments

The research instruments used for the analysis of the data included

- criteria to obtain the ten selected drugs;
- drugs used by the patients over a six months period (1 January 2000 to 30 June 2000);
- patient variables (e.g., age and gender);
- medical history of the patients; and
- medication used by the patients for identification of drug interactions.

(iv) Drug interaction tables

Drug interaction tables were constructed and used as research instruments to identify and evaluate the drug interactions that occurred. The information needed for constructing the tables included

~ the effects of patient variables (e.g. age) and disease states of the patients; and

~ the concurrent use of food and other medication with the ten selected drugs.

The information mentioned above was needed to indicate the effects on the pharmacodynamic, pharmacokinetic and therapeutic actions of the specific drug. This information was gathered through a comprehensive literature study. A significance rating (e.g. significance levels, degree of confidence in the interaction) by Tatro (2001:xiv) were used to describe the interactions (refer to Chapter 4, section 4.3.2.4).

(v) Reliability and validity

This study was done on an established database; therefore it can be assumed that the database is valid and reliable. The shortcomings in the study will be discussed in Chapter 6.

(vi) Data analysis

To analyse the data the Statistical Analysis System (SAS Institute, 2000) was used under the guidance of statistical consultation services, Potchefstroom University for CHE.

(viii) Discussion of the results of the empirical study

The results of the empirical study were tabulated, discussed and are related to the literature study.

(viii) Conclusions and recommendations

- Conclusions were made regarding the literature study.

- Recommendations and conclusions were made regarding the drug interactions based on the analysis of the interactions of the ten selected drugs.
- Recommendations were formulated to include the drug interactions data in the dispensing programme of Philani Prime Cure® medi centres.

1.4 DIVISION OF CHAPTERS

The chapters will be presented as follows:

Chapter 2: Pharmaceutical care and drug therapy problems

Chapter 3: Drug interactions of the ten selected drugs

Chapter 4: Research methodology

Chapter 5: Results and discussion

Chapter 6: Conclusions and recommendation

1.5 CHAPTER SUMMARY

In this chapter the problem statement, research objectives, research design, research method, and division of chapters were discussed.

Pharmaceutical care and drug therapy problems will be discussed in Chapter 2.

CHAPTER 2: PHARMACEUTICAL CARE AND DRUG THERAPY PROBLEMS

Pharmaceutical care and drug therapy problems will be discussed in this chapter. Pharmaceutical care is discussed to establish the background of this study. Drug therapy problems are discussed because the research project focuses on drug interactions (e.g. drug-food, drug-disease, drug-drug interactions).

2.1 PHARMACEUTICAL CARE AND OTHER RESEARCH FIELDS IN PHARMACY PRACTICE

According to Rovers *et al.* (1998:5) pharmaceutical care is at the heart of caring. It is about truly having concern for patients and spending time and effort needed to help another human being. Managed pharmaceutical care is a system that combines the financing and delivery of health services to members who are enrolled in a specific type of health care plan (AHA, 2000). The term *managed pharmaceutical care,* were described by MacKeigan and Larson (1988:261), as the role of pharmacy in the improvement of the quality of care and the control of health care resources utilisation. They suggested further that "*it should be tailored to the needs and corporate culture of each health care plan*". Serfontein (1998:1) defined managed pharmaceutical care as the practice with the aim to identify, prevent and resolve of medicine-related problems in a cost-effective way. The following aspects of managed pharmaceutical care were identified, namely clinical services, co-operative arrangements for the prevention of services, the formulary system and quality assurance (including drug therapy) (MacKeigan & Larson, 1988:261). Figure 2.1 shows how pharmaceutical care integrates into managed pharmaceutical care.

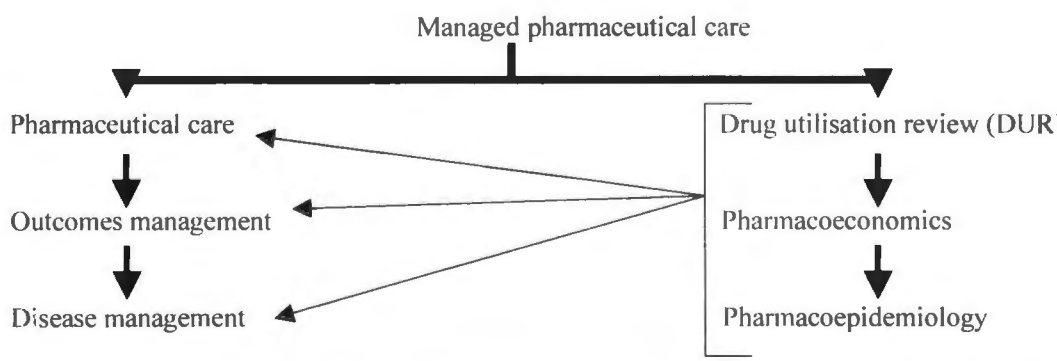

Figure 2.1: Schematic presentation of how pharmaceutical care integrates with the other fields of pharmacy practice (Adapted from Serfontein, 1998).

2.1.1 **Pharmaceutical care**

There are various definitions of pharmaceutical care. The following discussion is about the different definitions of pharmaceutical care.

2.1.1.1 *Initial definitions of pharmaceutical care*

Mikeal *et al.* (1975:567) first defined pharmaceutical care as *"the care that a given patient requires and receives which assures safe and rational drug usage"*. The term's elaboration was not substantially forthcoming (Cipolle *et al.*, 1998:10). Brodie *et al.* (1980:277) suggested that pharmaceutical care would include the determination of the drug needs for a given individual and the provision, not only required drugs, but also of the services necessary (before, during, and after treatment) to ensure optimally safe and effective therapy. According to Cipolle *et al.* (1998:11) Brodie's definition was primarily focused on controlling the availability and distribution of the drug product and not specifically on patient need within identifiable clinical parameters.

2.1.1.2 *Hepler (1987)*

According to Hepler (1987:376) the ideal for pharmaceutical care is a covenant relationship between a patient and pharmacist in which the pharmacist performs drug use control functions (with appropriate knowledge and skills) governed by awareness of and commitment to the patient's interest. Pharmacy can accelerate its professionalisation by asserting its authority in drug use control, while clarifying its commitment to patient welfare.

2.1.1.3 *Hepler and Strand (1990)*

Hepler and Strand (1990:539) published a paper that provided a conceptualisation of pharmaceutical care that stimulated widespread debate and ultimately produced broad-based agreement within the profession of pharmacy. The definition is as follows:

"Pharmaceutical care is the responsibility of achieving definite outcomes that improve a patient's quality of life. These outcomes are (1) cure of a disease, (2) reduction or elimination of symptoms, (3) arresting or slowing of a disease process, and (4) preventing a disease or symptoms" (Hepler & Strand, 1990:539).

The definition of Hepler and Strand (1990:539) best characterises the foundation of the conceptualisation: *"Pharmaceutical care is that component of pharmacy practice which entails the direct interaction of the pharmacist with the patient for the purpose of caring for the patient's drug-related needs."*

Although the profession accepted the concept as early as 1990, efforts to develop a practice consistent with the concept did not occur until 1992. In 1992 the Minnesota Pharmaceutical Care Project was

launched. This project serves as the foundation for a significant portion of what has become the practice of pharmaceutical care. Strand, Cipolle and Morley further focused their efforts on the clear definition of the responsibilities of a practitioner dealing with a patient's drug therapy (Cipolle *et al.*, 1998:12).

2.1.1.4 *Cipolle et al. (1998)*

According to Cipolle *et al.* (1998:13) "*pharmaceutical care is a practice in which the practitioner takes responsibility for a patient's drug-related needs and is held accountable for this commitment.*" The Minnesota Pharmaceutical Care Project was an action-oriented research project. It was conducted using the help of 54 pharmacists from 20 community pharmacy practice sites. The intent of the project was to explore the relationship between the therapy and practice of pharmaceutical care (Cipolle *et al.*, 1998:205). Through this study Cipolle and partners could formulate their above-mentioned definition of pharmaceutical care.

2.1.1.5 *Definitions of pharmaceutical care by different organisations*

2.1.1.5.1 American Pharmaceutical Association (APhA) and the American Society of Health System Pharmacists (ASHP)

The ASHP (1993:1721) defined pharmaceutical care as: "*the direct, responsible provision of medication-related care for the purpose of achieving definite outcomes that improve a patient's quality of life*".

According to the APhA (1995:1), pharmaceutical care is "*a patient-centred, outcomes oriented pharmacy practice that requires the pharmacist to work in concert with the patient and the patient's other healthcare providers. To promote health, to prevent disease, and to assess, monitor, initiate, and modify medication use to assure that drug therapy regimens are safe and effective*".

2.1.1.5.2 World Health Organisation (WHO)

The WHO (1993:7) described pharmaceutical care as a philosophy of practice in which the patient is the primary beneficiary of the pharmacist's action. Pharmaceutical care focuses the attitudes, behaviours, commitments, concerns, ethics, functions, knowledge, responsibilities and skills of the pharmacist on the provision of drug therapy with the goal of achieving definite therapeutic outcomes toward patient health and quality of life.

The Consultative Group of the WHO chose to expand the beneficiary of pharmaceutical care to the public as a whole and also to recognise the pharmacist as a health care provider who can participate in illness prevention and health promotion along with other members of the health care team (WHO, 1993:7).

2.1.1.5.3 International Pharmaceutical Federation (FIP)

The International Pharmaceutical Federation (1998:138) defined pharmaceutical care as *"the responsible provision of pharmacotherapy for the purpose of achieving definite outcomes that improve or maintain a patient's quality of life"*.

2.1.1.5.4 Pharmaceutical Care Network in Europe

The PCNE describes pharmaceutical care as *'the identification, solving, and preventing of drug-related problems for the individual patient through monitoring, review, documentation of process and outcomes and implementation in co-operation with other health care professionals"* (Herborg, 1995:150).

2.1.1.5.5 South African Pharmacy Council (SAPC)

The South African Pharmacy Council accepted the definition of the WHO for pharmaceutical care (SAPC, 1996:3). According to section 29 (3) of the Pharmacy Act (53/1973), the following are the South African Pharmacy Council views of pharmaceutical care:

- The evaluation of a patient's medicine-related needs by determining the indication, safety and effectiveness of the therapy.
- Dispensing of any medicine or scheduled substance on the prescription of a person authorised to prescribe medicine.
- Furnishing of information and advice to any person with regard to the use of medicine.
- Determining patient compliance with the therapy and follow up to ensure that the patient's medicine-related needs are being met.
- The provision of pharmacist initiated therapy.

2.1.1.5.6 Pharmaceutical Society of Australia and Canadian Pharmaceutical Association

The ideas of Hepler and Strand had influenced the pharmacy profession in Australia to review its practice (Newton, 1998:567). The Canadian Pharmaceutical Association adopted a mission statement that supported the pharmacist's provision of pharmaceutical care (Farris, 1998:565).

2.1.1.5.7 American Society of Consultant Pharmacists (ASCP)

Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life. Pharmaceutical care is provided for the direct benefit of the patient, and the pharmacist is responsible directly to the patient for the quality of that care (ASCP, 1996).

2.1.2 **Outcomes management**

According to Frankel (1996:113) outcomes management involves systematically improving health care results. The following outcomes can be measured, namely, economic, clinical, and humanistic outcomes (Sanchez, 1999:2). No single outcomes measure is considered optimal for all cases. For the evaluation of drug therapy and other health services, all three outcomes should be included (Serfontein, 1998:1). According to Sanchez (1999:2) clinical outcomes are the medical events that occur as a result of disease or treatment. Humanistic outcomes are the consequences of disease or treatment on patient functional status or quality of life. Economic outcomes consist of several medical and non-medical costs. Medical costs are those costs incurred from medical products and services to prevent or treat a disease. Non-medical costs are incurred as a result of illness but where no medical services are purchased (UCT, 1997:27).

During the provision of pharmaceutical care the pharmaceutical care practitioner takes responsibility for the outcomes of a patient's drug therapy. Outcomes, as applied to pharmaceutical care, refer to outcomes as a direct consequence of the collaborative efforts of the pharmaceutical care practitioner and the patient (Cipolle *et al.,* 1998:163). According to Lubbe (2000:425) pharmaceutical care is outcome oriented and therefore it might be of value to use outcome research techniques to assess the effectiveness on the economical, humanistic and clinical level. Outcomes management procedures can also be used to systematically improve pharmaceutical care results, typically by modifying the pharmaceutical care practice in response of the data obtained with outcomes research techniques (Lubbe, 2000:425) (refer to Figure 2.1).

2.1.3 **Disease management**

Disease management is defined as an integrated system with interventions, measurements and refinements of health care delivery designed to optimise clinical and economic outcomes within a specific population for a specific disease or therapy intervention (Gurnee & Da Silva, 1997:1). Disease management contracts typically specify a disease (e.g., asthma) or therapy intervention (e.g., lipid-lowering agents) for a certain population of patients (Armstrong & Langley, 1996:54). The process of disease management involves the following (Frankel, 1996:114):

- The identification of diseases or patients accounting for the majority of potential illnesses and costs.
- Represents a familiar frame of reference for physicians and patients.
- Incorporates a systematic management approach for the patient to improve.
- Provides basic information and directions for customised interventions (e.g. education, counselling, risk assessment).
- Assists in defining measurements or success parameters.

- Justifies the investment in planning and developing interventions that can potentially avoid or delay long-term and costly implications.
- Focuses on overall health outcomes and quality of life.

The emphasis of disease management is the management of isolated diseases in a group of patients. According to Lubbe (2000:425) pharmaceutical care does not focus only on the management of a defined set of diseases in a specific community. Pharmaceutical care focuses on all the drug-related needs of a specific patient to ensure that the patient does not experience one or more drug therapy problems and therefore aims to improve the quality of the patient's life (refer to Figure 2.1).

2.1.4 **Drug utilisation review (DUR)**

According to Rogenhaugh (1998:69) a drug utilisation review is a quantitative review to establish the medical appropriateness of providers giving medications to patients for particular medical conditions, performed by peers with feedback and education given to the providers, as appropriate. A drug utilisation review is an authorised, structured, and continuing procedure that reviews, analyses and interprets patterns of drug use (Edgren, 1996:120).

There are two types of drug utilisation reviews identified (Inesta, 1992:353):

- Quantitative drug utilisation review, which measures the amount and patterns of drug use.
- Qualitative drug utilisation review, which assesses the appropriateness of the drug used.

The purposes of a drug utilisation review, according to Truter (1995:338), are to improve the quality of care, containment of medical care costs, and the identification of fraud and abuse (refer to Figure 2.1).

2.1.5 **Pharmacoeconomics**

Pharmacoeconomics has been identified as the description and the analysis of the cost of drug therapy to health care systems and society. Pharmacoeconomic research is the process of identifying, measuring, and comparing the costs, risks, and benefits of programmes, services, or therapies and determining which alternative produces the best health outcomes for the resource invested (Sanchez, 1999:1).

According to Sanchez (1999:1) there is a distinct relationship between pharmacoeconimics, outcome research (management), and pharmaceutical care. Outcome research is defined as studies that attempt to identify, measure, and evaluate the results of health care services in general. Pharmacoeconomics is a division of outcomes research that can be used to quantify the value of pharmaceutical care products and services. Pharmaceutical care has been defined as the responsible provision of drug

therapy for the purpose of achieving definite outcomes (Sanchez, 1999:1). According to Bootman (1995:S17) it is important to use pharmacoeconomic methods to evaluate the impact of pharmaceutical care. This would enable the profession to delineate which pharmaceutical care services are cost-effective so as to improve efficiency in providing patient care (refer to Figure 2.1).

2.1.6 **Pharmacoepidemiology**

Pharmacoepidemiology is the study of the use and the effects of drugs in large numbers of people. Pharmacoepidemiology is a discipline that provides valuable information about the health and cost outcomes of drugs, devices, and biologics, particularly after their approval for clinical use (Stergachis & Hazlet. 1999:63) (refer to Figure 2.1).

2.2 **THE BROAD PICTURE OF PHARMACEUTICAL CARE**

According to Foppe van Mil *et al.* (1999:20) the individual patient is the main subject in pharmaceutical care and usually the pharmacist is the initiator and driving force of the process. In pharmaceutical care there are certain activities that can be separated into supportive pharmaceutical actions (carried out in the back office) and clinically oriented activities (disease or case oriented). Pharmaceutical care is aimed at the individual patient and can be carried out at the counter or in the consulting room.

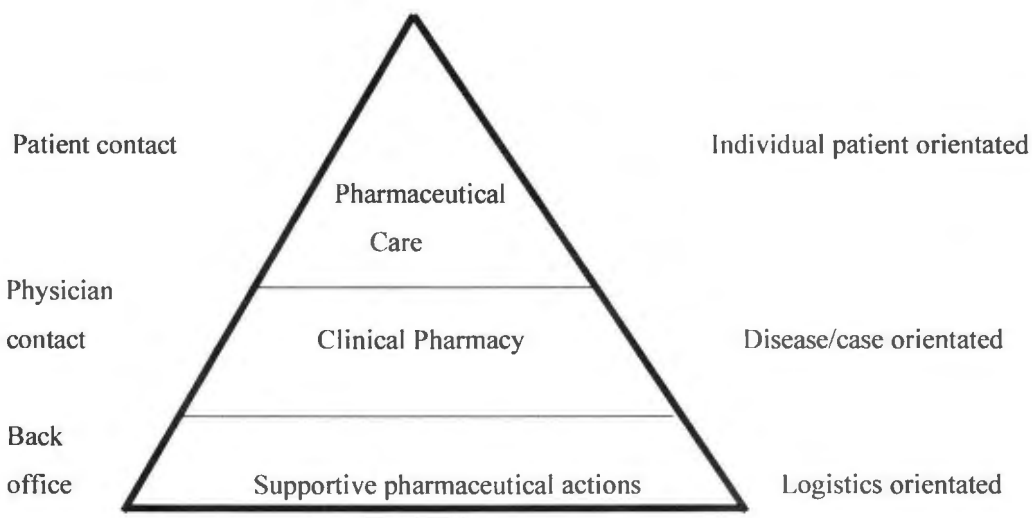

Figure 2.2: Activities in a pharmacy during the practice of pharmaceutical care (Adapted from Foppe van Mil *et al.*, 1999:205).

According to Anderson-Harper (1996:306) the job description of a pharmacist changes when pharmaceutical health care is implemented in his/her pharmacy.

Table 2.1: The pharmacist job description before and after implementing pharmaceutical care (Adapted from Anderson-Harper, 1996:306).

Before pharmaceutical care	After pharmaceutical care
Fill prescription in compliance with federal and state regulations in an accurate, timely, and courteous manner; and provide drug information and counselling to patients.	Interview patients to obtain information regarding medication use, medication allergies and sensitivities. Document the information in the patient's medical record or pharmacy information system when appropriate. Advise patients of directions for use. Medication storage requirements. Importance of compliance. Precautions and warnings for medication therapy. Advise the patient on the use of related devices and the co-ordination of medication therapy with diet, according to established policies and procedures.
Adhere to departmental patient service standards.	Evaluate and resolve, using professional judgement and established policies and procedures. Potential medication therapy problems identified through any and all available sources, including the patient and pharmacy information system.
Consult with health professionals.	Confer with medical personnel concerning pharmaceutical care and treatment of patients, related clinical diagnosis, drug combinations and dosage forms, and other factors that might influence the course of treatment and the activity of the medications. Suggest changes in medication therapy and/or use as appropriate to assure optimum therapeutic results.
Maintain a professional image.	Exemplify pharmacy's mission and the organisation's vision by contributing to health and satisfaction of patients by providing appropriate medications, information, and professional services in a helpful, caring, courteous, and efficient manner.

2.3 DIVISIONS OF PHARMACEUTICAL CARE

The pharmaceutical care practice is divided into three parts (Cipolle *et al.*, 1998:29):

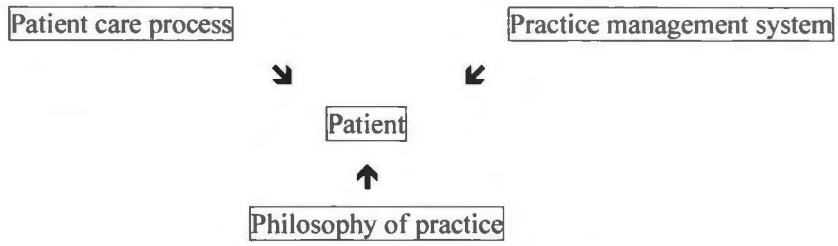

Figure 2.3: Pharmaceutical care practice (Adapted from Cipolle *et al.*, 1998:29).

2.3.1 Philosophy of practice

A philosophy of practice is a set of values that guides behaviours associated with certain acts; in this case, those of pharmaceutical care. A philosophy defines the rules, roles, relationships, and responsibilities of the practitioner (Cipolle *et al.*, 1998:15). Philosophy of pharmaceutical care practice consists of a number of elements (Cipolle *et al.*, 1998:17):

- A statement of social need.
- It continues with a patient-centred approach to meet this need.
- Caring for the patient through a therapeutic relationship.
- It leads to the description of the practitioner's specific responsibilities.

2.3.2 Patient care process

The patient care process will be discussed next. The emphasis in this study will be the patient care process.

The patient care process is defined by certain characteristics. First, the patient care process is centred on and "driven by" a patient's drug-related needs. Second, the patient care process describes the activities of the practitioner, as he or she interacts with the patient in a standard, systematic manner. And third, the success of the practitioner in meeting the patient's health care needs depends on very strict discipline to accomplish three objectives (Cipolle *et al.*, 1998:122), namely

(a) to assess the patient's needs;
(b) to bring the practitioner's available resources to meet these needs; and
(c) to complete a follow-up evaluation to determine the patient's actual outcomes.

According to other sources, such as Rovers *et al.* (1998:15), the patient care process can also be called the pharmaceutical care cycle. The entry point to the cycle is identifying a drug therapy problem.

Figure 2.4 shows how the cycle works and is the same as Cipolle's steps of the patient care process in figure 2.3.

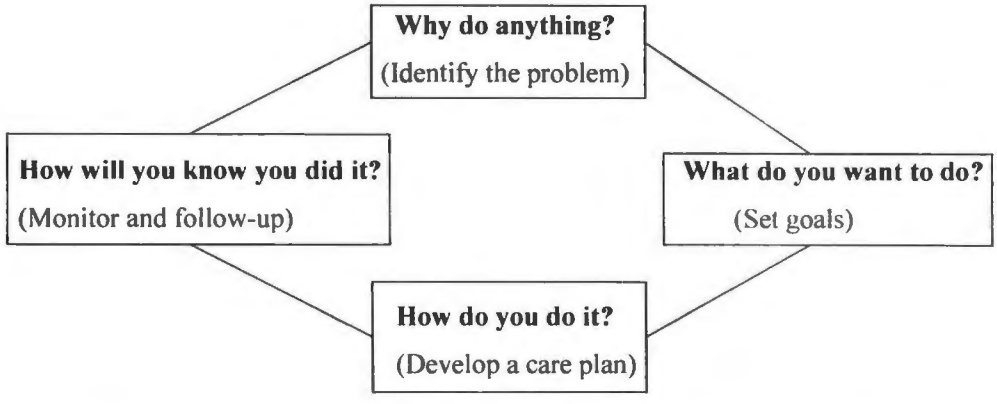

Figure 2.4: The pharmaceutical care cycle (Adapted from Rovers *et al.*, 1998:16).

Steps of the patient care process

The following are the three major steps in the patient care process:

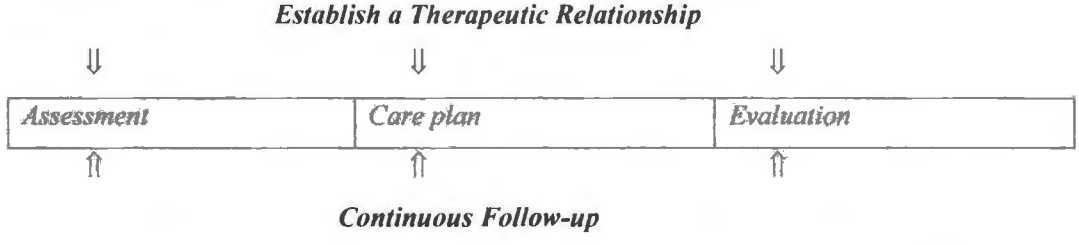

Figure 2.5: The three steps in the patient care process (Adapted from Cipolle *et al.*, 1998:124).

(a) *The assessment step*

Pharmaceutical care begins with an assessment of the patient's drug-related needs. An assessment is completed for three purposes. They are to (Cipolle *et al.*, 1998:125)

(i) determine that all of a patient's therapy is the most appropriate, most effective, safest, and most convenient available;

(ii) identify any drug therapy problems that might be interfering with the goals of therapy; and

(iii) identify any drug therapy problems the patient is at risk of developing in future – that is to say, any drug therapy problems the pharmacist must help the patient to prevent in future.

According to Stiglingh (1999:101) the assessment step represents a structured data- and information-gathering dialogue between the patient and the pharmacist.

(b) The care plan

According to Rovers *et al.* (1998:77) to create a care plan, the practitioner works with the patient to identify, evaluate, and choose methods for ensuring that drug therapy is effective and for minimising health-related problems.

The care plan is an outline of the responsibilities of both practitioner and the patient to meet stated, mutually agreed upon goals and interventions. Three purposes of the care plan (Cipolle *et al.,* 1998:126) are

(i) to resolve the drug therapy problems which were identified during the assessment;

(ii) to meet the goals of therapy for each of the patient's medical conditions, thereby achieving the outcomes desired by the patient; and

(iii) to prevent future drug therapy problems from developing.

Based on the patient's identified drug-related needs, the care plan will contain interventions that are designed to achieve the above mentioned purposes (Cipolle *et al.*, 1998:126).

The pharmacist or any other health care professional must integrate everything he/she knows about the patients, their pathophysiology, social or economic factors that relate to their health. For the care plan to work the health care professional must consider all these factors and use them to identify the best way to resolve the patient's drug therapy problems (Rovers *et al.,* 1998:82).

(c) The *follow-up evaluation*

A follow-up evaluation is a patient encounter, either in person or by telephone, which allows the practitioner to collect necessary information to determine whether the decisions made and actions taken during the assessment and care planning phase produced positive results. A follow-up evaluation is conducted for two purposes (Cipolle *et al.,* 1998:129):

(i) To determine progress toward meeting the established goals of therapy for each of the patient's medical conditions by evaluating the actual outcomes a patient experiences against these stated goals.

(ii) To assess whether any new drug therapy problems have developed or whether any new drug therapy problems need to be prevented in the future.

According to Rovers *et al.* (1998:6), the follow-up evaluation ensures continuity of care.

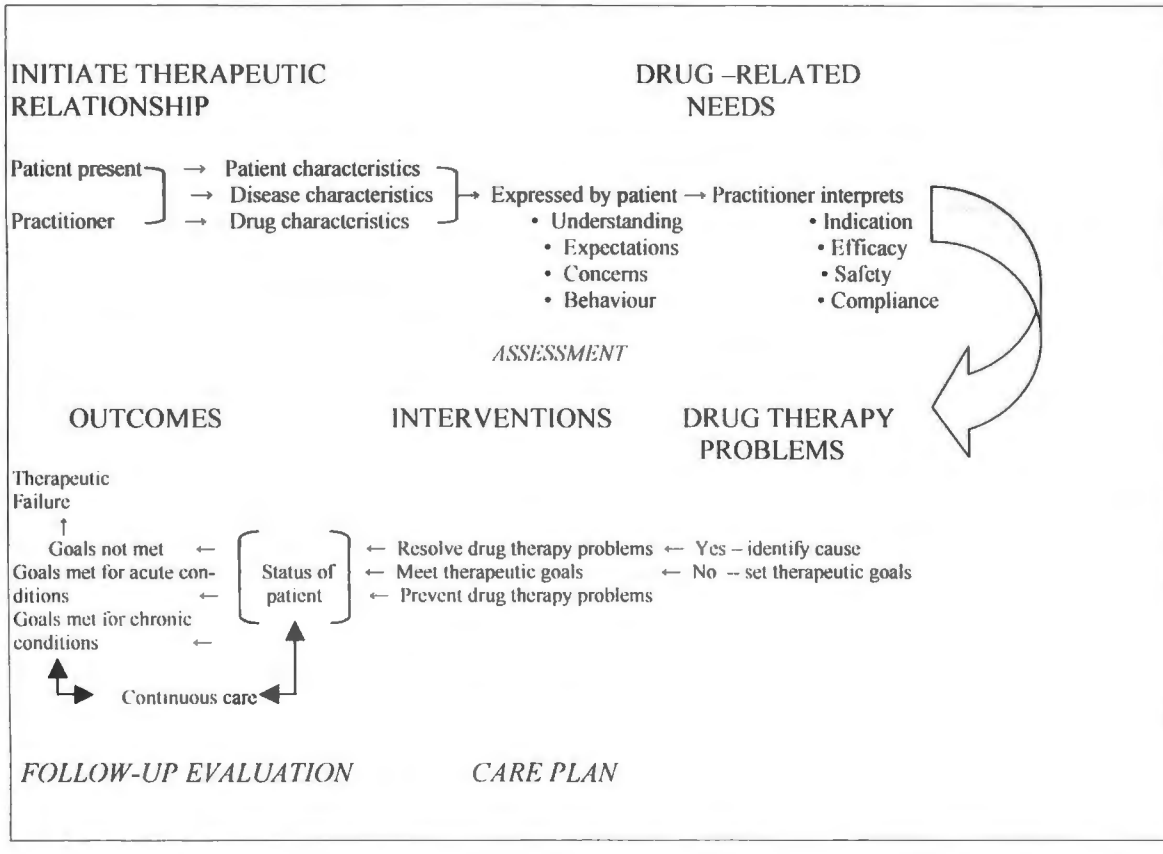

Figure 2.6: Continuous care process of pharmaceutical care practice (Adapted from Cipolle *et al.*, 1998:126).

2.3.3 **Practice management**

According to Lubbe (2000:432) the practice management system is the underlying organisational framework that supports the pharmaceutical care practice. Providing care to many patients, on a repeat basis, requires an efficient and effective organisation. A practice management system includes all the support required to provide the service to patients in an effective and efficient manner (Cipolle *et al.*, 1998:237). The patient care process and the practice management system directly impact each other on a constant basis (Cipolle *et al.*, 1998:238).

2.4 THE ROLE OF THE PHARMACIST AND OTHER HEALTH CARE PROVIDERS

A health care practitioner is an individual who possesses a body of knowledge and/or skills in any one of a number of health care fields and uses this knowledge to meet the health care needs of a patient (Cipolle *et al.*, 1998:342). The role of the health care professionals discussed will include pharmacists, nurses and physicians.

2.4.1 The responsibilities of the pharmaceutical care practitioner

The pharmaceutical care practitioner has the following responsibilities (Cipolle *et al.*, 1998:81-105):

- To ensure that there is an appropriate indication for every drug that the patient is taking.
- To ensure that all of the medications that are indicated as appropriate for the patient are available to the patient.
- To do whatever is necessary to ensure that a patient's drug therapy is effective.
- To ensure that all of the drug therapies the patient is taking are as safe as possible and harmless to the patient.
- To make sure the patient understands and is willing and able to adhere to the drug therapy and care plan instructions.

2.4.2 The role of pharmacists

To understand the role of a pharmacist, in South Africa specifically, one must know what the Pharmacy Act entails. According to the stipulations of section 29 (3) of the Pharmacy Act (53/1974), section 23(2)(a)(i) and 34 of the Veterinary and Para-Veterinary Professions Act, 1982 (19/1982), the following acts shall be regarded to be acts specially pertaining to the profession of a pharmacist:

- Provision of pharmaceutical care by taking responsibility for the patient's medicine related needs and being accountable for meeting these needs, which shall include but not be limited to the following functions:
  (a) the evaluation of a patient's medicine related needs by determining the indication, safety and effectiveness of the therapy;
  (b) the dispensing of any medicine or scheduled substance on a prescription of a person authorised to prescribe medicine;
  (c) furnishing of information and advice to any person with regard to the use of medicine;
  (d) determining the patient compliance with the therapy and follow up to ensure that the patient's medicine related needs are being met; and
  (e) the provision of pharmacist initiated therapy.
- The compounding, manipulation, preparation or packaging of any medicine or scheduled substance or the supervision thereof.
- The manufacturing of any medicine or scheduled substance or supervision thereof.
- The purchasing, acquiring, importing, keeping, possessing, using, releasing, storage, packaging, repackaging, supplying or selling of any medicine or scheduled substance or the supervision thereof.
- The application for the registration of a medicine in accordance with the Medicines Act (101/1965).

A pharmacist has certain activities in the scope of pharmacy practice. The following services or acts shall for purposes of the Pharmacy Act (53/1974) be regarded to be services or acts pertaining to the scope of practice of a pharmacist:

- The acts specially pertaining to the profession of a pharmacist as prescribed in section 29 (3) of the Pharmacy Act (53/1974) (refer to section 2.4.2).
- Formulation of any medicine for purposes of registration as a medicine.
- Distribution of any medicine or scheduled substance.
- The repackaging of medicine.
- Initiation and conducting of pharmaceutical research and development.
- The promotion of public health care.

As discussed in the above section, the pharmacist is compelled be the Pharmacy Act (53/1974) to perform pharmaceutical care and this section listed the activities of the pharmacist who performs pharmaceutical care according to the South African Pharmacy Council.

According to Hepler and Strand (1990:540) four criteria must be met before pharmacists should be granted the authority to provide pharmaceutical care and before pharmacists should accept that responsibility: (1) the provider must have adequate knowledge and skills in pharmaceutics and clinical pharmacology, (2) the provider must be able to mobilise the drug distribution system through which drug-use decisions are implemented, (3) the provider must be able to develop sound relationship with the patient and other health-care professionals that are needed in the provision of pharmaceutical care, and (4) as a practical matter, there must be a sufficient number of providers to serve society.

According to Smith and Benderev (1991:541) there are three levels of pharmaceutical care, namely, primary, secondary, and tertiary. Primary pharmaceutical care begins when it is first determined that drug therapy may be needed for a condition not requiring hospitalisation. Secondary pharmaceutical care begins with the initial drug therapy for a more complex medical condition than in primary care. Tertiary pharmaceutical care takes place in institutions that render critical-care services. The most comprehensive clinical pharmacy services are offered (Smith & Benderev, 1991:542-543). The three levels of pharmaceutical care have a common set of basic pharmacist functions. The following is a list of basic pharmacist functions common to all levels of care (Smith & Benderev, 1991:542 and Carroll & Burruss, 1996:547):

- Develop and use a patient profile.
- Interpret, question, clarify, verify, and validate all drug-related orders.
- Provide a safe and efficient drug-dispensing system.
- Monitor drug therapy for safety, efficacy, and desired clinical outcome.

- Screen for drug allergies, drug-drug interactions, drug-food interactions, and concomitant drug use.
- Detect and report drug allergies and adverse reactions.
- Recommend initial or alternative drug therapies.
- Respond to drug information requests from physicians, nurses, and patients.
- Teach health care providers and patients about drug use.
- Obtain medication histories by interviewing patients.
- Assist in the selection of the drugs of choice and dosage forms.
- Conduct drug-use evaluations to gauge the appropriateness of drug use and achievement of desired therapeutic outcomes.
- Apply pharmaceutical principles to selected drug therapies.

According to Dolinsky and Webb (1996:226) there are a few practical functions for pharmacists in every practice environment to meet patients' drug-related needs:

- Participate in the drug use decision-making process.
- Select the appropriate dosage form.
- Select the drug product source supply.
- Determine the dose and dosage schedule.
- Prepare medication for patient use.
- Provide drug products to patients.
- Counsel patients.
- Monitor patients to maximise compliance.
- Monitor patient progress with regard to therapeutic objectives.
- Monitor patients to prevent adverse drug reaction and drug interactions.

2.4.3 The various roles of nurses

A practitioner of nursing is the professionally trained and registered nurse who is legally empowered by the Nursing Act (50/1978), to carry joint responsibility with the doctor for patient care (Vlok, 1991:47). The nurse has two kinds of functions namely, dependent or independent functions. Dependent functions are those for which the nurse needs a prescription, usually by a doctor, e.g. intravenous feeding, medication. Independent functions are those for which she takes responsibility, e.g. the administration of the medicine (Vlok, 1991:49).

The following are the various roles of nurses (Dreyer, 1999:27-36):

- Advocate: Advocacy, in the context of community health care delivery, is both an action in support of the patient and a provision of information to the patient.

- Management: Nurses are responsible for the management of client services. Management functions include, supervising family health care, running clinics, planning health care programmes, referring patients to other health care professionals.
- Education: The educational role comprises, among others, health education, in-service training, orientation, formal teaching and training.
- Provider of health care: Nurses fulfil the roles and functions related to prevention of disease, the promotion of health and the provision of curative and rehabilitation health care.

2.4.4 **The role of physicians**

A general practitioner or family physician is the physician who is primarily responsible for providing comprehensive health care to every individual seeking medical care, and arranging for other health personnel to provide services when necessary (Bentzen *et al.*, 1991). A primary care physician is a generalist physician who provides definitive care to the undifferentiated patient at the point of first contact and takes continuing responsibility for providing the patient's care. There are various roles for a physician. These are a few of those roles (AAFP, 1996):

- To promote health and maintain the health of the patient.
- To counsel and educate the patient.
- To prevent disease, treat and diagnose acute and chronic illnesses in a variety of health care settings (e.g. office, inpatient, critical care, long-term care, home care, day care, etc.).

The general practitioner or family physician is not only committed to the individual, but also to the community. According to Bentzen *et al.* (1991) the commitments to the community will include

- A knowledge of the epidemiology of the community served.
- Maximum influence on any health problem in the community.
- Understanding for health-related behaviours in the community.
- Prevention of illness, promotion of health, management of illness and rehabilitation.

The commitments to the individual include (Bentzen *et al.*, 1991)

- Identification of all the problems presented by the patient, including undifferentiated problems, early states of illness, acute problems, chronic diseases, psychological problems, and rehabilitation needs.
- Determining what is needed to heal the patient in both biomedical and humanistic terms; that is, physically, mentally and socially.
- Diagnosis of the prevalent disease, elimination of possible serious disease, and coordination of other health services when needed.

2.5 PRIMARY HEALTH CARE

In this section various definitions of primary health care will be discussed. Primary health care is essential care for any person who is in need of health care. To ensure proper health care to the patients, the health care provider must provide pharmaceutical care and so take responsibility for the care and therapy of the patients. Thus, the health care provider becomes a pharmaceutical care provider.

At an international conference at Alma Ata in 1978 the following definition of primary health care was developed:

"Primary health care is essential health care universally accessible to individuals and families in the community by means acceptable to them through their full participation and at a cost that the community and the country can afford"(Smit *et al.*, 1994:2 & Smith, 1992:211). It is widely accepted that primary care is the key to making health care accessible, acceptable, appropriate and affordable, particularly in developing nations (Smith, 1993:1).

Primary health care is the central function and main function of the country's health system and of the social and economic development of the community (WHO, 2001).

Primary health care is the first point of contact between a patient and a member of the health care system (Smith, 1992:211). For the pharmacist or member of the health care team to provide pharmaceutical care one must come in contact with the patient. This is where primary health care comes to terms. If primary health care can be given, then pharmaceutical care is also possible.

According to the WHO (2001) primary health care rests on the following eight elements:

- Adequate supply of safe water and basic sanitation.
- Education on prevailing health problems and methods of preventing and controlling them.
- Promotion of food supply and proper nutrition.
- Maternal and child health care, including family planning.
- Immunisation against the major infectious diseases.
- Prevention and control of locally endemic diseases.
- Appropriate treatment of common diseases and injuries.
- Provision of essential medicines.

The pharmacist should consider the following important aspects when providing primary health care (Smit *et al.*, 1994:2):

- More cost-effective delivery of health care.

- The promotion of health and the prevention of diseases, in addition to the treatment of diseases.
- The provision of **accessible** basic health care services and facilities.
- The provision of health care relevant to the **main** health care problems.
- Provision of health care education.
- The provision of and education on the correct usage of essential drugs.
- The training of auxiliary and rural health care workers.

Philani Prime Cure® medi centres are primary health care facilities. No procedures, investigations or treatment can be performed at those centres that are beyond the scope of practice or qualification or clinical ability of a general practitioner. Philani Prime Cure® offers a comprehensive range of primary health care services to the patient. These services include (Philani Prime Cure®, 2002):

- Consultation with a general practitioner.
- Provision of acute and chronic medication.
- The services of radiology, pathology, optometry, dentistry and immunisation.
- Family planning and natal care.
- The treatment of minor trauma.

2.6 DRUG THERAPY PROBLEMS

Pharmaceutical care was clearly defined in section 2.1. The emphasis of pharmaceutical care is about the provision of care to the patient and assuring that the patient's quality of life is improved. Drug therapy problems can cause considerable harm to a patient, as discussed in this section. Through pharmaceutical care the health care provider can identify potential drug therapy problems and so help the patient.

According to Cipolle *et al.* (1998:75) a drug therapy problem can be defined as any undesirable event experienced by the patient that involves or is suspected to involve drug therapy and that actually or potentially interferes with a desired patient outcome.

A drug therapy problem always has two primary components (Cipolle *et al.,* 1998:75):

- An undesirable event or risk of an event experienced by the patient. This event can take the form of a medical compliant, symptom, diagnosis, disease, impairment, disability, or syndrome. The event can be the result of psychological, physiological, sociocultural, or economic conditions
- Some relationship must exist (or be suspected to exist) between the undesirable patient event and drug therapy. This relationship can be (a) the consequence of drug therapy, suggesting an

association or even a cause and effect relationship or (b) an event that requires drug therapy for its resolution or prevention.

2.6.1 Translating drug-related needs into drug therapy problems

According to Cipolle *et al.* (1998:76) drug-related needs include any concerns, expectations, or lack of understanding identified by the patient or practitioner and related to a drug substance. Table 2.2 will show how drug-related needs are translated into drug therapy problems.

Table 2.2: Translating drug-related needs into drug therapy problems (Adapted from Cipolle *et al.*, 1998:77).

PATIENT'S EXPRESSION	DRUG-RELATED NEEDS	DRUG THERAPY PROBLEMS
Understanding	Indication	1. Additional drug therapy 2. Unnecessary drug therapy
Expectations	Effectiveness	3. Wrong drug 4. Dosage too low
Concerns	Safety	5. Adverse drug reactions 6. Dosage too high
Behaviour	Compliance	7. Compliance

The pharmaceutical care practitioner depends, in large part, on the patient to provide the information needed to make a comprehensive assessment of the patient's drug-related needs and to determine whether the patient has a drug therapy problem. This is why the therapeutic relationship between the patient and pharmaceutical care practitioner is so important. Without the proper information, inappropriate decisions will be made and the wrong action taken. The process whereby the pharmaceutical care practitioner elicits the appropriate information to assess the patient's drug-related needs is the patient care process (Cipolle *et al.*, 1998:78). (Refer to 2.3)

2.6.2 Classifications of drug therapy problems

Table 2.3 contains the drug therapy problems.

Table 2.3: Drug therapy problems (Adapted from Strand *et al.*, 1990:535; ASCP, 1996:2).

CATEGORIES	DESCRIPTION
Untreated indication	The patient has a medical problem that requires drug therapy (an indication for drug use) but is not receiving a drug for that indication
Improper drug selection	The patient has a drug indication but is taking the wrong drug
Subtherapeutic dosage	The patient has a medical problem that is being treated with too little of the correct drug

Table 2.3 (continued)

Failure to receive drugs	The patient has a medical problem that is the result of his or her not receiving a drug (e.g. for pharmaceutical, psychological, sociological, or economic reasons)
Overdose	The patient has a medical problem that is being treated with too much of the correct drug (toxicity)
Adverse drug reactions (ADR)	The patient has a medical problem that is the result of an adverse drug reaction or adverse effect
Drugs used without indication	The patient is taking a drug for no medically valid indication
Drug interactions	The patient has a medical problem that is the result of a drug-drug, drug-food, or drug-laboratory interaction
Treatment failures	The desired therapeutic outcome is not achieved

The categories of drug therapy problems will be discussed:

(i) *Untreated indications:* The patient needs additional drug therapy.

In this drug therapy problem the patient is suffering from an illness or develops a new or worsening condition and is in need of pharmacotherapy (Cipolle *et al.,* 1998:81). For example, a patient is being appropriately treated for peripheral vascular disease but is not receiving treatment for a developing anaemia (Strand *et al.,* 1990:1094). The following patients are in this category:

- A patient requires new drug therapy to treat a new illness (Cipolle *et al.,* 1998:81), but is not receiving medication for that indication (e.g. for pharmaceutical, psychological, sociological, or economic reasons) (McDonough, 1996:455).
- A patient requires the addition of a second or third drug to treat a condition optimally (Cipolle *et al.,* 1998:81). Thus, the patient is in need for synergistic or prophylactic therapy for the condition (Rovers *et al.,* 1998:58).
- A patient who is at risk to develop a new illness or disease and the addition of a form of drug therapy designed to prevent that illness or disease (Cipolle *et al.*, 1998:81).
- A patient has a chronic disorder requiring continuation of drug therapy (Cipolle *et al.*, 1998:82).
- When a patient has one or more symptoms that are not being treated, the pharmacist cannot necessarily conclude that the patient has a drug therapy problem. Only after the symptom has been evaluated, and it is determined that a drug did not cause the drug therapy problem, can the pharmacist approve additional therapy for the patient (Rovers *et al.,* 1998:58).

(ii) *Improper drug selection*: The patient is taking the wrong drug.

If the patient is not experiencing the intended positive outcomes from a certain drug regimen, then the pharmaceutical care practitioner should consider that the patient could be receiving or taking the wrong drug (Cipolle *et al.*, 1998:88). According to ASCP (2000) improper drug selection occurs when a drug that is not the most appropriate for the special needs of the patient, is being taken.

The following patient cases are applying to the "wrong drug" category (Cipolle *et al.*, 1998:82):

- The patient has a medical problem for which the drug is not effective.
- A patient is allergic to the medication.
- The patient is receiving a drug that is not the most effective for the indication being treated.
- A patient has risk factors that contraindicate the use of this drug.
- The patient is receiving a drug that is effective but not the least costly.
- The patient is receiving a drug that is effective but is not the safest.
- A patient has an infection involving organisms that are resistant to this drug.
- The patient has become refractory to the present drug therapy.
- The patient is receiving an unnecessary combination product when a single drug would be appropriate.

According to Cipolle *et al.* (1998:89) the success and effectiveness of drug therapy is contingent upon the identification and eventual diagnosis of the patient's medical problem or problems. All of the components that constitute making drug therapy the correct regimen for a given patient can also contribute to making a particular drug therapy the wrong treatment for that patient. These include (Cipolle *et al.*, 1998:89):

- The patient's medical condition.
- The severity of the condition.
- The infectious process and organism involved.
- The age and general health status of the patient – including renal, hepatic, cardiovascular, neurological, cognitive, and immune functions.

(iii) *Subtherapeutic dosage*: The patient is taking too little of the correct drug.

Drug therapy problems resulting from patients receiving inadequate doses of potentially effective medications can develop into serious and expensive health care problems (Cipolle *et al.*, 1998:90). An example of a subtherapeutic dosage is when switching from phenythoin suspension to capsules, one must take into account that the capsules are formulated with phenythoin sodium, which contains only 92% phenytoin acid (Strand *et al.*, 1990:1095).

The following causes of drug therapy problems can occur when the dosage is too little (Cipolle *et al.*, 1998:82):

- The dosage used is too little to produce the response for the patient.
- The patient's serum drug concentrations are below the desired therapeutic range.
- Timing prophylaxis (e.g. presurgical antibiotic given too early) was inadequate for the patient.
- Drug, dose, route, or formulation conversions were inadequate for the patient.

- Dose, and interval flexibility were inadequate for the patient.
- Drug therapy was altered prior to adequate therapeutic trial for the patient.

(iv) *Failure to receive drugs:* The patient is non-compliant for several reasons.

The patients frequently do not take drugs as prescribed or instructed for a number of reasons. One of these reasons is that the patient perceives that the drug has caused or will cause some adverse event (Cipolle *et al.*, 1998:105). According to Winfield (1998:444) compliance is *'an action in accordance with a request or command'*. Non-compliance is usually thought of as not taking a dose, but it could be taking it at the wrong time or taking too much.

The patient's understanding and knowledge about his or her illness and medications are clearly important issues in determining the success of any form of pharmacotherapy (Cipolle *et al.*, 1998:106). Patients have their own health care beliefs, ideas about medications, and, most importantly, ideas about what they want and when they want it (Cipolle *et al.*, 1998:108).

The following are certain causes of non-compliance (Winfield, 1998:446-448):

- Understanding and comprehension: The patient may be unable to understand the instructions. Some people cannot read, others have poor eyesight, the writing may be too small, or the ink too faint. When patients are counselled, they may not be listening, may have a hearing difficulty, may have a problem with their educational level or their level of consciousness.
- Medicine management: The more different medicines the patient has, the more problems increase. Thus if all medicines are to be taken at the same time of day, compliance will be higher than if several different times throughout the day are used. Another problem is remembering whether a dose has been taken.
- Disease-related problems: Various aspects of a patient's state of health can influence compliance. Thus an arthritic may have problems opening a container, a skin condition may require application of a cream to a part of the body, which the person cannot reach. The state of mind of the patient will also have an impact on compliance. Depression, distress, tension and aggression can reduce people's motivation towards taking their medicines.
- Physical limitations: One aspect is how easy the patient finds it to either obtain a repeat prescription or have it dispensed. Distance, particularly where the patient has limited access to transport or lives in a rural area, can be a major problem. Dysphagia, a difficulty in swallowing, is often overlooked.
- Drug-related problems: The medicines themselves can also create compliance problems. Side effects of a drug, particularly if unpleasant, may deter the patient, although the effect is minor if the patient believes that the medicine is helping.

- Other factors: Social and psychological influences on patients will be important. Of importance is the level of confidence, which the patients have in the doctor. If confidence is low, they are less likely to comply, because they will also doubt the effectiveness of the treatment.

The following patients may be non-compliant (Cipolle *et al.*, 1998:83):

- The patient did not receive the appropriate drug regimen because of a medication error (prescribing, dispensing, administration, monitoring) that was made.
- The patient did not comply (adherence) with the recommended directions for using the medication.
- The patient did not take the drug(s) directed owing to the high cost of the product.
- The patient did not take the drug(s) as directed because of lack of understanding of the directions.
- The patient did not take the drug(s) as directed because it would not be consistent with their health beliefs.

(v) *Overdose*: The dosage is too high for the patient.

When a patient receives too high a dose of an agent and experiences a dose-dependent or more often a concentration-dependent toxic effect, he or she is experiencing a drug therapy problem (Cipolle *et al.*, 1998:101). A drug overdose is the accidental or intentional use of a drug or medicine in a dose that is higher than normally used (Edgren, 2001). An example of overdose is the rapid escalation of nicotinic acid doses very often associated with severe cutaneous reactions (Strand *et al.*, 1990:1095).

There are a few causes for this drug therapy problem (Cipolle *et al.*, 1998:83):

- Dosage is too high for the patient.
- The patient's serum drug concentrations are above the desired therapeutic range.
- The patient's drug dose was escalated too rapidly.
- The patient has accumulated a drug from chronic administration.
- Drug, dose, route, formulation conversions were inappropriate for the patient.
- Dose and interval flexibility was inappropriate for the patient

(vi) *Adverse drug reactions*: The patient is experiencing an adverse drug reaction.

According to Brown (2000) an adverse drug reaction can be defined as an unexpected diminished or enhanced pharmacologic activity or toxicity of a drug when used alone, or any noxious response to a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy.

Within the practice of pharmaceutical care, the definition of an adverse drug reaction is intended to encompass undesirable negative effects caused by the medication. Such effects are not predicted

because they contradict the expected or known pharmacology of the drug (Cipolle *et al.*, 1998:96). According to Kee and Hayes (2000:155) adverse reaction is an undesirable drug effect ranging from mild untoward effects to severe toxic effects, including hypersensitivity reaction and anaphylactic reaction.

Side effects are physiologic effects not related to desired drug effects. All drugs have side effects, desirable or undesirable. For example, the use of diphenhydramine hydrochloride at bedtime when its side effect of drowsiness is beneficial (Kee & Hayes, 2000:12). According to Edwards (1997:262) a side effect is any unintended effect of a pharmaceutical product, occurring at doses normally used in humans, and related to the pharmacological properties of the drug.

According to Lee and Rawlins (2000:34) most studies found that around 5% of hospital admissions are attributable to adverse drug reactions; that 10 to 20% of patients will experience an adverse drug reaction during their stay in hospital; and that, as a result, the length of stay may be increased in up to 50% of these patients.

There are two types of adverse drug reactions, namely, type A and type B reactions. Type A (augmented) reactions are normal pharmacologic effects of the drug exaggerated to the point of being undesirable or intolerable for patients. These adverse reactions are often dose-dependent. Examples of type A reactions are warfarin or heparin (which cause bruising) and diphenhydramine (which cause drowsiness) (Brown, 2000). Type A reactions also include unwanted pharmacological actions of a drug, e.g. antimuscarinic effects of tricyclic antidepressants which can cause blurred vision, tachycardia, dry mouth, and urinary tension (Cunningham & Krska, 1998:356). Type B (bizarre) reactions are often more severe adverse effects unrelated to the known pharmacologic action of the drug and include most immunologic reactions. A type B reaction is an anaphylactic reactions to penicillin (Brown, 2000). Other examples of type B reactions are haemolysis with methyldopa, or thrombocytopenia with angiotensin-converting enzyme (ACE) inhibitors (Lee & Rawlins, 2000:34).

There are several causes for a patient to experience an adverse reaction:

- The patient is receiving a drug product considered to be unsafe.
- The patient has an allergic reaction to the drug.
- Incorrect administration of the drug product causes an adverse drug reaction (Cipolle *et al.*, 1998:97). An adverse event can occur when a drug overdose takes place, whether accidental or intentional (Advanstar Pharmaceutical Group, 2000).
- Interaction with another drug precipitates an adverse drug reaction.
- The dosage is increased or decreased too rapidly and results in an adverse reaction.

- The patient experiences an undesirable effect that was otherwise not predictable (Cipolle *et al.*, 1998:97).
- If the patient is using another drug at the same time, the following can be a problem:

The bioavailability of the drug is altered due to an interaction with another drug or food that is being taken. The effect of the drug has been altered due to enzyme inhibition/induction. The effect of the drug has been altered due to displacement from the binding sites by another drug.

- The patient's laboratory test result has been altered due to interference from a drug the patient is taking.
- Drug abuse can lead to an adverse drug reaction (Advanstar Pharmaceutical Group, 2000).

The incidence of adverse drug reactions is affected by certain factors, namely: multiple drug therapy, age, multiple disease states, types of drugs prescribed, dosage, route of administration, formulation, sex, race, genetic factors, and patient compliance (Becic & Kusturica, 2001:40). The following is a short description of the factors (Cunningham & Krska, 1998:357-358; Lee & Rawlins, 2000:35):

- Multiple drug therapy: An obvious association exists between the number of drugs being taken and the risk of experiencing and adverse drug reaction.
- Age: The incidence of adverse drug reactions is known to rise with age. Neonates also have reduced drug clearance, resulting in increased risk of adverse drug reactions. A well-known example is the 'grey baby' syndrome with chloramphenicol. The elderly more often suffer from adverse reactions than younger patients.
- Multiple disease states: Some disease states may alter a patient's response to drug therapy. Examples include patients with peptic ulcer disease being at increased risk of bleeding when prescribed non-steroid anti-inflammatory drugs, and those with asthma who may suffer bronchospasm with beta-adrenoceptor blocking drugs.
- Types of drug prescribed: Adverse drug reactions may also be more likely to occur when the drug regimen includes medicines with a narrow therapeutic index. Examples of such drugs include digoxin, anticoagulants, and insulin.
- Dosage: Many type A adverse drug reactions seem to be related to the dose of the medication, and can be managed by a reduction in dose of the drug in question.
- Route of administration: If the intravenous route releases a drug too quickly, adverse drug reactions can arise especially with drugs that act on the heart. Rapid injection of digoxin may cause nausea and arrhythmias, and for this reason should be avoided.
- Formulation: Adverse drug reactions can be due to excipients in pharmaceutical formulations, for example colouring agents, sweeteners, preservatives.
- Gender: Some adverse drug reactions appear to occur more frequently in females. Women are reputed to be more susceptible to the toxic effects of digoxin, heparin and captopril.

- Race and genetic factors: Differences in susceptibility to adverse drug reactions have been demonstrated between races. This is probably due to differences in genetics and metabolism.
- Patient compliance: Non-compliance with drug therapy may also play a part in adverse drug reactions.

Pharmacists must be aware of the main factors, which influence the occurrence of adverse drug reactions so that they can prevent and identify the beginning of adverse drug reactions (Becic & Kusturica, 2001:40).

(vii) *Drug use without indication*: The patient is taking unnecessary drug therapy.
Drug therapy is considered unnecessary for the patient if there was not or is no longer a valid medical indication for a particular drug. The cost of unnecessary drug therapy should also be considered (Cipolle *et al.*, 1998:85). According to Chrisholm *et al.* (1997:371) it is the pharmacist's responsibility to see that patients are not exposed to potent drugs, for which there is no valid medical indication.

The following are possible causes for unnecessary drug therapy (Cipolle *et al.*, 1998:82; Chrisholm *et al.*, 1997:371):

- The patient accidentally or intentionally ingested a toxic amount of a drug or chemical, resulting in the present illness or condition.
- The patient's medical problem(s) are associated with drug abuse, alcohol use, or smoking.
- The patient's medical problem is better treated with non-drug therapy.
- The patient is taking multiple drugs for a condition for which only single-drug therapy is indicated.
- The patient is taking drug therapy to treat an avoidable reaction associated with another medication.
- The patient is receiving a drug therapy for which there is no identifiable rationale or scientific literature to support it.

(viii) *Drug interactions*: The drug the patient is taking has interactions with various components.
There are various drug interactions that can occur, for example, drug-drug interactions, drug-nutrient interactions, drug-disease interactions, drug-herbal interactions and drug-laboratory interactions (Brown, 2000; Kee & Hayes, 2000:159).

Drug-drug interactions can be defined as the modulation of the pharmacologic activity of one drug by the prior or concomitant administration of another drug. For example, administrating penicillins with probenecid significantly elevates serum levels of penicillin and prolongs its effectiveness (Brown,

2000). Drug-drug interaction refers to the possibility that one drug may alter the intensity of pharmacological effects of another drug given concurrently. The net result may be enhanced or diminished effects of one or both of the drugs or the appearance of a new effect that is not seen with either drug alone (Nies & Spielberg, 1996:51). Drug interaction can be defined as an altered or modified action or effect of a drug as a result of interaction with one or more other drugs (Kee & Hayes, 2000:155).

Drug-nutrient interactions occur when medication and food are taken together. Generally, administering oral medication along with food or at a mealtime is a convenient manner of drug dosing. Drug interactions can occur that modify the activity of the drug (decrease or increase drug effects) or impair the nutritional benefits of certain food (Refer to 2.11) (Brown, 2000).

Drug-disease interactions occur when certain drugs have the capability to exacerbate acute and/or chronic disorders. For example, beta-blocking agents precipitate and exacerbate diseases such as asthma, chronic obstructive pulmonary disease, and peripheral vascular disease. Prednisone can aggravate congestive heart failure and cause fluid overload (Brown, 2000). According to Chrisholm *et al.* (1997:371) medical references often refer to these as disease-drug interactions as absolute or relative contraindications for the medication. Absolute contraindications are where the risk of therapy given for certain diseases, clearly outweighs any benefit for the patient. With relative contraindication, the balance of risk and benefits must be assessed individually.

Drug-herbal interactions can occur because many patients do not tell their physician or pharmacist that they are using herbal products. For example, theophylline and St. John's wort can increase serum theophylline concentration by about by 50%. This leads to a dosage adjustment (Brown, 2000).

Drug-laboratory interactions occur when abnormal plasma or serum electrolyte concentration can affect certain drug therapies. For example, when digoxin is taken and there are decreased serum potassium and serum magnesium levels or increased serum calcium levels, then digitalis toxicity may result (Kee & Hayes, 2000:159).

(ix) *Treatment failure*: The patient has a medical problem that is being treated with a medication that is generally considered appropriate for the indication, but the desired therapeutic outcome is not achieved (ASCP, 1996).

2.7 DRUG-RELATED EVENTS (DRE)

A drug-related event has the potential to cause considerable patient harm, and its identification, relief and prevention form the major responsibilities for pharmacists (Wills & Brown, 2000:99). According to Wills and Brown (2000:99) a drug-related event (DRE) could be another person's drug-related problem. A drug-related event could be divided into two major groups, namely: procedural drug-related event and clinical drug-related event (Wills & Brown, 2000:100). Figure 2.7 shows the major categories of detrimental of drug-related events.

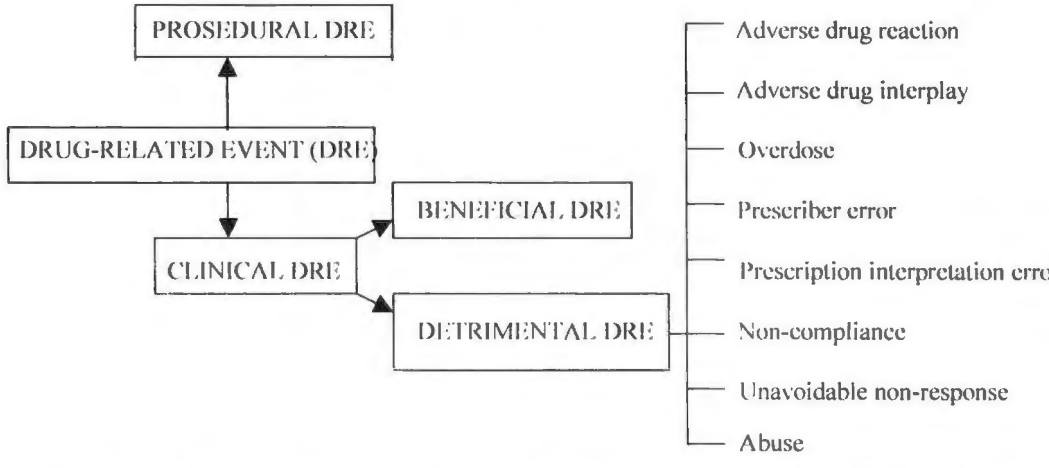

Figure 2.7: Major categories of detrimental drug-related events (Adapted from Wills & Brown, 2000:101).

The different drug-related events, according to figure 2.7, are procedural, clinical, beneficial and detrimental drug-related events. A procedural drug-related event is mainly concerned with the mechanism of supply and procurement of drugs. For the most part they are implementations of legal or local documentary requirements such as prescription writing requirements, clinical trial documentation and drug administration records. For example procedural drug-related events may be the subject of prescription audit, where the completeness of documentation is investigated (Wills & Brown, 2000:100).

Clinical drug-related events are the situations in which a drug plays a key role in events that directly affect, or potentially affect, a patient's health. Clinical drug-related events may be beneficial or detrimental to the patient. Beneficial drug-related events are interventions or actions, which are helpful, or at least not detrimental, to the patient's health. There are numerous examples including: successful responses to drug treatment, patient counselling, appropriate drug selection, correct drug administration and accurate drug dispensing. Detrimental drug-related events are incidents where a drug plays a key role in undesirable events that are harmful, or potentially harmful, to the patient. Refer to figure 2.7 for the categories of detrimental drug-related events (Wills & Brown, 2000:101).

According to Wills and Brown (2000:103) during the detrimental drug-related event, drug interactions are a part of the adverse drug interplay (refer to Figure 2.7).

2.8 CLASSIFICATION OF DRUG INTERACTIONS

Martin (1978:352) described drug effects as *homergic* which refers to two drug producing the same overt effect, *heterergic* which refers to two drugs when only one of them produce a given effect, *homodynamic* which refers to drugs producing a given effect by means of the same action or mechanism, and *heterodynamic* which refers to a drug producing the same effect by a different action or mechanism.

To understand drug interactions one must know how a combination of drugs can interact. There are three types of actions: addition, inhibition and potentiation of effects.

2.8.1 Addition of effects

When drugs with similar pharmacological effects are administered concurrently, an additive or synergistic response is usually seen (Hansten, 1998:1059). According to Klaassen (1996:68) an additive effect describes the combined effect of two chemicals that are equal to the sum of the effect of each agent given alone. An example of this effect is the effect of sulphonamides combined with trimethoprim (e.g. co-trimoxazole) and provides an effective method of treatment for infection caused by micro-organisms that may be resistant to sulphonamides on its own (Chambers & Sande, 1996:1048).

2.8.2 Inhibition of effects

This effect can refer to any type of drug interaction that occurs when a substance given prevents a drug from exerting its action and producing its full effects in a patient (Martin, 1978:352). Antagonism, the result of a reversible or irreversible chemical or biological interaction that decreases drug effects, occurs when a drug with a given activity (agonist) is blocked by a drug with a nullifying action (antagonist) (Martin, 1978:353). Antagonism is the interference of one chemical with the action of another. Antagonism at the receptor for the chemical entails the blockade of the effect of an agonist with an appropriate antagonist that competes for the same site (Klaassen, 1996:68). An example is when atropine is given with metoclopramide and the atropine antagonises the effects of metoclopramide (Turner, 2001:88). Metoclopramide is used for vomiting and nausea in adults during radiotherapy (Gibbon, 2000:45).

2.8.3 **Potentiation of effects**

This term refers to the enhancement of the effect of a drug by another substance (Martin, 1978:353). Potentiation is the increased effect of a toxic agent acting simultaneously with a nontoxic one (Klaassen, 1996:68).

Synergism, a type of potentiation, occurs when the combined given effect of two or more drugs acting simultaneously is greater than the algebraic sum of the individual effect that is produced when each drug is administered alone (Martin, 1978:353). A synergistic effect is one in which the combined effect of two chemicals is greater than the sum of the effect of each agent given alone (Klaassen, 1996:86). Examples of synergism are the following:

- Antimicrobial treatment of certain infections (Quinn & Day, 1997:302): Aminoglycosides are almost always used in combination with a beta-lactam antibiotic in order to extend coverage to include potential gram-positive pathogens. The combinations are used to take advantage of the synergism between these two classes of drugs. Penicillin aminoglycoside combinations are used to achieve bactericidal activity in treatment of enterococcal endocarditis (Chambers *et al.*,1998:754).
- Treatment of systemic hypertension (Quinn & Day, 1997:302): In the treatment of hypertension it is sometimes useful to combine three drugs, namely, a diuretic, an angiotensin-converting enzyme inhibitor, and a direct vasodilator (e.g. hydralazine or a calcium channel blocker) (Benowitz, 1998:173).
- Asthma (Quinn & Day, 1997:302): With mild asthma, only an inhaled beta-receptor agonist (e.g., albuterol) is needed. If nocturnal symptoms occur, additional treatment is needed, preferably an inhaled anti-inflammatory agent such as a corticosteroid or cromolyn (Boushey, 1998:338).

2.9 **DRUGS INVOLVED IN INTERACTIONS**

According to Grahame-Smith and Aronson (1985:159) it is not always possible to be sure about the clinical importance of a drug interaction. It is possible to predict which types of drugs are *likely* to be involved in important interactions. The drug, which precipitates the interaction, is the *precipitant* drug and the drug whose action is affected is the *object* drug.

2.9.1 **Precipitant drugs**

Precipitant drugs are:

- Drugs that are highly protein bound, and therefore likely to displace object drugs from protein binding sites, e.g. aspirin, phenylbutazone, sulphonamides, and tricholoracetic acid.
- Drugs that alter (stimulate or inhibit) the metabolism of other drugs. Drugs that may inhibit drug metabolism are metronidazole, cimetidine, chloramphenicol, phenylbutazone and related drugs,

monoamine oxidase (MAO) inhibitors, and allopurinol (Grahame-Smith & Aronson, 1985:159). Induction (stimulation) of hepatic microsomal drug-metabolising enzymes can be produced by drugs such as barbiturates, carbamazepine, glutethimide, phenytoin, primidone, and rifampicin (Hansten, 1998:1059).

- Drugs, which affect renal function and alter the renal clearance of object drugs, e.g. diuretics, probenecid (Grahame-Smith & Aronson, 1985:159).

2.9.2 **Object drugs**

The drugs, which are more likely to be object drugs in interactions are those which have a steep dose-response curve. For example, drugs for which a small change in dose results in a relative large change in therapeutic effect. Digoxin is an example of such a drug. The safety margin of digoxin is very narrow, even minor variations in bioavailability could cause serious toxicity or loss of effect (Katzung, 1998b:201). Another example is drugs, which have a low toxic: therapeutic ratio. These drugs have a certain dose at which toxic effects take place and it is a little more than the therapeutic dose (Grahame-Smith & Aronson, 1985:159). Phenytoin is an example of a drug with a low toxic:therapeutic ratio. A small increase in dose may produce very large changes in phenytoin concentrations and patients can quickly develop symptoms of toxicity (Porter & Meldrum, 1998:390).

2.10 TYPES AND MECHANISMS OF INTERACTIONS

Lien and Lien (1994:372) identified three types of interactions:

- Pharmaceutical interactions.
- Pharmacokinetic interactions.
- Pharmacodynamic interactions.

2.10.1 **Pharmaceutical interactions**

Pharmaceutical interactions are related to the physiochemical properties of a drug and may involve a loss of potency, increase in toxicity or other adverse effects (Hudson & Walker, 1995:418). Pharmaceutical interactions are when drugs interact in vitro so that one or both are inactivated, for example, the formation of a complex between thiopentone and suxamethonium, which must not be mixed in the same syringe (Rang *et al.,* 1999:752).

The interactions can occur when agents are combined in solution (e.g. intravenous admixtures). Examples of loss of drug potency include the addition of catecholamines to normal saline solutions, or ascorbic acid to solutions containing pH sensitive drugs, and precipitation due to the mixing of acidic and basic salt solutions (Lien & Lien, 1994:372). These interactions are more chemical than

pharmacological (Rang *et al.*, 1999:752). Thus, pharmaceutical interactions could also be called physiochemical interactions (Lien & Lien, 1994:372).

2.10.2 **Pharmacokinetic interactions**

Pharmacokinetic interactions are those in which one drug alters the rate or extent of absorption, distribution or elimination (metabolism or excretion) of another drug (Tatro, 1998:xix). This may result in increased or reduced plasma levels with an associated enhanced or compromised pharmacological action (Hudson & Walker, 1990:419). A pharmacokinetic interaction represents an altered effect of one, or possibly both, of the participating drugs and is predictable from a knowledge of what the individual drugs can do (Berkow *et al.*, 1992:2636).

- Altered absorption

Most interactions involving altered drug absorption occur in the gut (Tatro *et al.*, 1998:xx). Overall drug absorption may be reduced and its therapeutic activity compromised, or absorption may be delayed though the same amount of drug is eventually absorbed. Delayed drug absorption is undesirable when a rapid effect is needed to relieve acute symptoms, such as pain (Berkow *et al.*, 1992:2636).

The most clinically important interactions are (Berkow *et al.*, 1992:2637):

- Formation of a nonabsorbable complex by either chelation (e.g. tetracycline or ciprofloxacin and di- or trivalent cations), absorption (e.g. lincomycin and koalin-pectin), or ion exchange (e.g. cholestyramine-warfarin).
- Alteration in pH occurs when ketokonazole is administered and must dissolve in an acidic medium. Thus, drugs such as an antacid, anticholinergic agent, histamine H_2-receptor antagonist, or omeprazole should not be given simultaneously.
- Food may delay or reduce absorption of many drugs. Food in the gut will reduce the absorption of many antibiotics. It has also been reported that food decreases the absorption of many therapeutic agents including astemizole, captopril, and penicillamine, and it is important that these drugs be administered apart from meals.

- Altered distribution

Displacement of drugs from protein-binding sites may occur when two drugs capable of protein binding are given concurrently, especially when they are capable of binding to the same sites on the protein molecule. Since the number of plasma or tissue protein-binding sites is limited, drugs can displace one another (Berkow *et al.*, 1992:2637). For example, the interaction that occurs between warfarin and phenylbutazone or phenytoin and valproic acid (Tatro, 1998:xx).

Receptor binding sites other than protein sites are occasionally important. For example, quinidine displaces digoxin from binding sites in skeletal muscle, increasing the serum concertration of digoxin (Tatro, 1998:xx; Hansten, 1998:1059).

- Altered metabolism

Enzyme induction is a stimulated increase in enzyme activity (Tatro, 1998:xxii). A drug can induce the cytochrome P450 system by enhancing the rate of its synthesis or reducing its rate of degradation. Induction results in an accelaration of metabolism and usually in a decrease in the pharmacologic action of the inducer and also of coadministrated drugs (Correia, 1998:52). According to Berkow *et al.* (1992:2637) drug interactions can result from the ability of one drug to stimulate the metabolism of another by increasing the activity of hepatic enzymes involved in their metabolism. Clinically, phenobarbital, phenytoin, carbamazepine and rifampicin are enzyme inducers of greatest interest (Tatro, 1998:xxii). Phenobarbital increases the rate of metabolism of coumarin anticoagulants such as warfarin, resulting in a decreased anticoagulant response. Phenobarbital also accelerates the metabolism of other drugs such as steroid hormones (Berkow *et al.*, 1992:2637). The one form of enzyme that is induced by phenobarbital is CYP2B1 (cytochrome P450 2B1) (Correia, 1998:54).

Certain drug substrates may inhibit cytochrome P450 enzyme activity. The antibiotic chloramphenicol is metabolised by cytochrome P450 to a species that alkylates the enzymes protein and thus inactivates the enzyme (Correia, 1998:55). Enzyme inhibition occurs when metabolising enzymes become saturated when two or more drugs utilising the same metabolic pathway are administered together, resulting in a decrease in rate of metabolism of one or both drugs (Tatro, 1998:xxiii). For example, cimetidine inhibits oxidative metabolic pathways and is likely to increase the action of other drugs that are metabolised via this mechanism (e.g. carbamazepine, phenytoin, theophylline, warfarin, and certain benzodiazepine). Erythromycin has been reported to inhibit the hepatic metabolism of agents such as carbamazepine and theophylline, thereby increasing their effects (Berkow *et al.*, 1992:2638).

Table 2.4: Examples of drugs that induce the cytochrome P450 enzymes (Adapted from Tatro, 1998:xxi-xxii).

Cytochrome P450 enzymes	Inducing drugs
CYP1A2	Smoking Omeprazole Rifampin Barbiturates
CYP2E1	Ethanol Isoniazid
CYP3A4	Barbiturates Carbamazepine Glucocorticosteroids Macrolide antibiotics Phenytoin Rifampin

Table 2.5: Examples of drugs that inhibit the cytochrome P450 enzymes (Adapted from Tatro, 1998:xxi-xxii).

Cytochrome P450 enzymes	Inhibiting drugs
CYP1A2	Fluvoxamine Mexiletine
CYP2C8-10	Cimetidine Omeprazole Selective serotonin re-uptake inhibitors
CYP2D6	Amiodarone Cimetidine Selective serotonin re-uptake inhibitors Aminoquinolines Haloperidol Quinidine
CYP3A3	H2-receptor antagonists Nefazodone
CYP3A4	Macrolide antibiotics Grape fruit juice Selective serotonin re-uptake inhibitors Imidazole derivatives

Table 2.6: Examples of drugs that are metabolised by cytochrome P450 enzymes (Stockley, 1999:9).

Cytochrome P450 Enzymes	**Drugs metabolised**
CYP1A2	Caffeine, clozapine, imipramine, maprotiline, phenacetin, propranolol, r-warfarin, ropinirole, **theophylline***
CYP2D6	Amitriptyline, amphetamine, captopril, clomipramine, codeine, desipramine, dextromethophan, dihydrocodeine, **diphenhydramine***, flecainide, fluoxetine, haloperidol, hydrocodone, imipramine, labetolol, maprotiline, metoprolol, mexiletine, nortriptyline, ondensatron, oxycodeine, papverine, paroxitine, penbutolol, perphenazine, propafenone, propranolol, thioridazine, timolol, trimipramine, venalfaxine, yohimbine
CYP2C9	**Diclofenac***, dofetilide, fluvastitin, ibuprofen, mefenamic acid, naproxin, phenytoin, piroxicam, s-warfarin, tobutamine
CYP2C19	Clomipramine, diazepam, hexobarbital, imipramine, mephobarbital, omeprazole, phenytoin, propranolol, proguanil, s-mephenytoin
CYP3A4	Amiodarone, amitriptyline, alprazolam, asetmizole, carbamazepine, ciclosporin, cisapride, clindamycin, clomipromine, clonazepam, dapsone,
	dexamethasone, dextromethophan, diazepam, erythromycin, ethyl estradiol, felodipine, hydrocortisone, imipramine, indinavir, lidocaine, lovastatin, midazolam, nefazodone, nelfinavir, nevirapine, nifedipine, nimodipine, nisoldipine, propafenone, quinidine, r-warfarin, ritonavir, saquinavir, sertraline, simvastatin, tamoxifen, testosterone, triazolam, venlafaxine, verapamil, zolpidem

* *Three of the 10 selected drugs identified for the empirical study.*

- Altered elimination

Urinary pH influences the ionisation of weak acids and bases and thus affects their reabsorption and excretion (Berkow *et al.*, 1992:2638). A few drugs appear to be clinically affected by change in urine pH such as phenobarbital, salicylates, flecainide, quinidine and amphetamine (Tatro, 1998:xxiii; Hansten, 1998:1059).

An example of active transport occurs when probenecid increases the serum levels and prolongs the activity of penicillin derivatives, primarily by blocking their tubular secretion. Thus, the probenecid improves the effectiveness of penicillin. Such combinations have been used to therapeutic advantage (Berkow *et al.*, 1992:2639).

2.10.3 **Pharmacodynamic interactions**

Pharmacodynamic interactions include the concurrent administration of drugs having the same (or opposing) pharmacologic actions and alternation of the sensitivity or the responsiveness of the tissues to one drug by another (Berkow *et al.*, 1992:2634).

According to Tatro (1998:xxiii) the important pharmacodynamic interactions include additive central nervous system depression, additive anticholinergic effect, potentiation of neuromuscular blockade, additive cardiac depression, changes in various components of the coagulation system and changes in blood sugar.

Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action (Lee & Stockley, 2000:27). Such interactions may be termed either direct or indirect.

- Direct interactions

Direct pharmacodynamic interactions occur when two drugs either act on the same site or act on different sites with a similar end result (Grahame-Smith & Aronson, 1985:167).

(a) Antagonism at the same site

Antagonistic drug effect is when two drugs are combined that have opposite, or antagonistic effects, thus the two drugs eliminate each other's effect (Kee & Hayes, 2000:159). When an antagonist binds to the same locus (recognition site) on the receptor as another antagonist or agonist, the term is competitive antagonism (Berkow *et al.*, 1992:2629). For example, the reversal of the effects of opiates with naloxone, and treatment of arrhythmia due to tricyclic antidepressant overdose with physostigmine (Olson & Becker, 1998:971). Thiazides and certain other diuretics may elevate blood glucose levels. When a diuretic is prescribed for a diabetic who takes insulin or an oral hypoglycaemic action of the antidiabetic drug may be partially counteracted, necessitating a dosage adjustment (Berkow *et al.*, 1992:2634).

(b) Synergism or additive interactions at the same site

If two drugs which have the same pharmacological effect are given together, the effects may be additive (Lee & Stockley, 2000:27). Warfarin is frequently involved in such interactions with drugs such as the tetracycline, clofibrate, corticosteroids and estrogens (Grahame-Smith & Aronson, 1985:167). These interactions result in an increased risk of bleeding (Lee & Stockley, 2000:27).

(c) Summation or synergism of similar effects at different sites

Any drug that has a depressant action on central nervous function may potentiate the effect of another such drug whether or not they have effects on the same receptors (Grahame-Smith & Aronson, 1985:167). An example of this interaction is the increased central nervous system depressant effect that often occurs when persons taking antianxiety agents, antipsychotic agents, antihistamines, or other drugs having depressant effects drink alcoholic beverages (Berkow *et al.*, 1992:2635).

- Indirect pharmacodynamic interaction

In these interactions the precipitant drug has an effect, which is unrelated to the effects of the object drug (Grahame-Smith & Aronson, 1985:167). There are various examples of indirect pharmacodynamic interactions (Lee & Stockley, 2000:28):

- The use of β adrenoreceptor antagonists in patients taking insulin or oral hypoglycaemics can produce hypoglycaemia. Propranolol is known to reduce glycogen breakdown and delay the rise in blood glucose after hypoglycaemia, while cardioselective β adrenoreceptor antagonists are generally devoid of such effects.
- The serotonin syndrome has increasingly been recognised in patient who have received a combination of serotonergic drugs. The syndrome is caused by excess serotonin availability in the central nervous system.

2.11 DRUG-FOOD INTERACTIONS

Definition: Drug-induced nutritional deficiencies comprise symptoms, signs, or laboratory evidence of one or more micro- or macronutrient deficiencies occurring in individuals or groups while taking the drug (Roe, 1984:507). A drug-food interaction may be considered to occur when the effects of giving the drug with food concomitantly are qualitatively different from the effects of the drug when it is administered without food (Thomas, 1996:865).

Drug-induced malnutrition may be acute or chronic. Acute forms are usually due to effects of potent antinutrients, whereas chronic forms may develop because the drug reduces nutrient absorption, increases nutrient catabolism, increases losses via the urine, or otherwise decreases nutrient utilisation (Roe, 1984:507).

The development of drug-induced malnutrition occurs most commonly during long-term treatment for chronic disease (Mahan & Arlin, 1992:433).

2.11 **The effects of food and medication**

It is generally known that food can affect medication and vice versa. The recognition of interactions between drugs and nutrients plays a vital role in expanding the medical services available to patients (Pronsky, 1997:6). The following discussion will be about medication and food kinetics.

2.11.1.1 *The effect of food/nutrients on medication kinetics*

The medication kinetics consists of absorption, distribution, metabolism and excretion.

There are three situations in which food can alter medication absorption. These are the rate of absorption, decreasing or enhancing the absorption (Pronsky, 1997:7):

- The rate of absorption can be decreased by the presence of food. For example, the absorption of antihistamine astemizole can be decreased by 60% and a high fiber diet may decrease the absorption of tricyclic antidepressants such as amitriptylline (Pronsky, 1997:7).
- Absorption can decrease through chelation which occur between certain drugs and di- or trivalent cations. For example, ciprofloxacin forms an insoluble complex with cations. The cations are present in dairy products, supplements and antacids. The cations are calcium, magnesium, aluminium, iron and zink (Pronsky, 1997:7).
- Absorption can be enhanced by food. For example, the absorption of cefuroxime axetil is higher when given with food (Pronsky, 1997:7).

Once absorbed, a drug is distributed to its site of action, and during this process it may interact with other drugs or nutrients. Only unbound drug molecules are pharmacologically active (Lee & Stockley, 2000:24). A decrease in serum albumin may increase the free fraction of highly protein bound drugs. Hypoalbuminemia provides fewer binding sites for drugs such as phenytoin and warfarin .The increased free fraction results in increased drug effects (Pronsky, 1997:8).

Metabolism is the process of chemical alteration of drugs in the body. The liver is the principal, but not the sole, site of drug metabolism (Berkow *et al.,* 1996:2607). The hepatic metabolism of medication can be altered by food. The first pass metabolism of propranolol is reduced with ingestion of food.

Excretion is the process by which either a drug or a metabolite is eliminated from the body without further change in its chemical form. The kidneys are the major organ of excretion of drugs (Berkow *et al.,* 1996:2609). The renal excretion of drugs may be altered by food. For example, lithium and sodium compete for tubular absorption in the kidney. High sodium intake causes more lithium to be excreted and low sodium intake causes the kidney to retain lithium. This leads to a raise in blood level of lithium (Pronsky, 1997:8).

2.11.1.2 *The effect of medications on food/nutrient kinetics*

Nutrient kinetics consists of absorption, metabolism and excretion.

Drugs through prevention, gastric acidity or damage can change the absorption of nutrients to mucosal surface (Pronsky, 1997:8-9):

- Drugs form complexes with nutrients and prevent absorption. For example, tetracycline and ciprofloxacin chelate with cations. Vitamins A, D, E and K are absorbed by cholestyramine.
- Drugs can alter gastric acidity. Prolonged use of antiulcer drugs such as cimetidine may decrease absorption of vitamin B12, thiamine and iron.
- Certain drugs cause damage to mucosal surfaces. Antineoplastic drugs can decrease nutrient absorption by this damage.

Drugs can increase the metabolism of nutrients and this leads to deficiency. Anticonvulsants such as phenobarbital and phenytoin increase the metabolism of folic acid, vitamins D and K. Drugs can cause vitamin antagonism. Isoniazid inhibits the conversion of pyridoxine to the active form and causes deficiency. Nutrient excretion is through renal excretion. Urinary loss of nutrients is caused by furosemide that increases the excretion of natrium, calium, chloride, magnesium and calcium. Thiazide diuretics decrease the urinary excretion of nutrients. These diuretics increase the excretion of most electrolytes but decrease excretion of calcium due to increased renal absorption (Pronsky, 1997:9).

2.11.2 Factors affecting drug-food interactions

Predicting the risk of drug-induced nutritional deficiencies requires knowledge of the mechanism for nutrient depletion by the drug to be administered, the dose and duration of drug usage, as well as the characteristics of the patient.

Table 2.7: Risk assessment for drug-induced nutritional deficiencies (Adapted from Roe, 1984:506).

Host factors	**Drug factors**
Physiological stress → high nutrient requirements	Adverse nutritional effect unknown
Marginal diet	Reduces nutrient absorption
Catabolic disease	Increases nutrient losses in urine
Chronic disease	Reduces appetite
Malabsorption	Antinutrient effect
Hepatic dysfunction	Indication is for short-term use
Renal dysfunction	Indication is for chronic disease control

Table 2.7 (continued)

Slow drug dimination (pharmacogenetic)	
Alcohol abuse	

The probability of drug-drug or drug-nutrient interaction increases in proportion to the number of drugs ingested. There are certain high-risk populations, e.g. developing foetus, infants, pregnant women, the elderly, and the chronically ill are at high risk for drug-nutrient interactions (Mahan & Arlin, 1992:433).

2.11.3 **Types of drug-food interactions**

There are various drug-food interactions. The following are only a few of the possible drug-food interactions.

2.11.3.1 *Tobacco-drug interactions*

The primary mechanism for smoking on drug metabolism results from induction of hepatic microsomal enzymes by the constituents of tobacco smoke. The following drugs are affected by tobacco smoke and shown in table 2.8.

Table 2.8: Drugs affected by tobacco smoke (Adapted from May, 1993:80).

Antidiabetic, oral	Pentazocine
Benzodiazepines Chlordiazepoxide Diazepam	Propoxyphene
Chlorpromazine	Propranolol
Contraceptives, oral	Theophylline
Estrogens	Tricyclic antidepressants Amitriptylline Desipramine Imipramine Nortriptyline
Heparin	
Lidocaine	

2.11.3.2 *Tobacco-estrogens interactions*

Epidemiological studies indicate that the risk of cardiovascular adverse effects such as stroke, myocardial infarction, and tromboembolism, which are associated with oral contraceptive use, are increased in smokers (May, 1993:80).

2.11.3.3 *Tobacco-theophylline interactions*

Smoking stimulates the hepatic metabolism of theophylline. Some heavy smokers may require as much as twice the usual maintenance dose of theophylline (May, 1993:80).

2.11.4 *Alcohol-drug interactions*

According to Hift (1991:849) the many adverse effects of alcohol are widely recognised. Its potential for interaction with other pharmacological agents is often overlooked.

A dangerous drug interaction may occur when ethanol is combined with central nervous system (CNS) depressants such as antihistamines, barbiturates, tranquillisers, or other psychotropic drugs (May, 1993:80).

Ethanol antagonise the oral antidiabetic agents (e.g. chlorpropamide and tolbutamide). Chlorpropamide and possible other sulfonylureas may also interact with ethanol by producing the 'disulfiram reaction' (flushing, hypotension, nausea, tachycardia, vertigo, dyspnea and blurred vision) (May, 1993:80).

2.12 PHYSIOLOGIC FACTORS AFFECTING DRUG INTERACTIONS

2.12.1 Age

Drugs usage patterns change as a result of the increasing age in many individuals. General changes in the lives of older people have significant effects on the way drugs are used (Katzung, 1998a:989). For the elderly smaller drug doses must be given at less frequent intervals. Administration of what seems to be the correct drug dosage, as calculated from the adult dose, may cause a high degree of toxicity or even death for infants. (Stanaszek, 1972:206). Age itself affects the distribution and elimination of many drugs. Drug binding, metabolism, and excretion may change as a function of age (Gibaldi, 1991:242). Certain drugs are a high-risk group for elderly patients. These drugs include psychotropic agents (benzodiazepines), antihypertensive medications (including diuretics), digoxin, non-steroid anti-inflammatory drugs (NSAIDs), systemic corticosteroids, theophylline and warfarin. (Grymonpré, 1998).

2.12.1.1 *Elderly patients*

According to Titley-Lake en Barber (2000:53) the World Health Report of 1998 states that by the year 2025, the proportion of people over 65 will have risen from 6.6 % to 10 % of the total population.

Epidemiological studies verify the fact that as the number of drugs administered to a patient increases, the chance of encountering an adverse drug reaction or interaction markedly increases (Block, 1985:59).

Geriatric patients are particularly vulnerable to adverse reactions and interactions: the percentage of patients who experience adverse reaction is far greater in those past the age of 60 then in younger patients (Block, 1985:59). A drug's risk:benefit ratio may alter and the doses of drugs may need to be more carefully titrated (Titley-Lake & Barber, 2000:53).

More than eight out of ten elderly persons have chronic health problems for which they receive medical help. Multiple drug use for these chronic health problems coupled with a higher incidence of drug administration errors among the elderly increases the risk of occurrence of adverse reactions and interactions (Block, 1985:59).

In 1997 in the Royal College of Physicians of London reported that, in the United Kingdom, approximately one in 10 hospital admissions of elderly patients was a result of an adverse reaction (Titley-Lake & Barber, 2000:53).

2.12.1.1.1 Physiologic changes with ageing

There is great variation among older individuals as to the manifestation of age-related physical change (Erwin, 1993:66). Age-related changes in the gastrointestinal tact, liver and kidneys are (Shetty & Woodhouse, 2000:120)

- reduced gastric acid secretion;
- decreased gastrointestinal motility;
- reduced total surface area of absorption;
- reduced splanchnic blood flow;
- reduced liver size and blood flow; and
- reduced glomerular filtration and renal tubular filtration.

♦ The senses

Age-related changes effecting sensory capabilities include (Erwin, 1993:66):

- A decrease in lens transparency and diminution of the power of accommodation.
- A loss of auditory acuity (presbycusis).
- A diminished ability to taste sweet, sour and bitter, but not salty.
- A generalised decrease in the sensation of touch.
- A decreased thirst response with dehydration.

♦ Body composition

Older individuals maintain their same body weight until their seventies, when an overall decrease is noted. On the average, lean body mass decreases and body fat increases as a proportion of total body weight (Erwin, 1993:66; Gibaldi, 1991:247). For example, a water-soluble drug, such as gentamicin,

is not distributed to fat. Likewise, pentobarbital, which is distributed only to fat, may produce lower blood levels in the elderly patient (Hamilton, 1985:16).

- Central nervous system

Changes in intellectual function with age are unclear. Structurally, the brain decreases in weight and volume. The water content of the brain also decreases (Erwin, 1993:66).

- Digestive system

Delays in transit time in the esophagus have been implicated in drug-induced ulcerations (Erwin, 1993:66). The amount of drug that reaches the systemic circulation following oral drug administration depends on gastrointestinal absorption and presystemic metabolism during its first passage through the gastrointestinal mucosa and the liver. Changes in gastrointestinal function with ageing include an increase in gastric pH, delayed gastric emptying, decreased motility, and decreased intestinal blood flow. Some sugars, minerals and vitamins may therefore be decreased in elderly patients (Cusack *et al.,* 1997:176).

- Hepatic system

The hepatic system appears to be the least affected by the ageing process even though liver size and weight decline with age (Erwin, 1993:66). Hepatic blood flow and liver mass change in proportion to bodyweight and decrease with ageing (Cusack *et al.,* 1997:177-178). The elimination of drugs may be decreased when these drugs are dependent on liver blood flow for clearance (Gibaldi, 1991:247). Concurrent drug administration, illness, genetics, and environmental factors including smoking may have more important effects on hepatic drug metabolism than age (Cusack *et al.,* 1997:177-178).

- Renal system

There is a continuous loss of glomeruli with ageing, which has significant impact upon renal function (Erwin, 1993:67). Renal blood flow, glomerular filtration rate and tubular function all decline with ageing (Cusack *et al.,* 1997:178). For example, digoxin is excreted primarily through the kidneys. Renal eliminated drugs with a narrow therapeutic index (e.g. digoxin, aminoglycoside antibiotics, lithium) may accumulate to toxic serum levels since kidney function declines with age (Erwin, 1993:67). In addition to the physiological decline in renal function, the elderly patient is particularly liable to renal impairment due to dehydration, congestive heart failure, hypotension and urinary infection, or to intrinsic renal involvement, e.g., diabetic nephropathy or pyelonephritis (Cusack *et al.,* 1997:178).

♦ Endocrine system

The elderly patient is subject to numerous endocrinopathies. The thyroid gland atrophies with age, resulting in hypothyroidism occurring more frequently in patients older than 50 (Erwin, 1993:67).

♦ Immune system

Involution of the thymus gland and alterations in the balance of circulating lymphocytes contribute to impaired humoral and cell-mediated immune responses (Erwin, 1993:67).

2.12.1.2 *Paediatric patients*

In a study documenting prescription medication use in 222 paediatric patients, the average number of medication courses received was 8.5 during the first five years of life. It has been estimated that a 1.5-kg preterm infant receives about 20 prescribed drugs between conception and discharge from the nursery (Zenk, 1994:688). Absorption, distribution, metabolism and elimination of many drugs are different in premature infants, full-term infants and older children (Nahata, 1993:56).

♦ Absorption

Drugs may be administered to paediatric patients by a number of routes, including orally, parenterally, intraosseously, topically, and rectally (Walson, 1997:129).

♦ Gastrointestinal tract

Two factors affecting the absorption of drugs from the gastrointestinal tract are pH-dependent passive diffusion and gastric emptying time. Both processes are strikingly different in a premature infant compared with older children and adults.

The gastric emptying is slow in a premature infant. Thus, drugs with limited absorption in adults may be efficiently absorbed in a premature infant because of prolonged contact time with gastrointestinal mucosa (Nahata, 1993:56). Drugs such as cyclosporin, whose absorption depends on bile flow, diet, and intestinal transit, may also show greater inter- and intrapatient variability in children than in adults (Walson, 1997:130).

♦ Intramuscular sites

Differences in relative muscle mass, blood flow to various muscles, peripheral vasomotor instability, and insufficient muscular contraction in a premature infant compared with older children and adults can influence drug absorption from the intramuscular site (Nahata, 1993:57). Certain drugs (e.g., phenytoin, digoxin and diazepam) are poorly absorbed from any site and should not be administered intramuscularly (Walson, 1997:130).

♦ Percutaneous absorption

Percutaneous absorption of drugs is enhanced in infants, and to a lesser extent in children, especially in the presence of damaged skin or under an occlusive covering. This is because children have a much larger surface area to body weight ratio (Walson, 1997:130).

♦ Rectal absorption

The attractions of rectal administration are that it can be useful in patients who are vomiting and in infants and young children who are reluctant to take oral medication. It may partially avoid hepatic first-pass metabolism to which a number of orally administered drugs are susceptible (Walson, 1997:131).

♦ Distribution

Drug distribution is determined by the physicochemical properties of the drug itself and the physiologic factors specific for the patient. Total body water, as a percentage of total body weight, has been estimated to be 94 % in a foetus, 85 % in premature infants, 78% in full-term infants, and 60 % in adults. The amount of body fat is substantially lower in neonates compared with adults, which may affect drug therapy. Certain highly lipid-soluble drugs (e.g. corticosteroids, vitamin D) are distributed less in infants than adults (Nahata, 1993:57).

♦ Metabolism

Drug metabolism is substantially slower in infants compared with older children and adults. For example, the sulfation pathway is well developed, but the glucuronidation pathway has not matured in infants (Nahata, 1993:57). Older infants and children actually metabolise certain drugs more rapidly than adults. These drugs include antipyrine, clindamycin, phenobarbital, theophylline, and carbamazepine (Gibaldi, 1991:245).

♦ Elimination

The kidney often eliminates drugs and their metabolites. The processes of glomerular filtration, tubular secretion, and tubular reabsorption determine the efficiency of renal excretion. These processes may take several weeks from birth to one year after birth to develop (Nahata, 1993:58).

2.12.1.2.1 Factors affecting paediatric therapy

♦ Liver disease

Because the liver is the main organ of drug metabolism, drug clearance is usually decreased in patients with hepatic disease. A report has suggested that theophylline clearance may decrease by 45% in a child with acute viral hepatitis. Because of a lack of specific data on dosage adjustment in liver diseases, drug therapy should be monitored in paediatric patient to avoid potential toxicity from

excessive doses, particularly for drugs with a narrow therapeutic index (e.g. digoxin) (Nahata, 1993:59).

- Renal disease

Renal failure decreases the dosage requirement of drugs eliminated by the kidney. The dosage of drugs, with narrow therapeutic indices and that are eliminated largely by the kidney (e.g. aminoglycosides and vancomycin), must be decreased to optimise therapy in paediatric patients with renal dysfunction (Nahata, 1993:59).

- Cystic fibrosis

For unknown reasons, paediatric patients require increased doses of certain drugs including aminoglycosides and penicillin (Nahata, 1993:59).

2.12.2 **Body weight**

Lean body mass declines with age in males and females, and fat mass increases with age (Mayersohn, 1992:9.25). The composition of the body is very important. The amount of bone, fat, and fluid strongly affects the dosage calculation (Martin, 1978:105).

2.12.3 **Gender**

Although some sex differences in drug disposition have been reported (e.g. a lower renal clearance of amantadine in women), the clinical importance of these observations remains to be explored (Page *et al.*, 1997: 79). Chloramphenicol-induced aplastic anaemia is twice as common in women than in men, and phenylbutazone-induced agranulocytosis is three times as common (Lee & Stockley, 2000:35).

2.12.4 **Genetics**

In any large population one finds individuals who metabolise a drug much more slowly or more rapidly than the average person. It is evident that genetic factors contribute substantially to the large differences among people in metabolic clearance of drugs (Gibaldi, 1991:256). There are also racial differences in the expression of genetic variation among the cytochrome P-450 isoforms (Page *et al.*, 1997:80). The drugs, which are affected by this metabolic pathway include caffeine, acebutolol, dapsone, aminoglutethimide (Relling & Evans, 1992:7.16). Table 2.9 shows the racial differences in drug metabolism.

Table 2.9: Drug metabolic pathways affected by racial origin (Page *et al.*, 1997:80).

Metabolic reaction	Caucasian	Asian
Acetylation	50% slow	5-10% slow
CYP2D6 oxidation	5-10% deficient	1% deficient
CYPD2C18 oxidation	3-5% deficient	20% deficient

2.12.5 **Administration time**

Absorption is influenced by the time at which the drug is administered, particularly in regard to oral dosage and meals, since gastrointestinal tract contents affect absorption rates (Stanaszek, 1972:207). Administration time is influenced by other medication (e.g. possible interactions), meals, and sleep patterns (e.g. sedatives must be given before bedtime) (Martin, 1978:246).

2.12.6 **Tolerance**

Tolerance does not develop equally and may result in a decrease of therapeutic index of the drug (Stanaszek, 1972:207).

2.12.7 **Body temperature**

Drug action, distribution, binding, and excretion can be modified by changes of body temperature (Stanaszek, 1972:207).

2.13 IATROGENIC ILLNESS

An iatrogenic illness is caused by medical treatment. "Iatrogenic" comes from Greek roots: ***iatros***, meaning physician, and ***gen***, meaning origin or source (Anon, 2000). According to Ngo (1996) an iatrogenic illness literally means disease or illness caused by doctors. In an iatrogenic episode, a patient is harmed as a result of an error in diagnosis or treatment, or a result of a mishap during medical care. The harm is independent of the natural progression of the patient's illness and treatment and represents part of the risk that the patient must assume as an inevitable component of management of one's body.

An iatrogenic complication is an unfavourable response to medical treatment that is induced by the therapeutic effort itself. Serious or fatal iatrogenic complications occur in 4 to 9% of hospitalised patients (Anon, 1999). According to Anderson (1981) iatrogenic disease has become "*one of the most prevalent conditions facing modern health services, occupying countless hospital beds all over the Western world*". Iatrogenic diseases pose a major threat to health throughout the world.

Drug-induced iatrogenic illness encompasses a wide variety of complications, including drug allergies, adverse effects, toxicity, drug-drug and drug-food interactions, and a series of complications due to improper dosage regimens (Wartman, 1983:16).

In connections with interaction there are a number of factors that can be a risk to the patient. Age, gender and disease state are particularly relevant (D'Arcy & Green, 1972:2).

2.13.1 **Age**

Many cases of drug reaction can be attributed to predisposing factors in the patient. Basically, there is the problem of the same drug having diverse effects in different clinical conditions and in different individuals. For example, amphetamine is widely used as an appetite-suppressant drug in the treatment of obesity, yet the same drug is also used in patients with anorexia nervosa to stimulate appetite. In both circumstances, amphetamine provides effective therapy (D'Arcy & Green, 1972:2).

There are also other well-defined examples of age being a factor in drug metabolism and this has a direct bearing on incidence of iatrogenic disease. For example, a new-born has a relatively lower glomerular filtration rate and renal plasma flow than an adult and is also seriously deficient in drug metabolising enzymes for at least the first month after birth. The latter is particularly marked in their failure of glucoronation. Neonates may fail to metabolise vitamin K analogues, sulphonamides, chloramphenicol, barbiturates, morphine and curare effectively (D'Arcy & Green, 1972:2).

The toxicity of pharmaceuticals is dangerous in the elderly. This age group is by far the largest group consumers of medical drugs. The elderly are most easily harmed by the practice of prescribing multiple drugs with risk of complicated and potentially fatal interactions (Anderson, 1981).

In the geriatric patients drug overdose is particularly likely to occur if the drug remains active in the body until the kidneys excrete it. This is so because renal function diminishes with increasing age even in the absence of clinically detectable disease (D'Arcy & Green, 1972:2).

2.13.2 **Gender**

It is well-known that the agranulocytosis due to aminopyrine, phenylbutazone and chloramphenicol occurs far more frequently in females than in males; the ratio is about 3:1 for these drugs. There are no other clinical important gender differences in drug action (D'Arcy & Green, 1972:3).

2.13.3 **Disease State**

- Renal failure

Renal failure impairs the urinary excretion of drugs; drugs that are eliminated primarily by renal excretion accumulate excessively in a patient with renal insufficiency unless the dosage regimen is modified (Gibaldi, 1991:272). For example, prostaglandins help maintain residual renal function. The use of drugs that inhibit cyclooxygenase (e.g. non-steroid anti-inflammatory drugs) can therefore lead to rapid deterioration of residual renal function (Page *et al.,* 1997:81).

- Liver disease

When hepatic metabolism is an important route of drug elimination, dysfunction of the liver could lead to changes in the pharmacokinetics of the drug (Gibaldi, 1991:250). For example, morphine may precipitate coma in patients with cirrhosis and that paraldehyde causes profound sleep in some patients with liver disease (D'Arcy & Green, 1972:3).

- Porphyria

Certain drugs such as barbiturates, amiodarone and clonidine can precipitate attacks of porphyria in patients with acute intermittent porphyria (D'Archy & Green, 1972:4).

- Myasthenia Gravis

A dual block of neuromuscular transmission following succunylcholine is seen in certain normal patients for no apparent reason, but this type of block is particularly prevalent in patients suffering from Myasthenia Gravis (D'Archy & Green, 1972:4).

- Alcoholism

The continued intake of alcohol induces non-specific hepatic microsomal enzymes (D'Archy & Green, 1972:5).

2.14 **CHAPTER SUMMARY**

In this chapter pharmaceutical care was discussed. Special attention was paid to the patient care process. The various roles of the pharmacist were discussed. Drug therapy problems were discussed and special attention was paid to drug interactions. Drug interactions were discussed in detail (e.g., types, mechanism, food interactions, etc.).

The drug interactions of the ten selected drugs and their general information will be discussed in Chapter 3.

CHAPTER 3: DRUG INTERACTIONS OF THE TEN SELECTED DRUGS.

In this chapter the ten selected drugs from Philani Prime Cure® will be discussed. The ten selected drugs are given in Chapter 4, section 4.3.2.2. The individual drugs will be discussed under the following headings:

- The classification of the drug.
- The pharmacological properties of the drug.
- The mechanism of drug action.
- Therapeutic uses of each drug.
- Deficiencies, where possible.

The drug interaction tables are included in this chapter (section 3.12). The mechanism of these interactions is also discussed in section 3.11.

3.1 DIPHENHYDRAMINE

3.1.1 Classification

Diphenhydramine is a first-generation H_1 antagonist (Gibbon, 2000:468). Diphenhydramine is a sedating antihistamine and an ethanolamine (Turner, 2001:538; Babe & Serafin, 1996:589).

3.1.2 The pharmacological properties

Antihistamine has the following effects (Babe & Serafin., 1996:587-588):

- Smooth muscle: H_1 antagonists inhibit most responses of the smooth muscle to histamine.
- Capillary permeability: H_1 antagonists strongly block the action of histamine that results in an increased capillary permeability and formation of oedema and wheal.
- Central nervous system: The first-generation H_1 antagonists can both stimulate and depress the central nervous system. Stimulation includes restlessness, nervousness, and insomnia. Depression includes alertness, slowed reaction times and somnolence.

3.1.3 The mechanism of action

Diphenhydramine is a competitive antagonist at the H_1 receptors (Babe & Serafin, 1996:587). H_1 receptors may be located on glia and vessels as well as on neurons and may act to mobilise calcium in receptive cells (Bloom, 1996:285). Diphenhydramine causes smooth muscle contraction and prevents bronchoconstriction (Babe & Serafin, 1996:586).

3.1.4 Therapeutic uses

Diphenhydramine can by used for the following conditions:

- Allergic conditions: Prophylactically, antihistamine may prevent symptoms of hay fever and allergic rhinitis.
- Motion sickness: Antihistamine is effective against motion sickness (Girdwood, 1976:391).
- Nausea and vomiting: Antihistamine helps for nausea and vomiting in pregnancy and in other circumstances, e.g., radiation sickness.
- Anti-Parkinson effects: Diphenhydramine, with the anticholinergic activity, is useful in the treatment of tremor and rigidity associated with Parkinson syndrome.
- Sedatives: Antihistamine causes drowsiness and therefore can be used for sedation in children and preoperative (Girdwood, 1976:392).
- Local anaesthesia: Diphenhydramine is effective as a local anaesthesia and is more potent than procaine (Burkhalter *et al.*, 1998:268).
- Antihistamine is an adjunct therapy in anaphylactic shock (Gibbon, 2000:468).
- Antihistamine can treat pruritic conditions, urticaria, angioneurotic oedema and anaphylaxis (Dollery, 1999:D153).

3.2 TETRACYCLINE

Doxycycline and oxytetracycline are both antibacterial for systemic use from the tetracycline group (Turner, 2001:278). Tetracycline will be discussed as a group.

3.2.1 Classification

Tetracycline is a broad-spectrum antibiotic. It is active against a wide range of Gram-negative and Gram-positive bacteria (Dollery, 1999:T66).

3.2.2 The pharmacological properties

Tetracycline is absorbed after oral administration. Tetracycline penetrates into most tissues and body fluids. All tetracyclines, except doxycycline, are excreted primarily in the urine by glomerular filtration, and their blood levels increase in the presence of renal insufficiency. Doxycycline is excreted mainly in faeces. All teracyclines are partially excreted in bile, resulting in high biliary levels. They are then partially reabsorbed (Berkow *et al.*, 1992:40).

3.2.3 The mechanism of action

Tetracycline has its main mechanism of action on protein synthesis, and energy-dependent active-transport system pumps the drug, like all tetracyclines, through the inner cytoplasmic membrane of bacteria. Once inside the bacterial cell, tetracycline inhibits protein synthesis by binding especially to 30S ribosomes (Dollery, 1999:T66).

3.2.4 **Therapeutic uses**

The following is a combination of the therapeutic uses of tetracycline. It was combined from Dollery (1999:T67) and Kapusnik-Uner *et al.* (1996:1128):

- Rickettsia (Rocky Mountain spotted fever, typhus fever and the typhus group, Q-fever, rickettsialpox and tick fevers).
- *Mycoplasma pneumoniae.*
- Agents of psittacosis and ornithosis.
- Agents of lymphogranuloma venereum and granuloma inguinale.
- The spirochetal agent of relapsing fever (*Borrelia recurrentis).*
- Infections caused by the following Gram-negative organisms:

  Haemophilis ducreyi (chancroid)

  Pasteurella pestis and *Pasteurella tularensis*

  Bartonella bacilliformis

  Bacteroides and *Brucella* species

  Vibrio comma and *Vibrio fetus.*
- Infections with the following micro-organisms if bacteriologic testing indicates appropriate susceptibility to the drug:

a. Gram-negative organisms: *Escherichia coli, Enterobacter aerogenes, Shigella* species, *Mima* species, *Herellae* species, *Haemophilis influenzae* (respiratory infections), *Klebsiella* species (respiratory and urinary infections).

b. Gram-positive organisms: *Streptococcus* species, *Diplococcus pneumoniae, Staphylococcus aureus* (skin and soft tissue infections).

- When penicillin is contraindicated, tetacyclines are alternative drugs in the treatment of infections with:

  Neisseria gonorrhoea

  Treponema pallidum and *Treponema pertenue* (syphilis and yaws)

  Listeria monocytogenes

  Clostridium species

  Bacillus anthracis

  Fusobacterium fusiforme (Vincent's infection)

  Actinomyces species.
- Acute intestinal amoebiasis.
- Mild to moderate and severe acne.
- Rosacea.
- Trachoma.
- Inclusion conjunctivitis.

- Uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis.*

3.3 CO-TRIMOXAZOLE

3.3.1 Classification

Co-trimoxazole is a combination of trimethoprim and sulphamethoxazole. The combination is antibacterial for systemic use (Gibbon, 2000:265).

3.3.2 The pharmacological properties

Both trimethoprim and sulphamethoxazole are well absorbed orally and are excreted into the urine. They penetrate well into tissues and body fluids (Berkow *et al.*, 1992:48).

3.3.3 The mechanism of action

Sulphamethoxazole is a sulphonamide. Sulphonamides are structural analogues of para-aminobenzoic acid (PABA). They inhibit the synthesis of bacteria DNA. DNA synthesis requires thymidine, which is formed with the help of folinic acid. Folinic acid is the reduced form of folic acid, which in turn, has a constituent PABA. Sulphonamides competitively inhibit PABA incorporation into folic acid (Girdwood, 1976:84).

Trimethoprim inhibits the next step, namely enzymatic reduction of folate to folonic acid by dihydrofolate reductase. These two drugs combined as co-trimoxazole are synergistic. This results in a greater fall in bacterial DNA synthesis that could be predicted by using the two drugs separately (Girdwood, 1976:85).

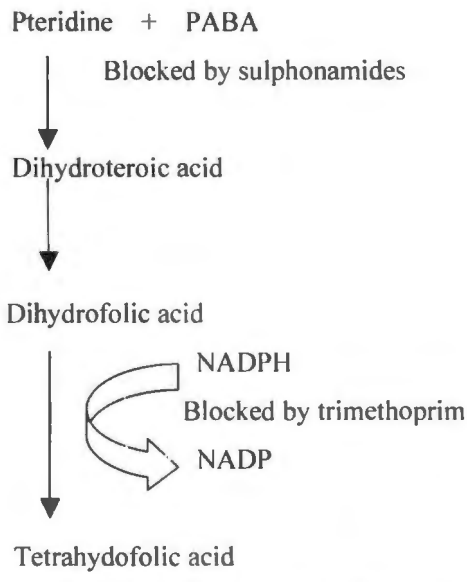

Figure 3.1: Steps in folate metabolism blocked by sulphonamides and trimethoprim (Mandell & Petri, 1996:1059).

3.3.4 Therapeutic uses

Co-trimoxazole can be used prophylactic and for the treatment of *Pneumocystis carinii* infections (e.g. abscesses). It can also be used for the treatment of norcardiosis, urinary tract infections, respiratory tract and prostatic infections caused by susceptible organisms. Co-trimoxazole is also used in treatment of paratyphoid fever, cholera, and in the treatment and prophylaxis of toxoplasmosis (Gibbon, 2000:265).

3.4 HYOSCINE

3.4.1 Classification

Hyoscine is the same as scopolamine. Scopolamine and atropine are both muscarinic receptor-blocking agents (Katzung, 1998:105).

3.4.2 The pharmacological properties

Hyoscine has the following pharmacological properties (Brown & Taylor, 1996:150-152; Katzung, 1998:110):

- Central nervous system: Scopolamine normally causes central nervous system depression manifested as drowsiness, amnesia, and fatigue. It also causes euphoria.
- Eye: Hyoscine is a muscarinic receptor antagonist that blocks the response of the sphincter muscle of the iris and ciliary muscle of the lens to cholinergic stimulation. Hyoscine can dilate the pupil (mydriasis) and paralyse accommodation (cycloplegia).
- Cardiovascular system: The main effect of atropine as well as hyoscine on the heart is to alter the heart rate. The dominant response is tachycardia.

- Respiratory tract: Hyoscine inhibits the secretion of the nose, mouth, pharynx, and bronchi; thus drying the mucous membranes of the respiratory tract.
- Gastrointestinal tract: Hyoscine can reduce the gastric secretion. The walls of the viscera are relaxed and both the tone and motility are diminished. Hyoscine prolongs gastric emptying time.

3.4.3 The mechanism of action

Atropine causes reversible blockade of the actions of cholinomimetics at muscarinic receptors (Katzung, 1998:106). Atropine and related compounds are competitive antagonists of acetylcholine. All muscarinic receptors are blocked by atropine – those in exocrine glands, smooth and cardiac muscle (Brown & Taylor, 1996:150).

3.4.4 Therapeutic uses

Hyoscine is chemically and pharmacologically similar to atropine. However, the drug is a central nervous system depressant. It is useful in the treatment of motion sickness (Girdwood, 1976:218). Certain vestibular disorders respond to antimuscarinic drugs such as hyoscine. Scopolamine is one of the oldest remedies for seasickness (Katzung, 1998:110).

3.5 THEOPHYLLINE

3.5.1 Classification

Theophylline is a selective beta-2-adrenoceptor agonist (Turner, 2001:522). Theophylline is a bronchodilator (Semnia *et al.*, 1997:797)

3.5.2 The pharmacological properties

Theophylline is effective in the management of asthma by relaxing bronchial smooth muscle (Edwards *et al.* 1992:13.1). It is most effective at the bronchi; especially if the bronchi are constricted either by a spasmogen or clinically in asthma (Serafin, 1996:673). Theophylline is a potent stimulant of the central nervous system (CNS). Progressive CNS stimulation is nervousness or anxiety, restlessness, insomnia, tremors, and hyperestesia. At higher doses, focal and generalised convulsions are produced. The methylxanthins appears to increase the sensitivity of medullar centres to the stimulatory actions of CO_2 (Serafin, 1996:674).

In the cardiovascular system theophylline decreases peripheral vascular resistance, cardiac stimulation, increased perfusion of most organs, and diuresis. At higher concentrations, theophylline produces definite tachycardia (Serafin, 1996:671).

At therapeutic doses, theophylline can improve diaphragmatic contractility and reduce diaphragmatic fatigue in patients with chronic obstructive pulmonary disease (COPD) (Serafin, 1996:675).

Theophylline increases the production of urine (Serafin, 1996:675). Theophylline is a weak diuretic (Homer, 1998:332).

3.5.3 The mechanism of action

A proposed mechanism is the inhibition of cell surface receptors for adenosine. These receptors modulate adenylyn cyclase activity, and adenosine has been known to cause contraction of isolated airway smooth muscle and to enhance histamine release from cells present in the lung. These effects are antagonised by theophylline, which blocks cell surface adenosine receptors (Homer, 1998:331). Another mechanism is the following:

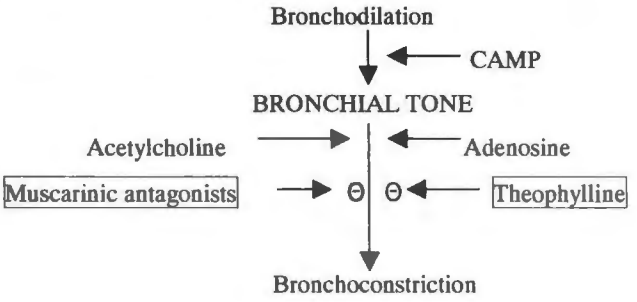

Figure 3.2: Bronchoconstriction can be inhibited by muscarinic antagonists and by adenosine antagonists such as theophylline (Adapted from Homer, 1998:331).

3.5.4 Therapeutic uses

Theophylline is primarily used for the relief of bronchospasm. Theophylline is a second-line treatment of acute, severe and chronic persistent asthma (Gibbon, 2000:458). Some paediatricians favour theophylline over inhaled glucocorticosteroids because of the theoretic potential growth suppression (Serafin, 1996:677). Recent evidence indicates that theopylline has some anti-inflammatory effect and theophylline decreases the pulmonary eosinophil numbers (Gibbon, 2000:458). Theophylline can be used for apnoea of preterm infants. Apnoea and bradycardia can pose the threat of recurrent hypoxemia and neurological damage (Serafin, 1996:677). Theophylline can be used in acute exacerbation of chronic obstructive lung disease, prophylaxis of sudden infant death syndrome and the treatment of Cheyne-Stokes respiration (Dollery, 1999:T77).

3.6 LOPERAMIDE

3.6.1 Classification

Loperamide is an antipropulsive and antidiarrhoea drug. It slows gastrointestinal motility by inhibiting contractions in both longitudinal and circular muscles (Gibbon, 2000:58). Loperamide is a phenylpiperidine derivative. This drug is thus an opoid agonist (Way *et al.*, 1998:511).

3.6.2 The pharmacological properties

Phenylpiperidines can have analgesia effects in the central nervous system (Reisine & Pasternak, 1996:540). Loperamide does not cross the bloodbrain barrier and thus has less sedation and is less addictive (Altman, 1998:1024). It slows gastrointestinal motility by inhibiting contractions in both longitudinal and circular muscle (Gibbon, 2000:58).

3.6.3 The mechanism of action

Loperamide inhibits the peristaltic activity of longitudinal and circular smooth muscle in the intestine by interacting with cholinergic and non-cholinergic neuronal mechanisms responsible for producing the peristaltic reflex (Dollery, 1999:L86). Opoid receptors exist in high density in the gastrointestinal tract, and the constipating effects of opoids are mediated through an action on the local enteric nervous system as well as central nervous system.

Table 3.1: The actions of loperamide on the gastrointestinal tract (Way *et al.*, 1998:506).

Place of action	Effect
Small intestine	Loperamide can increase the tone. Amplitude of nonpropulsive contractions are markedly decreased.
Large intestine	Propulsive peristaltic waves are diminished and the tones increased. This delays passage of faecal mass and allows increased absorption of water, which leads to constipation
Stomach	Loperamide decreases motility and the tone is increased

3.6.4 Therapeutic uses

Loperamide is mostly used for treating acute and chronic diarrhoea (Gibbon, 2000:59).

3.7 GLIBENCLAMIDE

3.7.1 Classification

Glibenclamide is an antidiabetic drug. It is an oral sulphonylurea (Semia *et al.*, 1997:387). Glibenclamide is a 'second-generation' sulphonylurea (Dollery, 1999:G64).

3.7.2 The pharmacological properties

The sulphonylureas bind to plasma proteins. All of the sulphonylureas are metabolised by the liver (Berkow *et al.*, 1992:1119). The primary effect is to potentiate glucose-stimulated insulin release from functioning pancreatic islet β-cells (Dollery, 1999:G64).

3.7.3 The mechanism of action

There are at least three proposed mechanisms of action for glibenclamide (Karam, 1998:696-697; Karam, 1999:1126):

- Glibenclamide can release insulin from β cells. The mechanism of action of the sulphonylureas when they are acutely administered is due to their insulinotropic effect on pancreatic β cells.
- Glibenclamide reduces the serum glucagon levels. Chronic administration of sulphonylureas to non-insulin dependent diabetics reduces serum glucagon levels. This is contributed to the hypoglycaemic effect of the drug.
- Glibenclamide can have an extrapancreatic effect to potentiate the action of insulin on its target tissues. There is an increased binding of insulin to tissue receptors occurring during sulphonylurea administration to patients with type II diabetes.

3.7.4 Therapeutic uses

Sulphonylureas are used for the treatment of hyperglycaemia in non-insulin dependent diabetes (Karam, 1998:696). Glibenclamide is widely used in the management of type II diabetes that cannot be controlled by a diet alone (Gibbon, 2000:69). Glibenclamide can by used as a substitute for other hypoglycaemic drugs. Glibenclamide can be a possible substitute for insulin in non-insulin dependent patients who have been treated with insulin but may not require it long term (Dollery, 1999:G66).

3.8 Multivitamin

The multivitamin complex includes the following:

- Vitamin A (retinol)
- Vitamin B_1 (thiamine)
- Vitamin C (ascorbic acid)
- Vitamin D (ergocalciferol)
- Nicotinamide (niacin)

3.8.1 Vitamin A

3.8.1.1 Classification

Vitamin A is essential for retinal function, growth and bone development, for integrity of epithelial tissue and reproduction (Gibbon, 2000:77).

3.8.1.2 The pharmacological properties

Vitamin A has an effect on the retina. Vitamin A deficiency interferes with vision in dim light, a condition known as night blindness (nyactalopia) (Marcus & Coulston, 1996b:1575). Vitamin A plays a major role in the induction and control of epithelial differentiation in mucus-secreting or keratinising tissues. The immune function is influenced by vitamin A. Vitamin A deficiency is

associated with increased susceptibility to bacterial, parasitic, and viral infections (Marcus & Coulston, 1996b:1576).

3.8.1.3 **The mechanism of action**

Vitamin A is needed for bone development, growth, visual adaptation to darkness, testicular and ovarian function, and as a cofactor in many biochemical processes (Taketomo *et al.,* 1998:766).

3.8.1.4 **Therapeutic uses**

Vitamin A is an antioxidant and is one of several dietary antioxidants that are being investigated for a protective role against tumour formation involving free radicals (Martin, 1991:23). Vitamin A is used to treat, prevent vitamin A deficiency and defined skin disorders (Dollery, 1999:R17).

3.8.1.5 **Deficiency**

Vitamin A deficiency: night blindness, xerophtalmia (dryness of conjunctiva), keratomalacia (softening of cornea) and hyperkeratosis of the skin, and increased morbidity and mortality following many viral and bacterial illnesses (Gibbon, 2000:77).

3.8.2 **Vitamin C (ascorbic acid)**

3.8.2.1 **The pharmacological properties**

Vitamin C is readily absorbed orally. Vitamin C is metabolised by the liver and eliminated in the urine (Semla *et al.,* 1998:70).

3.8.2.2 **The mechanism of action**

According to Semla *et al.* (1998:70) Vitamin C's biologic functions are not fully understood. Vitamin C is necessary for collagen formation and tissue repair in the body. It is involved in some oxidation-reduction reactions as well as other metabolic reactions, such as synthesis of carnitine, steroids, and catecholamines. Vitamin C is involved in the conversion of folic acid to folinic acid.

3.8.2.3 **Therapeutic uses**

The most important role of vitamin C is in the formation of collagen, a major component of all connective tissue (e.g., dentine, cartilage, bone matrix) in the body. Vitamin C plays a major antioxidant role in the body's fluid compartments, and appears to have a protective role against certain cancers, particularly gastric cancer. Vitamin C is important in the synthesis of neurotransmitters, steroid hormones, carnitine, conversion of cholesterol to bile acids and tyrosine degradation. Intestinal iron absorption can be enhanced by vitamin C supplementation and it may also be used in the management of methaemoglobinaemia (Gibbon, 2000:83). Vitamin C is used for

the treatment of ascorbic acid deficiency, especially frank scurvy, which occurs rather infrequently in infants and in adults (Marcus & Coulston, 1996a:1570).

3.8.2.4 **Deficiency**

Deficiency in the intake of vitamin C can lead to scurvy (Baron, 1999:1192). Scurvy is due to malnutrition, chronic alcoholism and can occur in the elderly (Marcus & Coulston, 1996a:1570). Early manifestations are weakness and malaise. Advanced stage includes perifollicular haemorrhages and hyperkeratotic papules, perechiae and purpura, bleeding gums, and haemarthrosis. Anaemia is common and wound healing impaired. Later stages include oedema, oliguria, neuropathy intracerebrial haemorrhage, and death (Baron, 1999:1192).

3.8.3 **Vitamin D (ergocalciferol)**

3.8.3.1 **The pharmacological properties**

Vitamin D enhances the intestinal absorption of calcium. Children with vitamin D-deficiency that have rickets type II have been treated with intravenous calcium and phosphate. Vitamin D promotes mobilisation of calcium from bone and large doses cause excessive bone turnover. Vitamin D increases retention of calcium independently of phosphate and probably enhances reabsorption of each by the proximal tubules (Kapusnik-Uner *et al.*, 1996:1532).

3.8.3.2 **The mechanism of action**

Vitamin D stimulates calcium and phosphate absorption from the small intestine and promotes secretion of calcium from bone to blood. Vitamin D promotes renal tubule phosphate resorption (Semla *et al.,* 1998:309).

3.8.3.3 **Therapeutic uses**

The therapeutic uses may be divided into four categories (Kapusnik-Uner *et al.*, 1996:1535):

- Prophylaxis and cure of nutritional rickets.
- Treatment of metabolic rickets and osteomalacia.
- Treatment of hypoparathyroidism.
- Prevention and treatment of osteoporosis.

Nutritional rickets occurs when there is inadequate exposure to sunlight or deficiency of dietary vitamin D (Kapusnik-Uner *et al.,* 1996:1535). Hypoparathyroidism is characterised by hypocalcaemia and hyperphosphatemia (Kapusnik-Uner *et al.*, 1996:1535). Hypocalcaemia occurs with tetanus, paraesthesiae, laryngospasm, muscle cramps and convulsions (Bikle, 1998:714).

3.8.3.4 **Deficiency**

Deficiency leads to rickets or infantile tetanus in children and osteomalacia in adults (Gibbon, 2000:78). Deficiency results in inadequate absorption of calcium and phosphate. In children, vitamin D deficiency results in a growth defect known as rickets. The bones of individuals with rickets are soft and this can lead to deformities. In adults, vitamin D deficiency results in osteomalacia characterised by generalised accumulation of undermineralised bone matrix. Muscle weakness, extreme bone pain and tenderness are symptoms of osteomalacia (Marcus, 1996:1533).

Vitamin D toxicity is hypervitaminosis D. The symptoms and signs of the toxicity are associated with hypercalcaemia. One episode of hypercalcaemia may result in arrest growth for six months or more. In infants, vitamin D toxicity may be manifested. Maternal hypercalcaemia also results in suppression of parathyroid function in the newborn, with resultant hypocalcaemia, tetanus and seizures. Treatment is the withdrawal of the vitamin, a low calcium diet, administration of glucocorticosteroids and fluid support (Marcus, 1996:1533).

3.8.4 **Nicotinamide (niacin)**

3.8.4.1 **The pharmacological properties**

Niacin is converted in the body to nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), two co-factors essential for a variety of oxidation-reduction reactions that comprise tissue respiration (Dollery, 1999:N59).

3.8.4.2 **The mechanism of action**

Niacin is a component of two coenzymes, which is necessary for tissue respiration, lipid metabolism and glycogenolysis. Niacin inhibits the synthesis of very low-density lipoproteins (VLDL) (Semla *et al.,* 1998:595). The mechanism with which niacin inhibits the synthesis of VLDL is uncertain. It is thought to be due to a combination of inhibition of lipolysis in adipose tissue, decreased esterification of triglycerides in the liver, increased activity of lipoprotein lipase and a possible direct effect on hepatic production of apolipoprotein B (Dollery, 1999:N59).

3.8.4.3 **Therapeutic uses**

Nicotinamide is used for prophylaxis and treatment of pellagra (Marcus & Coulston, 1996a:1561). Nicotinamide has shown to normalise the levels of LDL-cholesterol (low-density lipoproteins cholesterol) in most patients with heterozygous familial hypercholesterolemia (Malloy & Kane, 1998:571).

3.8.4.4 **Deficiency**

Deficiency leads to pellagra – characterised by gastrointestinal, skin and nervous system abnormalities (e.g. diarrhoea, dermatitis and dementia) (Gibbon, 2000:81). The deficiency is commonly due to alcoholism and nutrient-drug interaction (Baron, 1999:1191). An erythematous eruption resembling sunburn first appears on the back of the hands. Chief symptoms are referable to the digestive track. These are stomatitis, enteritis, and diarrhoea (Marcus & Coulston, 1996a:1560). Common complaints are anorexia, weakness, irritability, mouth ulceration, and weight loss (Baron, 1999:1191). Symptoms of the central nervous system are headache, dizziness, insomnia, depression and impairment of memory. In severe cases, delusions, hallucinations, and dementia may appear (Marcus & Coulston, 1996a:1561). Advanced pellagra can result in death (Baron, 1999:1191).

3.8.5 **Vitamin B_1 (thiamine)**

3.8.5.1 **The pharmacological properties**

Thiamine is practically devoid of pharmacodynamic actions when given in usual therapeutic doses. Rare instances of hypersensitivity can occur with the use of Vitamin B_1 (Marcus & Coulston, 1996a:1555). Thiamine is metabolised in the liver and eliminated in the urine (Taketomo *et al.*, 1998:712).

3.8.5.2 **The mechanism of action**

Thiamine is an essential coenzyme in carbohydrate metabolism. Thiamine combines with adenosine triphosphate to form thiamine pyrophosphate (Taketomo *et al.*, 1998:712).

3.8.5.3 **Therapeutic uses**

Thiamine is used for the treatment or prophylaxis of thiamine deficiency. Alcoholic neuritis is the most common cause of thiamine deficiency. Alcoholic neuritis is caused by an inadequate intake of thiamine. Infantile beri-beri is when thiamine deficiency occurs as an acute disease in infancy. It is significant in Third World countries and is related to the low content of thiamine in breast milk of thiamine-deficient women (Marcus & Coulston, 1996a:1557).

Cardiovascular disease of nutritional origin is observed in chronic alcoholics, pregnant women, persons with gastrointestinal disorders, and those whose diet is deficient for other reasons. Thiamine has been used to treat beri-beri for symptoms such as ulcerative colitis, gastrointestinal hypotonia and chronic diarrhoea. Neuritis of pregnancy increases the thiamine requirements slightly (Marcus & Coulston, 1996a:1558).

3.8.5.4 **Deficiency**

Thiamine deficiency may result from inadequate nutrition as intestinal malabsorption. Requirements may be increased during conditions such as hyperthyroidism, chronic infections, burns and malabsorption syndromes. The early stage of deficiency is anorexia, paraesthesias, calf tenderness and hyperactivity followed by hypoactivity of knee and ankle jerks. Gross manifestations are beriberi and encephalopathy (Gibbon, 2000:81).

Beriberi is the major symptom of thiamine deficiency and is related to the nervous system (dry beriberi) and to the cardiovascular system (wet beriberi). Neurological signs are peripheral neuritis, with sensory disturbances in the extremities. Personality disturbances, depression and lack of initiative can occur. Cardiovascular symptoms are dyspnea, palpitation, and tachycardia (Marcus & Coulston, 1996a:1557).

3.9 **DICLOFENAC**

3.9.1 **Classification**

Diclofenac, a phenylacetic acid derivative, is one of the non-steroid anti-inflammatory drugs available for oral, rectal and intramuscular administration (Gibbon, 2000:321).

3.9.2 **The pharmacological properties**

Diclofenac has analgesic, antipyretic and anti-inflammatory activities (Insel, 1996:637). It also has some uricosuric effect. Diclofenac causes gastric erosions and prolongs the bleeding time (Dollery, 1999:D88).

3.9.3 **The mechanism of action**

Diclofenac is an inhibitor of cyclooxygenase (Insel, 1996:637). There is a reduction in the tissue production of prostaglandins (Dollery, 1999:D88). Diclofenac appears to reduce intracellular concentrations of free arachidonate in leukocytes (Insel, 1996:637).

3.9.4 **Therapeutic uses**

Diclofenac is used for the relief of pain and inflammation in rheumatic disease and a wide variety of other conditions, including gout (Gibbon, 2000:324). Diclofenac can be used for long-term symptomatic treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. Diclofenac can be used for short-term treatment of acute musculoskeletal injury, acute painful shoulder, postoperative pain and dysmenorrhea (Insel, 1996:637). Diclofenac is used in the control of pain and inflammation in orthopedic, dental and other minor surgery. Diclofenac helps for postoperative pain and renal colic pain (Dollery, 1999:D89).

3.10 RESERPINE

3.10.1 Classification

Reserpine is an antihypertensive drug. It is a central acting and anti-adrenergic agent (Turner, 2001:162; Gibbon, 2000:124). Reserpine is an adrenergic neuron blocking agent (Oates, 1996:781).

3.10.2 The pharmacological properties

According to Oates (1996:791) both cardiac and peripheral vascular resistance are reduced during long-term therapy with reserpine. Orthostatic hypotension may occur but does not usually cause symptoms. The heart rate and renin secretion falls. Salt and water are retained, which commonly results in "*pseudotolerance*".

3.10.3 The mechanism of action

The drug lowers blood pressure by preventing normal physiologic release of norepinephrine from postganglionic sympathetic neurons (Benowitz, 1998:161). Reserpine binds to storage vesicles in central and peripheral adrenergic neurons, and the drug remains at such sites for prolonged periods of time. The storage vesicles are rendered dysfunctional as a result of their interaction with reserpine, and nerve endings lose their ability to concentrate and store norepinephrine and dopamine (Oates, 1996:791).

Reserpine lowers blood pressure by a combination of decreased cardiac output and decreased peripheral vascular resistance (Benowitz, 1998:163). Reserpine depletes the brain of norepinephrine and serotonin and also depletes the peripheral sympathetic nerve terminal of norepinephrine (Berkow *et al.*, 1992:426).

3.10.4 Therapeutic uses

Reserpine is used to treat mild to moderate hypertension (Gibbon, 2000:124). Low doses of reserpine are given concurrently with a diuretic. The major advantage of reserpine is that it is much less expensive than other antihypertensive drugs (Oates, 1996:791). Reserpine is used once daily with a diuretic, and several weeks are necessary to achieve a maximum effect (Oates, 1996:791). High doses, in the central nervous system, have been associated with a high incidence of unwanted effects (e.g., mental depression). Low doses are recommended and have little toxicity potential (Gibbon, 2000:124).

3.11 MECHANIMS OF DRUG INTERACTIONS

The mechanisms of actions that follow are to explain the interactions that occur between the ten selected drugs and other medication. The tables containing the interactions follow after the mechanisms of the drug interactions.

3.11.1 **Diphenhydramine** (refer to Table 3.11)

- Aminosalicylic acid

Diphenhydramine appears to impair the gastrointestinal absorption of aminos acid, possibly because of the effect of diphenhydramine on gastrointestinal motility (Hansten & Horn, 1989:209).

- Alcohol

When an interaction occurs it appears to be due to the combined or additive central nervous depressant effects of both the alcohol and the antihistamine (Stockley, 1999:18).

- Beta blockers

Diphenhydramine inhibit the cytochrome P450 metabolism of the beta-blockers, thus increasing the effects of certain beta-blockers such as propranolol, carvedilol and labetolol (Tatro, 2000).

3.11.2 **Tetracycline** (refer to Table 3.12)

- Antacids (containing divalent or trivalent cations)

Antacids (e.g. aluminium, calcium, and magnesium) impair the absorption of orally administrated tetracyclines. This effect has been attributed to chelation of the cation by tetracycline. Antacids may also affect the dissolution of tetracycline (Hansten & Horn, 1990:300; Tatro, 1998:1005).

- Anticoagulants

The proposed mechanisms for the interaction between tetracycline and anticoagulants are one of the following (Hansten & Horn, 1990:158):

- Intravenous tetracycline therapy may reduce plasma prothrombin activity by impairing prothrombin utilisation.
- Tetracycline decreases vitamin K production by gastrointestinal bacteria, but this effect is of questionable significance.
- Animal studies indicate that a combination of tetracycline, neomycin and bactracin may inhibit the enterohepatic circulation of warfarin.
- Fever has been shown to enhance the catabolism of clotting factors; thus, the infection for which the tetracycline is used could theoretically enhance oral anticoagulant hypoprothrombinemia.

- Barbiturates

Barbiturates presumably enhance the hepatic metabolism of doxycycline (Hansten & Horn, 1989:251). This increase is due to stimulation of microsomal enzymes (Tatro, 1998:452). Doxycycline elimination is enhanced (Zucchero *et al.,* 1999:182).

- Bismuth subsalicylate

Bismuth subsalicylate appears to inhibit the absorption of tetracyclines from the gastrointestinal tract (Hansten & Horn, 1990:301). The inhibition of the absorption of tetracycline is due to the formation of a chelate between the two drugs (Tatro, 1998:1006).

- Carbamazepine

Carbamazepine appears to stimulate hepatic doxycycline metabolism (Hansten & Horn, 1989:251). Carbamazepine is known to induce liver enzymes and possibly accelerate the metabolism of doxycycline (Zucchero *et al.,* 1999:182).

- Cimetidine

The dissolution of the capsule form of tetracycline depends on gastric acidity, and cimetidine raises the gastric pH (Zucchero *et al.,* 1999:205).

- Colestipol

Colestipol appears to bind tetracycline in the intestinal tract, inhibiting its absorption (Hansten & Horn, 1990:517; Tatro, 1998:1009).

- Corticosteroids

Prolonged tetracycline therapy may favour the emergence of organisms that are resistant to tetracycline. The corticosteroid-induced decrease in resistance to infection may enable these organisms to produce a serious infection (Hansten & Horn, 1989:252).

- Digoxin

A large amount of digoxin is metabolised by bacteria in the gastrointestinal tract to inactive metabolites. Tetracycline may reverse the process by altering gastrointestinal flora, allowing for more digoxin to be absorbed and increasing digoxin serum levels (Tatro, 2001:501).

- Diuretics (e.g. hydrochlorothiazide, furosemide, chlorthalidone, etc.)

Both tetracycline and diuretics have independently been reported to elevate blood urea nitrogen (BUN) levels (Hansten & Horn, 1990:302; Tatro, 2001:1169). The tetracycline effect probably is due to its anti-anabolic action (Hansten & Horn, 1990:302).

- Ethanol (alcohol)

Chronic ingestion of large amounts of ethanol may result in induction of hepatic microsomal enzymes. Doxycycline is metabolised by the liver; its metabolism may be enhanced in alcoholic patients (Hansten & Horn, 1989:252; Tatro, 1998:1011).

- Ferrous sulphate

Ferric and ferrous irons have been shown to form chelates with tetracycline (Zucchero *et al.*, 1999:206). The absorption and serum levels of both drugs are decreased (Tatro, 2001:1172).

- Food (milk and diary products)

Cations, such as calcium and magnesium, in food can chelate with tetracycline; thus impairing absorption of these drugs (Hansten & Horn, 1990:303; Tatro, 1998:1012).

- Insulin

Tetracycline can increase the extra-pancreatic response to insulin due to a reduction in blood glucose concentration (Tatro, 2000).

- Iron

Oral ferrous sulphate appears to impair the gastrointestinal absorption of various tetracyclines, possibly because of chelation or other types of binding in the gut (Hansten & Horn, 1989:253).

- Lithium carbonate

It has been proposed that tetracycline-induced renal impairment may reduce urinary lithium excretion, but the mechanism is unknown (Hansten & Horn, 1989:253).

- Magaldrate

Tetracyclines form an insoluble chelate with aluminium salts; thereby decreasing the absorption of tetracycline and magaldrate and their therapeutic effects are decreased (Tatro, 2000).

- Methotrexate

Methotrexate can be displaced from its binding to the plasma proteins. This may by a likely mechanism to explain the interactions (Tortajada-Ituren *et al.*, 1999:806). The exact mechanism remains unclear (Tatro, 2000; Tortajada-Ituren *et al.*, 1999:806).

- Methoxyflurane

The mechanism between tetracycline and methoxyflurane has not established. Combined nephrotoxic action appears to be involved. (Hansten & Horn, 1989:304).

♦ Oral contraceptives

Tetracycline may interfere with the enterohepatic circulation of estrogens by reducing bacterial hydrolysis of conjugated estrogens in the intestine (Hansten & Horn, 1990:302). The antibiotics destroy the gut flora and prevent steroid reabsorption (Zucchero *et al.*, 1999:206).

♦ Penicillin

Penicillin is a bactericidal agent and acts by inhibiting cell wall synthesis. Bacteriostatic agents such as tetracycline inhibit protein synthesis. The combination of these drugs could mask the bactericidal effect of penicillin and decreasing the effect of penicillin (Hansten & Horn, 1989:238).

♦ Phenytoin

Phenytoin stimulates hepatic microsomal enzymes and thus induces the metabolism of doxycycline (Tatro, 1998:454). The displacement of doxycycline from plasma proteins may also contribute to this phenomenon (Tatro, 2000).

♦ Quinapril

The quinapril has magnesium carbonate in the formulation. The magnesium carbonate and tetracycline form a less soluble chelate in the gut, which is less well absorbed (Stockley, 1999:198).

♦ Rifamycins

Rifamycins may increase the hepatic metabolism of doxycycline (Tatro, 1998:455). According to Gibbon (2000:260) the increase in metabolism can cause doxycycline serum concentration to decrease and this can result in lower doxycycline effects.

♦ Thimerosal

Tetracycline is known to penetrate into ocular fluid and may chelate with the mercury in thimerosal (Zucchero *et al.*, 1999:207). The doxycycline and thimerosal therapeutic effects will be decreased.

♦ Tromethamine

Urinary alkalinisers can possibly alter the tubular reabsorption of tetracycline due to the alkaline urine. The increased gastric pH may decrease tetracycline absorption (Tatro, 2000).

♦ Urinary alkalinisers (Sodium bicarbonate and tromethamine)

Some reports indicate that sodium bicarbonate raises the intragastric pH (Tatro, 1998:1015). Tetracycline dissolves slower at a higher intragastric pH (Zucchero *et al.*, 1999:206; Tatro, 2000).

- Zinc

Zinc appears to impair the gastrointestinal absorption of tetracycline, possibly by chelation (Hansten & Horn, 1989:254; Tatro, 2001:1175).

The mechanisms of interaction between tetracycline and the listed drugs below are unknown as indicated in the following table. Refer to Table 3.8 for the interactions.

Table 3.2: Tetracycline interactions.

Drugs involved in interactions	References
Antidiabetic drugs	Hansten & Horn, 1989:172
Ergotamine	Stockley, 1999:797
Theophylline	Hansten & Horn, 1990:499

3.11.3 **Co-trimoxazole (trimethoprim/sulphamethoxasole)** (refer to Table 3.13)

- Amantadine

Both amantadine and trimethoprim are secreted by the renal tubules and may inhibit each other's renal clearance, resulting in accumulation of toxic plasma concentrations (Hansten & Horn, 1990:500; Tatro, 1998:27).

- Anticoagulants

Sulphamethoxasole appears to impair the hepatic metabolism of oral anticoagulants. Competition for plasma proteinbinding sites may play an additional role (Hansten & Horn, 1989:106).

- Antidiabetic agents

Co-trimoxazole reduces the metabolism of tolbutamide and possibly glipiside (Hansten & Horn, 1990:215) and the hypoglycaemic effects of the antidiabetic agents are potentiated by co-trimoxazole (Gibbon, 2000:266).

- Diuretics (e.g. hydrochlorothiazide)

The mechanism between trimethoprim and diuretics has not been established (Stockley, 1999:348).

- Ethanol

Co-trimoxazole may inhibit acetaldehyde dehydrogenase. This leads to accumulation of acetaldehyde, thus causing the disulfiram-like reaction (Tatro, 2000).

- Methotrexate

Co-trimoxazole may act synergistically to produce folic acid deficiency, which can lead to megaloblastic changes. Perhaps methotrexate predisposes patients to the effects of co-trimoxasole

(Hansten & Horn, 1989:255). Sulphonamides displace methotrexate from the protein binding sites and decrease the renal clearance of methotrexate (Tatro, 1998:739).

- Oral contraceptives

The oestrogen levels in the body rise due to sulphamethoxazole, which is concerned with the liver enzymes. The liver enzymes handle the metabolism and clearance of the oestrogen (Stockley, 1999:425). The steroid microsomal hydroxylation enzymes are inhibited (Zucchero *et al.*, 1999:204).

The mechanisms of interaction between co-trimoxazole and the listed drugs are unknown as indicated in the following table. Refer to Table 3.9 for the interactions.

Table 3.3: Co-trimoxazole.

Drugs involved in interactions	**References**
Folic acid	Stockley, 1999:132
Mercaptopurine	Stockley, 1999:437

3.11.3.1 **Trimethoprim**

- Dapsone

Trimethoprim may reduce the elimination of dapsone; dapsone reduces the elimination of trimethoprim (Hansten & Horn, 1990:262; Tatro, 1998:952).

- Phenythoin

Trimethoprim appears to inhibit the hepatic metabolism of phenytoin (Hansten & Horn, 1990:196; Tatro, 1998:599). According to Gibbon (2000:265) prolonged concurrent use may aggravate folate antagonism and increase the risk of megaloblastic anaemia.

- Procainamide

Trimethoprim and procainamide are weak bases, which are actively secreted by the renal tubules. Trimethoprim competes with the renal secretion of procainamide. It also inhibits the metabolism of procainamide, probably by inhibiting hepatic uptake of procainamide (Hansten & Horn, 1990:102; Tatro, 1998:861).

- Dofetilide

Trimethoprim inhibit the renal cation transport system that is responsible for dofetilide elimination. The plasma concentrations of dofetilide are elevated and this has as increased risk of ventricular arrhythmias (Tatro, 2000).

♦ Zidovudine

The renal clearance of zidovudine and its glucoronide metabolite appear to be decreased. The pharmacological effects of zidovudine may be increased in patients with impaired hepatic function who receive trimethoprim (Tatro, 1998:1139).

3.11.3.2 **Sulphonamide**

♦ Aminobenzoic acid (PABA)

Sulphonamide acts by competitive inhibition of PABA in micro-organisms, PABA administration in sufficient doses antagonises the antibacterial effect of sulphonamide (Hansten & Horn,1989:249).

♦ Cyclosporin

Sulphonamide appears to increase the metabolism of cyclosporin, resulting in decrease plasma concentrations (Hansten & Horn, 1990:298). The leads to reduction in the action of cyclosporin and oral sulphonamides may increase the risk of nephrotoxicity (Tatro, 1998:366).

♦ Hypoglycaemic agents (e.g. chlorpropamide, tolbutamide, acetohexamide, etc.)

The mechanism between sulphonamide and hypoglycaemic agents is not fully understood. The sulphonamides may inhibit the metabolism of the sulphonylureas so that they accumulate in the body (Stockley, 1999:530; Tatro, 1998:977).

♦ Methenamine

The use of methenamine with some sulphonamides enhances the danger of crystalluria (Hansten & Horn, 1990:280).

♦ Oxacillin

Sulphonamide appears to inhibit the gastrointestinal absorption of oxacillin; others may reduce the elimination of penicillin G (Hansten & Horn,1990:286).

♦ Sulphinpyrazone

Sulphinpyrazone may displace some sulphonamides and from plasma protein binding, resulting in more active (free) drug in the plasma (Hansten & Horn, 1989:250).

3.11.4 **Hyoscine** (refer to Table 3.14)

♦ Calcium channel blockers

Acute administration of verapamil may increase sympathetic nervous system activity. This increased activity may cause an increase in the heart rate during atropine-induced vagal blockade that is not observed in the absence of atropine (Hansten & Horn,1990:526).

3.11.5 **Theophylline** (refer to Table 3.15)

- Aciclovir

Mechanism is uncertain, but evidence suggests that aciclovir inhibits the metabolism of theophylline; theophylline accumulates in the body and the potential for theophylline toxicity can increase (Stockley, 1999:705).

- Adenosine

Theophylline is an adenosine antagonist and is capable of attenuating the vasodilatation effect of adenosine (Hansten & Horn, 1989:574). Theophylline antagonises the cardiovascular and respiratory effects of adenosine (Biaggioni *et al.,* 1991:591).

- Allopurinol

Allopurinol may impair liver degradation of theophylline and the clearance of theophylline is decreased. This effect can lead to increased theophylline plasma levels and possible toxicity (Tatro, 1998:1017).

- Aminoglutethimide

Aminoglutethimide stimulates the hepatic oxidation of several drugs. Theophylline is metabolised by oxidation (Hansten & Horn, 1989:490). Aminoglutethimide is a potent inducer of hepatic microsomal enzymes responsible for the metabolism of theophylline. The clearance of theophylline is increased, leading to the reduction in theophylline serum concentration (Tatro, 1998:1018).

- Amiodarone

Amiodarone is known to be an enzyme inhibitor and probably inhibits the metabolism of theophylline (Hansten & Horn, 1990:491; Soto, *et al.,* 1990:1115). The theophylline levels are increased due to amiodarone and this leads to theophylline toxicity (Tatro, 1998:1019).

- Antacids

Factors such as gastrointestinal fluid pH may influence the degradation and/or absorption of some slow release theophylline formulations. Antacids can change the pH and so increase theophylline absorption (Zucchero *et al.,* 1999:332).

- Barbiturates

Phenobarbital may enhance the metabolism of theophylline by induction of hepatic microsomal enzymes (Hansten & Horn, 1990:445). Clearance of theophylline is increased by the induction of cytochrome P450 system (Tatro, 2000; Tatro, 1998:1020).

♦ Bensodiazepine (e.g. chlordiazepoxide)

A possible antagonistic action between theophylline and bensodiazepine occurs by competitive binding to intracerebral adenosine receptors. The sedative effects of bensodiasepines may be antagonised by theophylline (Tatro, 2000).

♦ Caffeine

The mechanism between theophylline and caffeine is unknown. It does appear that there is interference with theophylline metabolism (Tatro, 1998:1022). Saturation of theophylline metabolism and/or competition between caffeine and theophylline may result in the delay of theophylline elimination (Zucchero *et al.,* 1999:332).

♦ Calcium channel blockers

Verapamil inhibits metabolism of theophylline, through an effect on hepatic microsomal enzymes. Diltiasem and nifedipine appear to have less consistent and less potent effects on theophylline metabolism (Hansten & Horn, 1990:71).

♦ Carbamazepine

Carbamazepine probably stimulates hepatic metabolism of theophylline (Hansten & Horn, 1990:479). Theophylline increases the metabolism of carbamazepine (Zucchero *et al.,* 1999:333). The enhanced metabolism of theophylline can increase the dose needed to achieve therapeutic levels (Gibbon, 2000:458).

♦ Cefaclor

The mechanism of interaction between theophylline and cefaclor is unknown. The presence of an acute viral illness has been associated with decreased hepatic cytochrome P450 activity and decreased theophylline metabolism (Zucchero *et al.,* 1999:333).

♦ Charcoal

Activated charcoal adsorbs oral theophylline, limiting its absorption from the gastrointestinal tract. and decreases enterohepatic recirculation, increasing theophylline clearance (Zucchero *et al.,* 1999:334).

♦ Cimetidine

Cimetide inhibits the hepatic metabolism of theophylline (Hansten & Horn, 1989:395; Tatro, 2001:1184). This inhibition may cause cimetidine to bind to an enzyme system or to theophylline, forming a complex that interrupts metabolism (Zucchero *et al.,* 1999:334).

- Ciprofloxacin

Ciprofloxacin inhibits the hepatic metabolism of theophylline and the increased levels of theophylline lead to toxicity of theophylline (Tatro, 2000).

- Diltiazem

Diltiazem may inhibit the metabolism of theophylline (Tatro, 1998:1027; Gardner *et al.,* 1983:278). The pharmacological and toxic effects of theophylline may be increased (Tatro, 1998:1027).

- Disulfiram

Disulfiram inhibits hepatic microsomal metabolism of several drugs. Both hydroxylation and demethylation of theophylline appear to be inhibited (Hansten & Horn, 1990:457; Tatro, 2001:1188). The pharmacological and toxic effects of theophylline may be increased (Tatro, 1998:1028).

- Erythromycin

Erythromycin appears to inhibit metabolism of theophylline. Theophylline increases the renal clearance of erythromycin (Hansten & Horn, 1989:221). Theophylline reduces the bioavailability of erythromycin (Tatro, 2000).

- Felodipine

The mechanism of interaction between theophylline and felodipine is unknown. A possibility for the mechanism is a decrease in gastrointestinal absorption of theophylline (Tatro, 2000).

- Fluvoxamine

Fluvoxamine may inhibit the hepatic metabolim of theophylline and raising theophylline levels (Tatro, 1998:1032).

- Furosemide

The mechanism of interaction between theophylline and furosemide is not known. Furosemide may reduce the volume of distribution of theophylline and increase its serum concentration (Hansten & Horn, 1990:343). Furosemide may decrease hepatic congestion, increasing theophylline clearance, or displace theophylline from serum proteins (Zucchero *et al.,* 1999:336).

- Influenza vaccine

Some preparations of influenza vaccine may be capable of inhibiting the metabolism of theophylline, especially when the vaccine contains proteins from the virus or culture media that can act as interferón stimulators (Hansten & Horn, 1990:479). Influenza vaccine may decrease theophylline

biotransformation because of a depression of the cytochrome P450 system (Zucchero *et al.*, 1999:337).

- Isoniazid (INH)

INH appears to gradually decrease the clearance of theophylline during chronic administration (Hansten & Horn, 1989:555; Thompson & Self, 1990:909). Isoniazid may increase the hepatic metabolism of theophylline by enzyme induction or an unknown mechanism (Zucchero *et al.*, 1999:337).

- Ketoconazole

The mechanism of interaction between theophylline and ketoconazole is not known. It is possible that ketoconazole enhances the metabolism of theophylline since it has been suggested that long-term ketoconazole administration may induce hepatic drug metabolism; however, this would be opposite its expected effect since ketokonazole has been shown to inhibit the hepatic metabolism of other agents (Zucchero *et al.*, 1999:338).

- Lithium

Theophylline enhances renal clearance of lithium, thus tending to reduce serum lithium concentrations (Hansten & Horn, 1989:410).

- Macrolide antibiotics

Macrolide antibiotics inhibit the metabolism of theophylline. Theophylline reduces the bioavailability and increases the renal clearance of oral erythromycin (Tatro, 1998:1044).

- Mexiletine

Mexiletine reduces hepatic metabolism of theophylline (Hansten & Horn, 1989:579) via the cytochrome P450 oxidase system (Tatro, 1998:1045). There is a significant decrease in demethylation of theophylline with co-administration of mexiletine (Ueno *et al.*, 1991:729). The serum theophylline levels may be increased, resulting in an increase in the pharmacological and toxic effects of theophylline (Tatro, 1998:1045).

- Moricizine

Moricizine appears to increase metabolism of theophylline (Hansten & Horn, 1990:98). Moricizine may cause decreased theophylline concentrations and exacerbation of pulmonary symptoms can occur (Tatro, 1998:1046).

♦ Nondepolarising muscle relaxants

The mechanism of interaction between theophylline and the muscle relaxants is not clear. Antagonistic activity is being speculated (Tatro, 2000).

♦ Omeprazole

Theophylline may be released more rapidly from the sustained-release formulation (Tatro, 1998:1048). Gastric hypoacidity produced by omeprazole adminstration may amplify peristalsis in the small intestine and antiperistalsis in the proximal colon (Tatro, 2001:1208).

♦ Oral contraceptives

Oral contraceptives decrease the oxidative degradation of theophylline (Tatro, 1998:1025). The serum levels of theophylline are raised to some extent (Stockley, 1991:779).

♦ Phenytoin

Phenytoin probably enhances hepatic theophylline metabolism (Hansten & Horn, 1989:148). Theophylline induces the metabolism of phenytoin or interferes with its absorption (Zucchero *et al.*, 1999:340; Tatro, 1998:1035).

♦ Propafenone

The mechanism of interaction between theophylline and propafenone is uncertain (Stockley, 1999:723). An inhibition of theophylline hepatic metabolism may occur (Zucchero *et al.*, 1999:340; Tatro, 1998:1049).

♦ Propranol (Beta-blockers)

Beta-blockers (e.g. carteolol, timolol, propranolol) inhibit hepatic microsomal drug metabolism, in particular, the demethylation of theophylline. Beta-blockers (non-selective) may antagonise the bronchodilatation produced by theophylline (Hansten & Horn, 1990:57). These two groups of drugs are pharmacologic antagonists (Tatro, 1998:1021). Propranolol has a great inhibitory effect on theophylline clearance (Corsi *et al.*, 1990:267).

♦ Pyrantel

The mechanism of interaction between theophylline and pyrantel is not understood (Stockley, 1999:723). Pyrantel may inhibit theophylline clearance by inhibition of hepatic enzymes, or it may increase the rate of drug release, increasing theophylline levels (Zucchero *et al.*, 1999:341).

- Quinolones

Ciprofloxacin and enoxacin probably inhibit the demethylation pathway of theophylline metabolism (Hansten & Horn, 1989:241). The theophylline levels are increased and toxicity can occur (Tatro, 1998:1050).

- Radioactive iodine

Rate of theophylline elimination tends to be increased in hyperthyroidism and reduced in hypothyroidism. Iodine treatment of hyperthyroidism may result in increased serum theophylline concentrations, especially if the iodine therapy results in hypothyroidism (Hansten & Horn, 1990:480).

- Rifampin

Rifampin increases the metabolic clearance of theophylline (Hansten & Horn, 1989:246). It is speculated that the increased activity of the hepatic cytochrome P450 system by rifampin is involved in this interaction (Zucchero *et al.,* 1999:342).

- Smoking

Smoking stimulates hepatic metabolism of theophylline (Hansten & Horn, 1989:419) and the dosage of theophylline is increased to meet therapeutic needs (Gibbon, 2000:458).

- St. John's wort

An increased hepatic metabolism of theophylline is suspected (Tatro, 2000). St John's wort may have induced hepatic enzymes necessary for theophylline clearance (Nebel *et al.,* 1999:502). The increase in hepatic metabolism of theophylline can result in decreased plasma concentration of theophylline and thus increasing the dosage (Tatro, 2000).

- Sucralfate

Sustained-release theophylline products release the drug over a prolonged period, allowing greater opportunity for an interaction to occur. This may explain the differences in the interaction between sustained-release and immediate-release theophylline and sucralfate (Zucchero *et al.,* 1999:342).

- Sulphinpyrazone

The hepatic metabolism of theophylline may be increased and renal clearance may be decreased (Tatro, 1998:1053). The metabolism is increased because of the induction caused by sulphinpyrazone. Renal clearance may be decreased, because theophylline is a weak acid. Theophylline may undergo active tubular secretion, which is inhibited by sulphinpyrazone (Birkett, *et al.,* 1983:568).

♦ Tacrine

Tacrine can possibly inhibit the hepatic metabolism of theophylline. Theophylline concentrations are increased to toxic levels (Tatro, 1998:1055).

♦ Tetracycline

The mechanism of interaction between theophylline and tetracycline is not known (Hansten & Horn, 1990:499). Gastrointestinal complaints may occur with both agents, and this interaction may be a summation response (Zucchero *et al.*, 1999:342).

♦ Thiabendazole

The mechanism of interaction between theophylline and thiabendazole is not known. Thiabendasole appears to inhibit the metabolism of theophylline (Hansten & Horn, 1990:305; Tatro, 1998:1057).

♦ Thyroid hormones

The rate of theophylline elimination tends to be increased in hyperthyroidism and tends to be reduced in hypothyroidism. Thus, thyroid hormone replacement in a clinically hypothyroid patient may increase theophylline administration (Hansten & Horn, 1989:515). There appears to be a positive correlation or a direct relationship between plasma thyroxine levels and theophylline clearance (Tatro, 2000).

♦ Ticlopidine

Ticlopidine impairs theophylline elimination. Theophylline toxicity can occur in the form of nausea, vomiting, seizures and arrhythmias (Tatro, 1998:1060).

♦ Tobacco

Tobacco and cannabis smoke contain polycyclic hydrocarbons which act as liver enzymes inducing agents, and this results in a more rapid clearance of theophylline from the body (Stockley, 1999:730; Gardner *et al.*, 1983:271).

♦ Verapamil

Verapamil inhibits the hepatic metabolism of theophylline (Tatro, 1998:1061). Substances that may compete with its metabolism affect theophylline clearance, and theophylline and verapamil have a metabolic process in common (Zucchero *et al.*, 1999:343).

♦ Vidarabine

The mechanism of interaction between theophylline and vidarabine has not been established. Vidarabine purportedly inhibits the metabolism of theophylline (Hansten & Horn, 1990:481). This leads to an increase in serum concentrations (Zucchero *et al.,* 1999:344).

♦ Viloxazine

Viloxazine competitively antagonises the metabolism of theophylline by the liver, thereby reducing its loss from the body and resulting in an increase in its serum levels (Stockley, 1999:730).

♦ Zileuton

There can be a possible inhibition of theophylline metabolism. The theophylline plasma concentrations may be elevated and increasing the pharmacological and adverse effects (Tatro, 2000).

The mechanisms of interaction between theophylline and the listed drugs are unknown as indicated in the following table. Refer to Table 3.14 for the interactions.

Table 3.4: Theophylline interactions.

Drugs involved in interactions	**References**
Beta-agonists	Tatro, 1998:1054
Corticosteroids	Tatro, 1998:1026
Ephedrine	Hansten & Horn, 1989:400
Food	Stockley, 1999:714
Halothane	Tatro, 1998:1034
Interferon	Tatro, 1998:1037
Isoetharine	Tatro, 2000
Ketamine	Tatro, 2000
Methotrexate	Hansten & Horn, 1990:323
Zafirlukast	Tatro, 2000

3.11.6 **Loperamide** (Refer to Table 3.16)

♦ Cholestyramine

The actions of loperamide may be reduced by cholestyramine, but the mechanism is unknown (Tatro, 1998:698).

3.11.7 **Glibenclamide** (Refer to Table 3.17)

- Anabolic steroids

Anabolic steroids may decrease blood glucose in some diabetic patients. Some have proposed that anabolic steroids also may inhibit the metabolism of oral hypoglycaemic agents such as glibenclamide (Hansten & Horn, 1989:162).

- Antacids

Antacids appear to increase the absorption of glibenclamide, but the clinical importance of their effect has not been established (Hansten & Horn, 1990:202; Neuvonen & Kivistö, 1991:218). The increased absorption of glibenclamide results in the increased hypoglycaemic effects of glibenclamide (Tatro, 1998:968).

- Antidepressants, tricyclic

Tricyclic antidepressants may alter the response to hypoglycaemia or increase the sensitivity to insulin; however, the actual mechanism has not been established (Hansten & Horn, 1990:203).

- Calcium channel blockers

The mechanism of interaction between theophylline and verapamil is not known. It appears that verapamil inhibits the metabolism of glibenclamide and the pharmacological effects of glibenclamide are increased (Hansten & Horn, 1989:575).

- Chloramphenicol

The proposed mechanism is the reduction in sulphonylurea hepatic clearance by chloramphenicol and this leads to sulphonylureas accumulation and hypoglycaemia can occur (Tatro, 1998:956).

- Cimetidine

The metabolism of glibenclamide may be inhibited or the absorption enhanced by H_2-blockade (Hansten & Horn, 1989:163). Sulphonylureas will then accumulate in the body and the reduced clearance of sulphonylureas may result in hypoglycaemia (Tatro, 1998:964).

- Clofibrate

It is proposed that clofibrate enhances the activity of hypoglycaemic drugs by displacing sulphonylureas from plasma protein binding, decreasing insulin resistance. The mechanism of glibenclamide inhibition of clofibrate-induced antidiuresis in patients with diabetes insipidus has not been established (Hansten & Horn, 1990:204).

♦ Clonidine

The increased production of catecholamines in response to insulin-induced hypoglycaemia is apparently inhibited by pre-treatment with clonidine (Hansten & Horn, 1989:164).

♦ Corticosteroids

Corticosteroids have intrinsic hyperglycaemic activity; thus the dose of sulphonylureas must be increased (Hansten & Horn, 1989:165).

♦ Cyclosporin

The mechanism of interaction between theophylline and cyclosporin is unknown. A possible enzyme inhibition, resulting in delayed metabolism of either agents (Tatro, 2000).

♦ Dextrothyroxine

Dextrothyroxine probably causes an increase in blood glucose due to an intrinsic metabolic effect (Hansten & Horn, 1990:206).

♦ Diuretics

Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion or increase potassium loss, causing hyperglycaemia (Tatro, 2000).

♦ Epinephrine

Epinephrine may increase blood glucose by inhibiting glucose uptake by peripheral tissues and by promoting glycogenolysis (Hansten & Horn, 1989:165).

♦ Ethanol

Ethanol may exhibit intrinsic hypoglycaemic activity, although hyperglycaemia has also been noted (Hansten & Horn, 1990:208).

♦ Fenfluramine

Fenfluramine appears to increase the up-take of glucose by skeletal muscles (Hansten & Horn, 1989:166). The hypoglycaemic activity of sulphonylureas is augmented (Tatro, 1998:961).

♦ Gemfibrozil

Gemfibrozil is strongly bound to plasma proteins, and glibenclamide may be displaced from its binding sites by gemfibrozil (Zucchero *et al.*, 1999:300).

- Glucagon

Glucagon has hyperglycaemic activity that may antagonise the hypoglycaemic effect of antidiabetic agents (Hansten & Horn, 1989:167).

- Guanethidine

Guanethidine has been known to possess antidiabetic activity (Hansten & Horn, 1989:167).

- Omeprazole

There can be a possible inhibition of sulphonylurea metabolism and serum sulphonylurea concentrations may be elevated, increasing the hypoglycaemic effects (Tatro, 1998:971).

- Rifampin

Rifampin appears to stimulate the hepatic metabolism of glibenclamide (Hansten & Horn, 1990:213). Rifampin may decrease the half-life and serum levels while increasing the clearance of glibenclamide, possibly resulting in hyperglycaemia (Tatro, 1998:974).

- Salicylates

Salicylates reduce basal plasma glucose levels and enhance insulin secretion (Tatro, 1998:975). Inhibition of prostaglandin synthesis may inhibit acute insulin responses to glucose. Displaced sulphonylurea protein binding has been suggested (Tatro, 2000).

- Sulphonamides

More than one mechanism may be involved in the effect of sulphonamides on antidiabetic agents (Hansten & Horn, 1989:171). Sulphonamides may impair hepatic metabolism of sulphonylureas or alter plasma protein binding (Tatro, 2001:1125).

The mechanisms of interaction between glibenclamide and the listed drugs are unknown as indicated in the following table. Refer to Table 3.13 for the interactions.

Table 3.5: Glibenclamide interactions.

Drugs involved in interactions	References
Androgen	Tatro, 2000
Beta blockers	Tatro, 1998:955
Captopril	Hansten & Horn, 1989:162
Colestipol	Hansten & Horn,1990:205
Contraceptives, oral	Hansten & Horn, 1989:164
Fluconazole	Stockley, 1999:519

Table 3.5 (continued)

Fluvastatin	Tatro, 2000
Halofenate	Hansten & Horn, 1989:167
Loop diuretics	Tatro, 2000
Marijuana	Hansten & Horn, 1989:167
Monoamine oxidase inhibitors (MAOIs)	Hansten & Horn, 1989:68
Phenytoin	Tatro, 1998:965
Potassium salts	Hansten & Horn, 1990:212
Thyroid hormones	Hansten & Horn, 1989:173

3.11.8 **Multivitamin** (refer to Table 3.18)

3.11.8.1 **Vitamin A**

- Aminoglycosides, oral

Aminoglycosides may decrease the gastrointestinal absorption of vitamin A (Tatro, 1998:1125).

- Mineral oil

Mineral oil may decrease the gastrointestinal absorption of vitamin A (Tatro, 1998:1126).

- Neomycin

Neomycin is thought to interfere with activity of bile acids, reducing uptake of vitamin A, and neomycin may cause morphologic changes in the small intestine, interfering with vitamin A absorption (Zucchero *et al.*, 1999:325).

3.11.8.2 **Vitamin C (Ascorbic acid)**

- Alcohol (ethanol)

The activity of alcohol dehydrogenase may be enhanced by increased ascorbic acid saturation (Hansten & Horn, 1990:355).

- Aspirin

Aspirin has been reported to alter the uptake of ascorbic acid into the leukocytes. Aspirin may displace ascorbic acid from albumin binding sites. Ascorbic acid in large doses may cause a uricosuric effect (Zucchero *et al.*, 1999:320).

- Ferrous sulphate

The prolonged reduction of gastric acid secretion induced by high doses of cimetidine may decrease the gastrointestinal absorption of ferrous sulphate (Zucchero *et al.*, 1999:323).

♦ Oral contraceptives

This interaction may result from competition for sulphate, increasing the bioavaibility and plasma concentrations of oestrogens. The breakthrough bleeding may be a withdrawal effect of the ascorbic acid, causing sudden falls in the oestrogen levels (Zucchero *et al.,* 1999:320).

♦ Propranolol

Vitamin C can possibly decrease the gastrointestinal absorption of propranolol (Tatro, 2000).

♦ Warfarin (anticoagulants)

The mechanism of interaction between vitamin C and warfarin has not been established (Hansten & Horn, 1989:76; Tatro, 1998:64).

3.11.8.3 **Vitamin D**

♦ Phenytoin

Phenytoin increases the metabolism of vitamin D, thereby reducing its effects (Stockley, 1999:854). Phenytoin may cause an increase in hydroxylation and hepatic glucuronidation of ergocalciferol, decreasing serum calcium and increasing serum alkaline phosphatase levels (Zucchero *et al.,* 1999:321).

♦ Thiazide diuretics

Thiazide diuretics may decrease urinary excretion of calcium. The administration of vitamin D and thiazide diuretics may potentiate the increase in serum calcium levels (Tatro, 1998:1130).

♦ Verapamil

Vitamin D may counteract the activity of verapamil (Tatro, 2000).

3.11.8.4 **Nicotinamide**

♦ Clonidine

Clonidine is thought to inhibit nicotinamide-induced vasodilatation, thus inhibiting the skin flushing commonly associated with the latter drug (Hansten & Horn, 1990:227).

♦ Lovastatin

Lovastatin therapy, alone or combined with other hypolipidemic drugs, has been associated with elevations in creatine kinase with and without symptoms of myopathy. It is possible that niacin somehow enhances the propensity of lovastatin to produce myopathy (Hansten & Horn, 1989:443).

♦ Salicylate

Glycine conjugation is an important elimination pathway for both nicotinamide and salicylic acid, and it is proposed that competitive inhibition of metabolism may occur (Hansten & Horn, 1990:415).

3.11.9 **Diclofenac** (refer to Table 3.19)

♦ Amikacin

Non-steroid anti-inflammatory drugs may cause an accumulation of aminoglycosides by reducing the glomerular filtration rate (Tatro, 2000).

♦ Anticoagulants

Diclofenac-induced gastric erosions and inhibition of platelet function would theoretically increase the risk of bleeding in a patient receiving oral anticoagulants (Hansten & Horn, 1989:84; Tatro, 1998:107).

♦ Biphosphonates

The concurrent use of non-steroid anti-inflammatory drugs and biphosphates may cause gastric ulcers (Tatro, 2000).

♦ Colestipol

Colestipol may interfere with the absorption of diclofenac and reduce the bioavailability of diclofenac (Tatro, 2001:914).

♦ Probenecid

Plasma clearance of diclofenac is reduced via renal and biliary pathways (Tatro, 1998:800).

♦ Salicylate

Aspirin increases the plasma clearance of diclofenac, possibly by decreasing diclofenac plasma protein binding (Hansten & Horn, 1989:583; Tatro, 1998:801).

♦ Sucralfate

The absorption of diclofenac may be decreased; however, the precise mechanism is not known (Tatro, 2000). There is a possibility that diclofenac and sucralfate can form a complex and thereby decreasing the absorption of the two drugs. According to Pedrazzoli *et al.* (1997:106) further investigation is underway.

- Triamterene

The non-steroid anti-inflammatory drugs inhibition of prostaglandins unmasks triamterene nephrotoxicity (Tatro, 2000).

The mechanisms of interaction between diclofenac and the listed drugs are unknown as indicated in the following table. Refer to Table 3.15 for the interactions.

Table 3.6: Diclofenac interactions.

Drugs involved in interactions	References
Cimetidine	Tatro, 2000
Digitalis glycosides	Stockley, 1999:481
Methotrexate	Hansten & Horn, 1989:273

3.11.10 **Reserpine** (refer to table 3.20)

- Barbiturates

The mechanism for this interaction is unknown. However, reserpine causes a depletion of catecholamines and serotonin in the central and peripheral nervous systems and cardiovascular tissue (Zucchero *et al.*, 1999:39).

- Digitalis

Direct or indirect effects of digitalis and reserpine may actually underlie this interaction (Zucchero *et al.*, 1999:268). The mechanism is not fully understood. A possible explanation is that reserpine depletes the sympathetic nerve supply to the heart of its neurotransmitter which allows the parasympathetic vagal supply (i.e. heart slowing) to have full rein (Stockley, 1999:496).

- Halothane

A possibility is the depletion of neurotransmitters caused by reserpine (Tatro, 1998:903). Halothane adds to the catecholamine depleting action of reserpine, causing enhanced depressant effects on the heart and resulting in decreased cardiac output and hypotension (Zucchero *et al.*, 1999:170).

- Levodopa

The depletion of the brain monoamines, including dopamine, results in the decreased effect of L-dopa (Stockley, 1999:380). Dopamine depletion would be in direct opposition to the antiparkionistic effects of L-dopa (Hansten & Horn, 1990:240).

- Monoamine oxidase inhibitors (MAOIs)

Reserpine depletes the adrenergic neurones of norepinephrine (Stockley, 1999:605). MAOIs cause accumulation of norepinephrine in storage sites within the adrenergic neuron (Hansten & Horn,

1990:241). If reserpine is given to patients already taking a MAOI, the sudden release of large amounts of accumulated norepinephrine can be caused, and in the brain serotonin as well, resulting in excessive stimulation of the receptors which are seen as gross central excitation and hypertension (Stockley, 1999:605).

♦ Quinidine

Reserpine depletes myocardial tissue of its catecholamine stores and causes a decrease in the electrical automaticity and excitability of myocardial tissue. This effect may enhance quinidine's direct myocardial tissue depressant activity and could result in quinidine toxicity (Zucchero *et al.,* 1999:64).

♦ Sympathomimetics

Reserpine depletes stores of catecholamines, increasing the receptor sensitivity to the direct-acting sympathomimetics (e.g., dobutamine, epinephrine, methoxamine, norepinephrine, phenylephrine) while antagonising the effects of the indirect-acting agents (e.g., dopamine, ephedrine, metaraminol) which release norepinephrine from the neurons (Tatro, 1998:993). When reserpine is given before ephedrine, it may antagonise the indirect action of ephedrine, resulting in a decreased cardiovascular response to this sympathomimetic (Zucchero *et al.,* 1999:169).

♦ Tricyclic antidepressants

When reserpine is added to tricyclic antidepressant therapy, there is a release of norepinephrine into the synapse where the depressants inhibit its uptake (Zucchero *et al.,* 1999:145). Reserpine causes adrenergic and serotoninergic neurones to become deplete of their normal stores of neurotransmitter. The brain possesses both types of neurones and failure in transmission is believed to be responsible for the sedation and depression (Stockley, 1999:362).

3.12 DRUG INTERACTION TABLES

The following tables consist of patient variables, disease states and the concurrent use of food and other medication, on the therapeutic, pharmacokinetic and pharmacodynamic effects of the ten selected drugs. The possible adverse effects of each drug were also included in the tables. The discussion of the significance rating included in the tables was discussed in chapter 4, section 4.3.2.4.

The following sources were used to construct the interaction tables:

1. STOCKLEY, I.H. 1991. Drug interactions: A source book of drug interactions; their mechanisms, clinical importance and management. 2nd ed. London : Blackwell Scientific Publications. 674p.

1.1. STOCKLEY, I.H. 1999. Drug interactions: A source book of drug interactions; their mechanisms, clinical importance and management. 5th ed. London : Pharmaceutical Press. 948p.

2. HANSTEN, P.D. & HORN, J.R. 1989. Drug interactions: Clinical significance of drug-drug interactions. 6th ed. London : Lea & Febiger. 631p.

3. HANSTEN, P.D. & HORN, J.R. 1990. Drug interactions and Updates. Pennsylvania, Pa. : Lea & Febiger. 630p.

4. KATZUNG, B.G., *ed.* 1998. Basic and clinical pharmacology. 7th ed. Norwalk, Conn. : Appleton & Lange. 1151p.

5. TIERNEY, Jr. L.M., McPHEE, S.J. & PADADAKIS, M.A., *eds.* 1999. Current medical diagnosis and treatment. 38th ed. Stamford, Conn. : Appleton & Lange. 1672p.

6. GIBBON, C.J. 2000. South African Medicines Formulary. 5th ed. South Africa : South African Medical Association, Health and Medical Publishing Group. 537p.

7. HARDMAN, J.G. & LIMBIRD, L.E., *eds.* 1996. Goodman & Gilman's The pharmacological basis of therapeutics. 9th ed. New York : McGraw-Hill. 1905p.

8. REYNOLDS, J.E.F., *ed.* 1993. Martindale: The extra pharmacopoeia. London : Pharmaceutical Press. 2363p.

9. BOEHRINGER INGELHEIM. 2000. The NOCSA (National Olympic Committee of South Africa) quick guide 2000 to drug-free sport. Cape Town : Infosource. 169p.

10. TAKETOMO, C.K., HODDING, J.H. & KRAUS, D.M. 2001. Pediatric dosage handbook, including neonatal dosing, drug administration & extemporaneous preparations. 7th ed. Hudson, Cleveland : American Pharmaceutical Association. 1458p.

11. SEMNIA, T.P., BEIZER, J.L. & HIGBEE, M.D. 1997. Geriatric dosage handbook including monitoring, clinical recommendations, and OBRA guidelines. 3rd ed. Hudson, Cleveland : American Pharmaceutical Association. 968p.

12. PROWSKY, Z.M. 1997. Powers and Moore's food medication interactions. 10th ed. USA. 291p.

13. TATRO, D.S., *ed.* 1998. Drug interaction facts. St. Louis, Mo. : Facts and comparisons Publishing Group. 1226p.

14. TAKETOMO, C.K., HODDING, J.H. & KRAUS, D.M. 1997. Pediatric dosage handbook, including neonatal dosing, drug administration & extemporaneous preparations. 4th ed. Hudson, Cleveland : American Pharmaceutical Association. 953p.

15. TATRO, D.S., *ed.* 2000. Drug interactions facts on disc V1.0 for Windows®. (*In* Microsoft Word '97.) [CD-ROM.]

16. ZUCCHERO, F.J., HOGAN, M.J. & SCHULTZ, C.D. 1999. Pocket guide to evaluations of drug interactions. 3rd ed. Washington, D.C. : American pharmaceutical association. 450p.

17. TURNER, L., *ed.* 2001. Daily drug use. Revised edition. Cape Town : Tincture Press. 629p.

18. TATRO, D.S., *ed.* 2001. Drug interaction facts. St. Louis, Mo. : Facts and comparisons Publishing Group. 1424p.

In the interaction tables only the number of reference and the page numbers are listed. The reasons for possible interactions are listed below and are referred to in the tables under "*message code*". The list was constructed in the order that the drug interactions were identified. In the tables the numerical values of the listed reasons for the interactions are only referred to.

Reasons for possible drug interactions are the following:

1. Absolute contraindication.
2. (a) Absolute contraindication due to this medication in patient history.
   (b) Absolute contraindication due to this condition in patient history.
3. Relative contraindication
4. (a) Relative contraindication due to this medication in patient history.
   (b) Relative contraindication due to this condition in patient history.
5. (a) The condition in patient history may increase prescribed drug action.
   (b) The condition in patient history may decrease prescribed drug action.
6. (a) The medication in patient history may increase prescribed drug action.
   (b) The medication in patient history may decrease prescribed drug action.
7. The medication in patient history has a therapeutic index overlap with the medicine item prescribed.
8. Prescribed medicine item contains a banned substance for sportsmen.
9. Safe to use.
10. A doctor can only prescribe the medicine item.
11. The patient is already using the medicine item prescribed.
12. Use with caution.
13. The dose of the medicine item must be lowered.
14. Use not recommended.
15. (a) Prescribed drug may increase this medicine's action.
    (b) Prescribed drug may decrease this medicine's action.
16. (a) The combination may lead to toxic effects of prescribed drug.
    (b) Prescribed drug may lead to toxic effects of this drug.
17. (a) CNS stimulation.
    (b) CNS depression.
18. (a) Increased sedation.
    (b) Decreased sedation.
19. (a) Respiratory stimulation.

(b) Respiratory depression.

20. (a) Increased pharmacological effect of prescribed drug.
    (b) Decreased pharmacological effect of prescribed drug.
    (c) Prescribed drug increases the pharmacological effect of this drug.
    (d) Prescribed drug decreases the pharmacological effect of this drug.
21. (a) Increases therapeutic effects of prescribed drug.
    (b) Decreases therapeutic effects of prescribed drug.
    (c) Prescribed drug increases therapeutic effects of this drug.
    (d) Prescribed drug decreases therapeutic effects of this drug.
22. (a) Increased absorption of prescribed drug.
    (b) Decreased absorption of prescribed drug.
    (c) Prescribed drug increases the absorption of this drug.
    (d) Prescribed drug decreases the absorption of this drug.
23. (a) Increased effectiveness of prescribed drug.
    (b) Decreased effectiveness of prescribed drug.
    (c) Prescribed drug increases the effectiveness of this drug.
    (d) Prescribed drug decreases the effectiveness of this drug.
24. (a) Increased elimination of prescribed drug.
    (b) Decreased elimination of prescribed drug.
    (c) Prescribed drug increases the elimination of this drug.
    (d) Prescribed drug decreases the elimination of this drug.
25. (a) Increased activity of prescribed drug.
    (b) Decreased activity of prescribed drug.
    (c) Prescribed drug increases the activity of this drug.
    (d) Prescribed drug decreases the activity of this drug.
26. (a) Prescribed drug increases the absorption of food substances.
    (b) Prescribed drug decreases the absorption of food substances.
27. Safety not established.
28. Severity unknown. Further research needed.

3.13 CHAPTER SUMMARY

This chapter includes the ten selected drugs from Philani Prime Cure®. Each drug is discussed separately. The chapter also includes the mechanisms of action for the drug interactions in Table 3.7 – 3.16. The reasons for the interactions are listed in the chapter and the drug interaction tables are included.

The research methodology used in this study will be discussed in Chapter 4.

Table 3.7: Drug interactions of diphenhydramine

Patient-factor (drug-patient interaction)	Severity 1	2	3	4	5	Message code	Recommendations
Gender							No effects listed in documents used
Age							
Younger than 6 months Older than 6 months and younger than 2 years						14	Children are more prone to paradoxical central nervous system stimulation with seizures, hallusinations and dystonic reactions. Linked with sudden infant death syndrome (SIDS): not recommended in children under 2 years of age (6:467)
Older than 2 and younger than 6 years						9	Safe to use (10:328)
Older than 6 years and younger than 12 years						9	Safe to use (10:328)
Older than 12 and younger than 50 years						9	Safe to use (11:183)
Older than 50 and younger than 70 years Older than 70 years						12; 13	Use with caution in the elderly. Elderly patients are more susceptible to the central nervous system and anticholinergic effects of the antihistamine. Lower doses are recommended, especially for sedation (6:467)
Blood pressure							No effects listed in documents
Temperature							No effects listed in documents
Weight / height / age							No effects listed in documents
Blood sugar							No effects listed in documents
Pregnancy						27	Safety not established. Exposure at term has been described to cause respiratory depression and impaired platelet aggregation in the neonate (6:467)
Lactation						14	Excreted in breast milk; use not recommended (6:467)
Sport involvement						9	Diphenhydramine is safe to use (9:16)
Tobacco							No effects listed in documents
Occupation						14	Antihistamines cause drowsiness and dulling of mental alertness. Patients undergoing treatment with these drugs should not take charge of vehicles, other means of transport or machinery where loss of attention may lead to accidents (8:1288)
Adverse effects							
Cardiovascular							Hypotension, palpitations, tachycardia (10:328)
Central nervous system							Insomnia, paradoxical excitement, sedation, dizziness and fatigue (10:328)
Dermatologic							Photosensitivity, rash, urticaria (10:328)
Gastrointestinal							Vomiting, anorexia, constipation, epigastric distress, nausea and xerostomia (10:328)

Table 3.7 (continued)

Adverse effects	Severity					Message code	Recommendations
	1	2	3	4	5		
Hemotologic							Rarely: haemolytic anaemia, aplastic anaemia, thrombocytopenia (10:328)
Neuromuscular and skeletal							Paresthesia of hands, tremor (10:328)
Ocular							Blurred vision (10:328)
Respiratory							Chest tightness, wheezing, thickened bronchial secretions (10:328)
Medical conditions (drug-disease interaction)							
Epilepsy, cardiac disease, hepatic disorders, asthma, narrow-angle glaucoma and prostate hyperthrophy						4b	Relative contraindicated (6:467)
Hyperthyroidism						4b	Relative contraindicated (10:328)
Peptic ulcers and urinary tract obstruction						4b	Relative contraindicated (10:328)
Porphyria						9	Safe to use (6:467)
Therapeutic index (drug-drug interaction)							
Antipsychotic agents, opioid sedatives, analgetics, anxiolytics and barbiturates						20a; 21a	Adverse anticholinergic effects may be enhanced (6:467). Sedation is enhanched (17:536).
Atropine and tricyclic antidepressants							Additive anticholinergic effects (17:536)
Aminosalicylic acid			x			22d; 23d	Diphenhydramine can reduce the concentration of amino acids (2:209). Diphenhydramine can mask the signs of hearing damage (17:536)
Beta-blockers						20c; 21c	Increased plasma concentrations and cardiovascular effects of beta-blockers (15).
Sedatives						21a	Effects may be potentiated (6:467)
Food (drug-interaction)							
Administration with food							Avoid gastrointestinal distress (10:249)
Alcohol						25a; 21a; 20a	Antihistamines cause drowsiness which is increased by alcohol (1:19)

Table 3.8: Drug interactions of tetracycline

Patient-factor (drug-patient interaction)	Severity 1	2	3	4	5	Message code	Recommendations
Gender							No effects listed in documents used
Age							
Younger than 6 months						1	Contraindicated (10:349)
Older than 6 months and younger than 2 years						1	Contraindicated (10:349)
Older than 2 and younger than 6 years						1	Contraindicated (10:349)
Older than 6 and younger than 12 years						3	Contraindicated: children under 8 years (6:259). Tetracycline is deposited in growing bones, causing growth retardation, and discoloration of teeth and occationally enamel hypoplasia (6:259)
Older than 12 and younger than 50 years						9	Safe to use (10:349)
Older than 50 and younger than 70 years						9	Safe to use (11:290)
Older than 70 years						3	Contraindicated: frail or elderly patients (6:259)
Blood pressure							No effects listed in documents used
Temperature							No effects listed in documents used
Weight / height / age							No effects listed in documents used
Blood sugar							No effects listed in documents used
Pregnancy						12	Crosses the placenta, is deposited in fetal bone and teeth, should be avoided. Fatty infiltration of maternal liver may occur (6:259). Caution during pregnancy in women with pyelonephritis (8:1188)
Lactation						14	Excreted in breast milk. Generally not recommended, although infant exposure is low due to chelation with calcium in milk (6:259)
Sport involvement						9	Tetracycline is safe to use (9:100-105)
Tobacco							No effects listed in documents used
Occupation							No effects listed in documents used
Adverse effects Doxycycline							
Central nervous system							Increased intracranial pressure causing bulging fontanels in infants (10:348)
Dermatologic							Rash, photosensitivity and nail discoloration (10:348)
Gastrointestinal							Geriatrics: Nausea, diarrhoea and esophagitis (11:290). Paediatrics: Anorexia, pseudomembrane colitis and oral candidiasis (10:348)
Hematologic							Neutropenia and eosinophilia (10:348)

Table 3.8 (continued)

Adverse effects Doxycycline	Severity 1	2	3	4	5	Message code	Recommendations
Hepatic							Hepatotoxicity (10:348)
Local							Phlebitis, pain at site of injection (10:348)
Neuromuscular							Retardation of skeletal development in infants (10:348)
Oxytetracycline							
Central nervous system							Pseudotumor cerebri (11:632)
Dermatologic							Photosensitivity (11:632)
Gastrointestinal							Nausea, vomiting, diarrhoea, antibiotic-associated pseudomembrane colitis and staphylococcal enterocolitis (11:632)
Hepatic							Hepatotoxicity (11:632)
Local							Thrombophlebitis (11:632)
Miscellaneous							Candida superinfection, discoloration of teeth, enamel hypoplasia and hypersensitivity reactions (11:632)
Neuromuscular and skeletal							Injury to growing bones and teeth (11:632)
Renal							Renal damage (11:632)
Medical conditions (drug-disease interaction)							
Impaired renal function						4b	Relative contraindicated (6:259)
Porphyria						12	Use tetracycline with extreme caution (6:259)
Severe hepatic dysfuntion						4b	Contraindicated (10:264)
Therapeutic index (drug-drug interaction) Tetracycline							
Antacids	x					23b; 21b	Therapeutic effectiveness of tetracycline antibiotics can be reduced or even abolished with the concurrent use of antacids containing aluminium, bismuth, calcium and magnesium (1:213)
Anticoagulants			x			20c; 21b; 15a	Action of oral anticoagulants may by increased by tetracycline (15)
Bismuth subsalicylate		x				22b; 23b	Bismuth subsalicylate can reduce the bioavailability of tetracyclines and result in reduced antibacterial efficacy (3:301)

Table 3.8 (continued)

Therapeutic index (drug-drug interaction) Tetracycline	Severity					Message code	Recommendations
	1	2	3	4	5		
Calcium, magnesium, iron and zinc		x				22b; 21b	Chelation with di- and trivalent cations in preparations containing calcium, magnesium, zinc and iron decrease absorption of tetracycline (6:259)
Calciumcarbonate, calamine, acacia, tragacanth, methylcellulose and sodium alginate						23b;21b	Tetracycline has a loss of activity (8:1186)
Cimetidine			x			28; 23b	Further study needed. There can be a decrease in the efficacy of tetracycline (16:205)
Colestipol				x		22b	Reduce the absorption of tetracycline (1:215)
Corticosteroids						14	A single report suggests that prolonged tetracycline-corticosteroid co-therapy may contribute to the development of a resistant infection (2:252)
Diuretics					x	14	Concurrent use of diuretics and tetracycline should be avoided because of their association with the increase in the blood urea nitrogen levels (1:216)
Ergot						16b	Ergotamine or dihydroergotamine with doxycycline or tetracycline lead to ergotism (1:867)
Ferrous sulphate	x					22a; 22d	The coadministration of these two drugs cause an interference with the absorption of tetracycline and the ferrous ion (16:205)
Hepatoxic drugs: erythromycin, triacetyl-oleandomycin, chloramphenicol, sulphonamides, aminosalicyclic acid, isoniazid, chlorpromazine, phenylbutazone, chlorpropamide, methyltestosterone, testosterone, phenidone, chlorthiazide, phenytoin and other anticonvulsants						14	Tetracycline should not be administrated with these drugs (8:1188)
Koalin-pectin						22b	Reduce absorption of tetracycline (1:218)
Lithium carbonate		x				16b	Lithium concentration increased after following tetracycline administration (2:253)
Magaldrate						20b; 21b	Co-administration of tetracycline and aluminium salts decrease the serum levels of tetracycline; a decreased anti-infective response may occur (15)
Magnesium carbonate, -oxide, -trisilicate, carboxymethylcellulose and bentonite						23b; 21b	Tetracycline has a great loss in activity against *Staphylococcus aureus* (8:1186)

Table 3.8 (continued)

Therapeutic index (drug-drug interaction) Tetracycline	Severity 1	2	3	4	5	Message code	Recommendations
Methotrexate						16b	Methotrexate concentration may be elevated, increasing the risk of toxicity (e.g. bone marrow suppression) (15)
Methoxyflurane		x				16b	Increased nephrotoxic effects of methoxyflurane (1:220)
Oral contraceptives		x				23d	Efficacy may be reduced; additional contraception is advisable (6:259)
Penicillin	x					23d	Tetracycline administration may impair the efficiency of penicillin therapy (2:238)
Quinapril						22b	Absorption of oral tetracycline is reduced by magnesium carbonate excipient in quinapril (1:219)
Sodium carbonate					x	23b	Sodium carbonate administration may cause some reduction in tetracycline serum concentration (2:254)
Theophylline				x		25a	A case report indicated that tetracycline administration increased theophylline plasma concentration (3:499)
Thiomersal			x			12	Patients being treated with tetracycline who use contact lens solutions containing thiomersal (thiomerosal, thiomersalate, mercuriothiolate) may experience an inflammatory ocular reaction (1:220)
Tromethamine						24a; 21b; 28	Tetracycline with urinary alkalinizers may result in an increased excretion of the tetracycline and decreased serum levels. A decreased therapeutic response occur. More research is needed (15)
Vitamin A, etretinate and isotretinoin						20c	Enhanced risk of increased intracranial pressure (6:259)
Doxycycline							
Carbamazepiene, phenytoin and barbiturates		x				24a 21b	Serum levels of doxycycline may be reduced (6:259) Decreased therapeutic levels of doxycycline (13:452)
Digoxin	x					16b	Digoxin concentrations may be increased (11:290)
Insulin				x		21c; 20c	May increase effects of insulin (11:290)
Rifampicin		x				21b; 12	Some patients show a marked fall in serum doxycycline levels if given rifampicin. Treatment failure may occur (1:219)
Oxytetracycline							
Antidiabetic drugs		x				20c; 21c	Oxytetracycline may increase the hypoglycaemic effect of insulin or tolbutamide (2:172)

Table 3.8 (continued)

Food (drug-food interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
Alcohol					x	21b	Doxycycline serum levels may be significantly reduced by alcohol (1:144)
Coffee / Orange juice						9	Orange juice and coffee do not interact (1:215)
Food		x				22a	Calcium in food can complex with tetracycline and reduce its absorption (1:216)
Milk and dairy products						22a; 21b	Absorption of tetracycline can be reduced (up to 70 - 80%) if they are allowed to come into contact in the gastrointestinal tract with diary products. Therapeutic effects may be diminished or abolished (1:218)

Table 3.9: Drug interactions of co-trimoxazole

Patient-factor (drug-patient interaction)	Severity 1	2	3	4	5	Message code	Recommendations
Gender							No effects listed in documents used
Age							
Younger than 6 months						3	Contraindicated: infants 1 to 2 months old has a risk of kernicterus (6:264)
Older than 6 months and younger than 2 years						9	Safe to use (10:259)
Older than 2 and younger than 6 years						9	Safe to use (10:259)
Older than 6 and younger than 12 years						9	Safe to use (10:259)
Older than 12 and younger than 50 years						9	Safe to use (11:226)
Older than 50 and younger than 70 years						9	Safe to use (11:226)
Older than 70 years						14	Increased risk of adverse effects, such as thrombocytopenia (particularly in those receiving thiazide diuretics), megablastic anaemia (in those with reduced intake of dietary folate) and impaired renal function (6:266)
Blood pressure							No effects listed in documents used
Temperature							No effects listed in documents used
Weight / height / age							No effects listed in documents used
Blood sugar						12	Caution with diabetics using sulphonylurea - decrease blood sugar (12:233)
Pregnancy						3; 14	Sulphonamides are contraindicated during the third trimester due to risk of hyperbilirubinaemia and kernicterus. Trimethoprim should be avoided during pregnancy (6:266)
Lactation							No effects listed in documents used
Sport involvement						9	Co-trimoxasole is safe to use (9:100-105)
Tobacco							No effects listed in documents used
Occupation							No effects listed in documents used
Adverse effects Co-trimoxazole							
Central nervous system							Confusion, depression, hallucinations, seizures, fever and anorexia (11:225). Kernicterus in infants and aseptic meningitis (10:258)
Dermatologic							Rash, erythema multiforme, epidermal necrolysis and Steven-Johnson syndrome (10:258). Photosensitivity and urticaria (11:225)
Gastrointestinal							Nausea, vomiting, glossitis, stomatitis, diarrhoea and pseudomembrane colitis (11:225). Pancreatitis and splenomegaly (10:258)

Table 3.9 (continued)

Adverse effects Co-trimoxazole	Severity					Message code	Recommendations
	1	2	3	4	5		
Hematologic							Thrombocytopenia, megaloblastic anaemia, granulocytopenia, aplastic anaemia and hemolysis (11:225)
Hepatic							Hepatitis and cholestatic jaundice (10:258)
Renal							Interstitual nephritis and renal tubular acidosis (10:258). Increased serum creatine (11:225). Permanent renal impairment (7:1064)
Miscellaneous							Serum sickness (11:225)
Sulphametoxazole							
Allergy							Hypersensitivity reactions (6:266)
Gastrointestinal							Gastrointestinal disturbances (6:266)
Central nervous system							Headache, depression, and hallucinations (7:1064)
Trimethoprim							
Hematologic							Megoblastic anaemia, leukopenia, and granulocytopenia (4:764)
Skin							Rash and pruritis (6:266)
Gastrointestinal							Epigastric pain (6:266)
Medical conditions (drug-disease interaction)							
Hypersensitivity						4a	Contraindictated: Hypersensitivity to co-trimoxazole, trimethoprim or sulphonamides (6:265)
Severe renal or hepatic impairment						3	Contraindicated (6:265)
Serious haematological disorders						3	Contraindicated (6:265)
Porphyria						14	Co-trimoxazole must be avoided (6:266)
Megaloblastic bone marrow						14	Trimethoprim enhance antifolate metabolism and co-trimoxazole should not be given to these patients (8:1484)
Glucose 6-phosphate dehydrogenase (G6PD) deficiency						3	Relative contraindicated (6:259)
Therapeutic index (drug-drug interaction) Co-trimoxazole							
Amantadine				x		16b	A patient taking amantadine developed mental confusion after additional co-trimoxazole therapy (3:500)
Digoxin			x			16b	Digoxin levels may be increased (6:266)

Table 3.9 (continued)

Therapeutic index (drug-drug interaction) Co-trimoxazole	Severity 1	2	3	4	5	Message code	Recommendations
Folic acid						20d; 21d	The effects of folic acid used to treat megaloblastic anaemia can be reduced or abolished by co-trimoxazole (1:157)
Hydrochlorothiazide						20c	Increased risk of thrombocytopenia, particularly with thiazides (6:266)
Lithium carbonate						16b	Lithium intoxication (1:641)
Mercaptopurine						16b	Haematological toxicity occur (1.1:437)
Methotrexate	x					16b	Administration of co-trimoxazole following metotrexate has resulted in megoblastic pancytopenia (2:255)
Oral contraceptives			x			23d	Efficacy may be reduced; additional contraception is advisable (6:266)
Phenytoin or phenobarbitone		x				16b	Prolonged concurrent use may aggravate folate antagonism and increase the risk of megaloblastic anaemia (6:266)
Pyrimethamine						16b	Megaloblastic anaemia associated with concurrent use (6:266)
Sulphonylureas		x				20c; 21c	Increased effect of sulphonylureas (11:226)
Tricyclic antidepressant, viloxazine						20d; 21d	Relaps occurred when given co-trimoxazole (1:826)
Warfarin	x					20c; 21c	Slight increase in anticoagulation (6:266)
Zidovudine or lamivudine				x		16b	Increased risk of toxicity (6:266). Increased lamivudine serum concentration (17:286)
Sulphonamide							
Antidiabetic agents						20c; 21c	Sulphonamides can enhance the hypoglycaemic effects of oral antidiabetic agents (3:215)
Aminobenzoic acid (PABA)		x				21b	PABA may interfere with the antibacterial activity of sulphonamide (3:299)
Cyclosporin			x			16b; 23d	Sulphonamide may produce additive nephrotoxicity with cyclosporin or reduce its plasma concentration; potentially reducing cyclosporin efficiency (3:298)
Methenamine						20c	The combination of sulphonamide and methenamine may result in crystalluria (3:280)
Oxacillin			x			28	Oxacillin serum concentration may be reduced, but the clinical significance of of this effect is unknown (3:286)
Sulphinpyrasone			x			28	Sulphinpyrasone administration may result in some increasing in sulphonamide concentration, but this increase is unlikely to be clinically significant (2:250)

Table 3.9 (continued)

Therapeutic index (drug-drug interaction) Trimethoprim	Severity 1	2	3	4	5	Message code	Recommendations
Dapsone			x			24b; 24d	Trimethoprim appears to increase dapsone serum concentration and effects; dapsone increases trimethoprim concentration (3:262)
Dofetilide						20c; 25c	Increased dofetilide plasma concentration may occur with increased risk of ventricular arrhythmias, including torsades de pointes (15)
Phenytoin		x				16b; 13	Trimethoprim may increase serum phenytoin concentration; adjust the phenytoin dosage as needed (3:196)
Procainamide		x				16b	Trimethoprim significantly increases serum procainamide and N-acetylprocainamide and this may lead to toxicity (3:102)
Terfenadine						2a	Contraindicated. QT interval prolonged (17:288)
Food (drug-food interaction)							
Ethanol				x		14	Disulfiram-like reaction including flushing, palpitations, tachycardia, nausea and vomiting may occur (15)
Food						22b	Decreased absorption of trimethoprim (17:286)

Table 3.10: Drug interactions of hyoscine

Patient-factor (drug-patient interaction)	Severity 1	2	3	4	5	Message code	Recommendations
Gender							No effects listed in documents used
Age							
Younger than 6 months						20a	More prone to adverse effects (6:123)
Older than 6 months and younger than 2 years						14	Use not recommended (10:498)
Older than 2 and younger than 6 years						9	Safe to use (10:498)
Older than 6 and younger than 12 years						9	Safe to use (10:498)
Older than 12 and younger than 50 years						9	Safe to use (11:428)
Older than 50 and younger than 70 years						9	Safe to use (11:428)
Older than 70 years						20a	More prone to anticholinergic side effects (6:123)
Blood pressure							No effects listed in documents used
Temperature							No effects listed in documents used
Weight / height / age							No effects listed in documents used
Blood sugar							No effects listed in documents used
Pregnancy						12	Crosses the placenta (6:122). Produce tachycardia in fetus when given to pregnant women (8:224)
Lactation						9	Excreted in breast milk (6:123)
Sport involvement						9	Anti-cholinergics is safe to use (9:106)
Tobacco							No effects listed in documents used
Occupation							No effects listed in documents used
Adverse effects							
Cardiovascular							Tachycardia, bradycardia and orthostatic hypotension (10:498). Arrhythmias (6:123)
Central nervous system							Headache, dizziness, short-term memory loss, fatigue, delireum, restlessness, ataxia, insomnia, psychosis, euphoria, nervousness, confusion, fever (10:498)
Dermatologic							Dry skin (10:498). Photosensitivity, rash and urticaria (6:123)
Gastrointestinal							Xerostomia, nausea, vomiting and dysphagia (10:498). Constipation (6:123)
Genitourinary							Urinary retention (6:123)
Neuromuscular and skeletal							Weakness and tremor (10:498)
Ocular							Blurred vision, increased intra-ocular pressure (6:123). Photophobia, mydriasis and cycloplegia (10:498)

Table 3.10 (continued)

Adverse effects	Severity					Message code	Recommendations
	1	2	3	4	5		
Respiratory							Dry nose (10:498)
Miscellaneous							Decreased diaphoresis (10:498)
Medical conditions (drug-disease interaction)							
Angle-closure glaucoma						2a	Antimuscarinic drugs are contraindicated (4:114)
Gastric ulcers						12	These agents slow gastric emptying, they may increase symptoms in patients with gastric ulcers (4:114)
Porphyria						14	Use with extreme caution only (6:123)
Chronic lung disease						4b	Relative contraindicated (10:498)
Prostatic hyperplasia						2a	Elderly men must avoid antimuscarinic agents (4:114)
Therapeutic index (drug-drug interaction)							
Antacids						22b	Decreased absorption (10:498)
Antipsychotic, tricyclic antidepressant, antihistamine, amantadine, quinidine, disopyramide, haloperidol and phenothiazine				x		20a	Additive anticholinergic adverse reactions may occur (6:122 and 10:498)
Calcium channel blockers						28; 25a	Verapamil pretreatment increases the tachycardia produced by atropine, the clinical importance of this is not clear (3:526)
Digoxin				x		22c; 16b	May increase the degree of absorption of digoxin (6:122)
Ketoconasole						22d	Concurrent use may reduce absorption of ketoconasole (6:122)
Metoclopramide						20d; 21d	By delaying gastric emptying, anticholinergic may antagonise the effects of metoclopramide (6:122)
Food (drug-food interaction)							No effects listed in documents used

Table 3.11: Drug interactions of theophylline

Patient-factor (drug-patient interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
Gender							No effects listed in documents used
Age							
Younger than 6 months						12	Use with caution in neonates. Hyperglycaemia has been reported in pre-term infants. Behavioural and cognitive functions in children may be affected adversely (6:459)
Older than 6 months and younger than 2 years						9	Safe to use (10:912)
Older than 2 and younger than 6 years						9	Safe to use (10:912)
Older than 6 and younger than 12 years						9	Safe to use (10:912)
Older than 12 and younger than 50 years						9	Safe to use (11:798)
Older than 50 and younger than 70 years Older than 70 years						12	Use with caution in patients over 55 years; decreased plasma clearance is possible, which leads to an increased potential for toxicity (6:459)
Blood pressure							No effects listed in documents used
Temperature							No effects listed in documents used
Weight / height / age							No effects listed in documents used
Blood sugar							No effects listed in documents used
Pregnancy						12	Neonates of mothers on theophylline should be monitored: apnoea, tachycardia, jitteriness, irritability, gagging and vomiting have been reported (6:458)
Lactation						12	Excreted in breast milk; adverse effects seldom occur in the nursing infant. Irritability and insomnia have been reported (6:459)
Sport involvement						9	Theophylline is safe to use (9:122-124)
Tobacco							
Tobacco or cannabis smokers	x					24a; 21b	Tobacco or cannabis smokers and non-smokers, heavily exposed to smoke, need more theophylline than other non-smokers to achieve the same therapeutic benefits because the theophylline is cleared from the body more quickly. May also occur in those who chew tobacco or snuff, but not them who chew nicotine gum (1:803)
Occupation							No effects listed in documents used

Table 3.11 (continued)

Adverse effects	Severity					Message code	Recommendations
	1	2	3	4	5		
Cardiovascular							Palpitations, sinus tachycardia, extrasystoles, hypotension, ventricular arrhythmias and flushing (11:797)
Central nervous system							Irritability, restlessness, fever, headache, insomnia and seizures (11:797). Convulsions (6:459). Nervousness (10:910)
Endocrine and metabolic							Hyperglyceamia (11:797)
Gastrointestinal							Diarrhoea, nausea, vomiting and abdominal pain (10:910). Hematemesis, rectal bleeding (11:797)
Neuromuscular and skeletal							Tremors and muscle twisting (11:797)
Renal							Proteinuria and diuresis (11:797)
Respiratory							Tachypnoea and respiratory arrest (11:797)
Medical conditions (drug-disease interaction)							
Ischaemic heartdisease, hypertension, hyperthyroidism, epilepsy or a history of peptic ulcer disease						4b	Contraindicated (6:458)
Congestive cardiac failure, chronic obstructive airway disease and the elderly						4b; 16a	Contraindicated: Risk of toxicity because of reduced hepatic clearance (6:458)
Porphyria						14	Use with extreme caution (6:459)
Diabetes						12	Caution - increased glucose with a high dose of theophylline (12:223)
Alcoholism						12	Use with caution (11:797)
Therapeutic index (drug-drug interaction)							
Aciclovir		x				23a; 16a	Aciclovir can increase serum levels of theophylline causing toxicity (1.1:705)
Adenisone			x			20d; 21d	Theophylline inhibits the hemodynamic effects of adenosine (2:574)
Alprasolam						23d	Theophylline reduces the serum levels (1:696)
Allopurinol		x				23a; 21a; 24b 16a	Effects of theophylline may be increased with concurrent use of allopurinol (1:771). Increased risk of toxicity (16:331)
Aminoglutethimide				x		24a; 23b; 21b	The loss of theophylline from the body will be increased by concurrent use of of aminoglutethimide. Reduction in theophylline serum levels and therapeutic effect (1:772)
Amiodarone				x		16a; 24b	Raised theophylline levels and toxicity when amiodarone is added (1:772)

Table 3.11 (continued)

Therapeutic index (drug-drug interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
Antacids			x			22a; 23a	Some antacid preparations may increase theophylline absorption (16:332)
Atracurium, doxacurium, mivacurium, pancuronium		x				20d; 21d; 15b	A dose-dependent reversal of neuromuscular blockade induced by non-depolarising muscle relaxants may occur (15)
Barbiturate		x				24a; 21b	Theophylline serum levels can be reduced by concurrent use of phenobarbitone or pentobarbitone (1:774)
BCG vaccine			x			23a; 21a	BCG vaccine can cause a small increase in serum levels of theophylline (1:775)
Bensodiasepines			x			20d	Sedative effects of bensodiasepines may be antagonised by theophylline (15)
Beta-agonist bronchodilators		x				20a; 23b	Concurrent use of theophylline and beta-agonist brochodilator is common and considered advantageous, but some adverse reactions can occur. The most serious being hypocalaemia (with salbutamol) and increased heart rate with high dosage theophylline. Fall in serum theophylline levels when given oral salbutamol or isoprenaline (1:775)
Beta-blockers		x				24b; 20b 12	Propranolol reduces the clearance of theophylline. Non-selective B-blockers (nadolol and propranolol) cause bronchospasm in astmatic patients. Selective B-blockers (atenolol, bisoprolol, metoprolol) must be used with caution (1:776)
Calcium channel blockers		x				24b	Concurrent use normally seems to have no adverse effects on the control of asthma, despite the small or modest changes in serum theophylline levels reported with diltiazem, felodine, nifedipine and verapamil (1:777)
Carbamazepine		x				24a; 21b 21d	Fall in serum theophylline levels during concurrent use. Fall in serum levels of carbamazepine (1:778)
Cefaclor			x			16a	Implicated in theophylline toxicity in children (1:779)
Charcoal	x					22b; 25a	Charcoal absorbs theophylline; reducing absorption and increasing clearance (16:333)
Cimetidine	x					24b; 21a	Diminished hepatic biotransformation significantly, resulting in raised theophylline levels (6:458)
Ciprofloxacin		x				16a; 12	Increased theophylline levels with toxicity can occur (15)
Corticosteroids				x		23a; 21a	Concurrent use causes increases in serum theophylline levels (1:780)
Diltiazem		x				24b; 20a; 16a	Toxic and pharmacological effects of theophylline may be increased (13:1027)
Dimercaptosuccinic acid (DMSA)						23b	Fall in serum theophylline levels (1:781)

Table 3.11 (continued)

Therapeutic index (drug-drug interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
Disulfiram		x				24b; 13; 16a	Blood theophylline levels are increased. Theophylline dosage may be reduced to avoid toxicity (1:781)
Dobutamine						20a	A patient on theophylline, about to undergo surgery, developed tachycardia when treated with dobutamine (1:761)
Doxapram						20a	Agitation and increased muscle activity may occur in adults. No problems in infants (1:864)
Ephedrine					x	16a	Increased theophylline toxicity; not a consistent finding (2:400)
Erythromycin	x					24b; 21a; 24c; 21d; 24b	Theophylline serum levels can be increased. Erythromycin levels may possibly fall to subtherapeutic concentrations (1:781). Erythromycin decrease the elimination of theophylline (16:335)
Felodipine		x				20b; 21b	Serum theophylline levels decrease, producing a decrease in pharmacologic effects of theophylline (15)
Fluconazole						23a	Rise in theophylline levels (1:789)
Fluvoxamine, fluoxetine			x			24b; 16a; 13	Theophylline levels can be increased. Intoxication will develop if theophylline dosage is not reduced (1:782)
Furosemide		x				23a	Single dose furosemide administration increased the theophylline concentrations (3:343)
Halothane	x					20a	Cardiac arrhythmias can develop during concurrent use (1:730) and seizures (17:524)
Idrocilamide						13; 16a; 23a	Increase theophylline levels. Reduction in theophylline dosage to avoid toxicity (1:787)
Imipenem						20a	Seizures developed with theophylline when imipenem was given (1:787)
Influenza vaccine				x		21a; 24b	Rise in theophylline levels (1:787). Decreased theophylline metabolism (16:337)
Interferon				x		24b	Clearance of theophylline from the body is reduced (1:788)
Ipriflavone						23a	Increased theophylline levels (1:788)
Isoetharine						16b; 25b	Increased toxicity, particularly cardiotoxicity, has been noted. Decreaced theophylline concentrations may occur (15)
Isoniazid				x		23a	Increased theophylline levels (1:788)
Ketamine				x		14	Unexpected and unpredictable adverse effects in the form of seizures have been reported with the coadministration of theophylline and ketamine (15)
Ketoconazole				x		23b	Fall in theophylline levels (1:789)

Table 3.11 (continued)

Therapeutic index (drug-drug interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
Lithium carbonate		x				23d; 24d	Serum lithium levels are moderately reduced (1:650)
Loperamide			x			23b	Delays the absorption of theophylline from a sustained-release preparation (1:789)
Macrolide antibiotics		x				16a	Triacetyloleanodomycin (TAO) increases theophylline levels, causing toxicity if dosage is not reduced. Clarithromycin, roxithronycin and spiramycin only cause modest changes or do not interact at all (1:790)
Methotrexate			x			24b	Modest reduction in loss of theophylline from body (1:791)
Metoclopramide						9	No interaction with slow-release preparations of theophylline (1:791)
Mexiletine		x				13; 24b	Theophylline levels are increased. Dosage reduced to avoid toxicity (1:792)
Moricizine		x				24a	Increased loss of theophylline from body. Increased dosage needed during concurrent use (1:793)
Omeprazole				x		22a; 21a	The rate of theophylline absorption from slow release forms of theophylline may be increased (13:1048)
Oral contraceptives		x				21a; 24b	Serum theophylline levels are raised to some extent. No toxicity (1:779)
Oxpentifylline						23a	Raise theophylline levels (1:793)
Phenylpropanolamine						24a; 16a	Reduce clearance of theophylline from body, toxicity may occur (1:794)
Phenytoin		x				24a; 23b	Phenytoin reduces theophylline concentration and may increase theophylline dosage requirements. Theophylline may decrease phenytoin concentration, but the clinical importance is not established (2:148)
Propafenone		x				16a; 23a	Theophylline toxicity and raised serum levels (1:795)
Pyrantel		x				16a; 23a	Increased theophylline levels in children given pyrantel embonate (1:796). Theophylline toxicity (16:341)
Pyridoxine (vit B6)						20b	Reduction in theophylline-induced hand tremors may occur (1:796)
Quinolone antibiotics		x				23a; 13; 24b	Theophylline levels increase. Theophylline dosage must be halved to avoid toxicity. Norfloxacin causes serious toxicity. Pipemidic acid interact to a lesser extent (1:796)
Radioactive iodine				x		16a	A patient developed theophylline toxicity following iodine therapy for thyrotoxicosis (3:480)
Rifamycins		x				23b	Reduced theophylline levels (1:799). Increase theophylline dosage (17:524)

Table 3.11 (continued)

Therapeutic index (drug-drug interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
St John's wort						20b; 25b	Plasma theophylline concentrations may be decreased (15)
Sucralfate		x				22b	Absorption of sustained-release theophylline is reduced (1:800)
Sulphinpyrazone					x	23b	Small reduction in theophylline levels (1:800)
Sympathomimietic agents					x	20a	Potentiation of cardiac effects, particularly in severe resistant cases of asthma with marked hypoxia (6:458)
Tacrine				x		16a; 24b	Increased theophylline concentrations and toxicity may occur (13:1055)
Tetracyclines				x		23a	Theophylline levels can be increased in patients given doxycycline, minocycline or tetracycline (1:801)
Theophylline						12; 13	Patients on theophylline should not take other medication containing theophylline, unless the total dosage can be adjusted (1:793)
Thiabendazole		x				23a; 24b	Theophylline levels increase (1:801)
Thioamines		x				24a	Alterations in theophylline clearance can be expected in hyperthyroid patients (13:1058)
Thyroid hormones		x				23b; 24b; 25b	Initiation of thyroid replacement therapy in patients receiving theophylline may reduce theophylline levels (2:515). Decreased clearance of theophylline (15).
Ticlopidine		x				24b; 23a	Reduces loss of theophylline from the body and is expected to raise levels (1:802)
Verapamil		x				23a; 21a	Effects of theophylline may increase (13:1061)
Vidarabine			x			23a	Increased theophylline levels (1:803)
Viloxazine						23a; 16a	Increased theophylline levels. Intoxication if dosage is not reduced (1:804)
Zafirlukast				x		20a; 16a; 25a	Theophylline serum levels may be elevated, resulting in an increase in pharmacologic toxic effects. Zafirlukast levels may decrease (15)
Zileuton		x				23a; 20a; 12	Theophylline levels are raised (1.1:730). Increased pharmacologic and adverse effects (15)
Food (drug-food interaction)							
Alcohol						12; 24b	Caution with alcohol - a single large dose decreases drug clearance (12:223)

Table 3.11 (continued)

Food (drug-food interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
Caffeine		x				23a; 25a	Caffeine can raise serum theophylline levels (1:776)
Food		x				24a	Bioavailability of theophylline from a number of sustained-release formulations can be increased or decreased by food.
						24b	High protein diets increase the loss of theophylline from the body, whereas high carbohydrate diets reduce the loss. No interactions appear to occur with dietary fibres (1:783)
Grapefruit juice						9	No interaction (1:784)

Table 3.12: Drug interactions of loperamide

Patient-factor (drug-patient interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
Gender							No effects listed in documents used
Age							
Younger than 6 months						3	Relative contraindicated: children (6:59)
Older than 6 months and younger than 2 years						14; 20a	May cause excessive sedation especially in young children, while dehydration
Older than 2 and younger than 6 years							may result in variable response (6:59)
Older than 6 and younger than 12 years							Not recommended; dietary treatment is preferred where possible (6:59)
Older than 12 and younger than 50 years						9	Safe to use (11:497)
Older than 50 and younger than 70 years						9	Safe to use (11:497)
Older than 70 years						3	Relative contraindicated (6:59)
Blood pressure							No effects listed in documents used
Temperature							No effects listed in documents used
Weight / height / age							No effects listed in documents used
Blood sugar							No effects listed in documents used
Pregnancy							No effects listed in documents used
Lactation						27	Safety not established (6:59)
Sport involvement						9	No problems (6:59)
Tobacco						9	Loperamide is safe to use (9:108)
Occupation							No effects listed in documents used
Adverse effects							
Central nervous system							Sedation, fatigue, dizziness (10:580). Drowsiness (11:497). Headache (6:59)
Dermatologic							Rash (10:580)
Gastrointestinal							Nausea, vomiting, constipation, abdominal cramping and dry mouth (10:580). Abdominal distention (11:497)
Miscellanous							Hypersensitivity reactions (10:580)
Ocular							Blurred vision (6:59)
Medical conditions (drug-disease interaction)							
Bloody diarrhoea, high fever or systemic toxicity						4b	Contraindicated (5:548)
Dehydration and impaired hepatic function						4b	Relative contraindicated (6:59)

Table 3.12 (continued)

Medical conditions (drug-disease interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
Porphyria						9	Safe to use (6:59)
Pseudomembrane colitis, diarrhoea of infective origin or severe colitis from inflammatory bowel disease						2b	Absolute contraindicated (6:59)
Therapeutic index (drug-drug interaction)							
Cholestyramine					x	23b; 21b; 22b	Effects of loperamide can be reduced (1:881)
Central nervous system depressants e.g. antidepressants, antipsychotics, hypnotics and anxiolytics						20c; 25c; 21c	Loperamide can enhance the action of these drugs (11:497)
Co-trimoxazole						23a	Increases the bioavailability of loperamide (17:102)
Opoids, e.g. opoid analgesics or remedies containing chlorodyne						20a; 21a	Increased risk of constipation (6:59)
Theophylline - slow release						22d; 21d	Loperamide delays theophylline absorption (17:102)
Food (drug-food interaction)							
Alcohol						25c; 20c	Loperamide may enhance the action of alcohol (11:497)

Table 3.13: Drug interactions of glibenclamide

Patient-factor (drug-patient interaction)	Severity 1	2	3	4	5	Message code	Recommendations
Gender							No effects listed in documents used
Age							
Younger than 6 months						1	Contraindicated (6:70)
Older than 6 months and younger than 2 years						1	Contraindicated (6:70)
Older than 2 and younger than 6 years						1	Contraindicated (6:70)
Older than 6 and younger than 12 years						1	Contraindicated (6:70)
Older than 12 and younger than 50 years						9	Safe to use (11:388)
Older than 50 and younger than 70 years						9	Safe to use (11:388)
Older than 70 years						3; 14	Avoid in elderly patients (5:1129). More susceptible to hypoglycaemia. Long-acting sulphonylureas are contraindicated (6:70)
Blood pressure							No effects listed in documents used
Temperature							No effects listed in documents used
Weight / height / age							No effects listed in documents used
Blood sugar							
Dextrothyroxine						12	Dextrothyroxine administration may result in increased blood glucose concentrations (3:206)
Epinephrine						12	Epinephrine has intrinsic hyperglycaemic activity and may increase the blood blood glucose in patients with diabetes (2:165)
Guanethidine						13; 12	Guanethidine lower blood glucose in patients with diabetes (2:167)
Marijuana						12	Marijuana may result in increased serum glucose concentrations (2:168)
Neuroleptics						13; 12	Chlorpromazine administration may result in loss of blood glucose control in patients with diabetes (3:211)
Potassium salts						13; 12	Treatment of hypocalaemia with potassium salts may result in a tendency toward hypoglycaemia (3:212)
Nicotinic acid						12	High dose can increase blood glucose (12:119)
Pregnancy						1	Contraindicated; insulin remains the agent of choice for the management of diabetes during pregnancy. If used near the end of the term, severe prolonged neonated hypoglycaemia may result (6:70)
Lactation						1	Contraindicated (7:1509)

Table 3.13 (continued)

Patient-factor (drug-patient interaction)	Severity 1	2	3	4	5	Message code	Recommendations
Sport involvement						9	Glibenclamide is safe to use (9:41)
Tobacco							No effects listed in documents used
Occupation							No effects listed in documents used
Adverse effects							
Central nervous system							Headache, dizziness, weakness and paraesthesia (6:70). Coma (7:1509)
Dermatologic							Pruritus, rash, photosensitivity (14:346). Erythema(6:70)
Endocrine and metabolic							Hypoglycaemia (11:388).
Gastrointestinal							Nausea, epigastric fullness, heartburn (14:346). Constipation, diarrhoea, anorexia (11:388)
Hematologic							Leukopenia, thrombocytopenia, hemolytic anaemia (14:346). Aplastic anaemia (6:70)
Hepatic							Cholestatic jaundice (11:388)
Neuromuscular and skeletal							Joint pain and paresthesia (14:346)
Renal							Diuretic effect (11:388)
Medical conditions (drug-disease interaction)							
Brittle or unstable diabetes, diabetes complicated by ketosis, acidosis and coma						4b	Contraindicated (6:70)
Porphyria						14	Use with extreme caution (6:70)
Presence of hepatic impairment						2b	Absolute contraindicated (5:1129)
Severe renal impairment						4b	Contraindicated (6:70)
Severe infections, trauma or those undergoing major surgery						3	Contraindicated. Treatment should be changed to insulin (6:70)
Type I diabetes mellitus						4b	Contraindicated (11:387)
Therapeutic index (drug-drug interaction) Glibenclamide							
Adrenaline, corticosteroids and thiazide diuretics		x				23b	Diminshed hypoglycaemic effect of glibenclamide (8:810)
Antacids			x			22a; 20a; 21a	Increased glibenclamide concentration (3:202)

Table 3.13 (continued)

Therapeutic index (drug-drug interaction) Glibenclamide	Severity 1	2	3	4	5	Message code	Recommendations
Beta-blocking agents					x	16a	May mask warning symptoms of hypoglycaemia and produce hypoglycaemia in certain diabetes, e.g. during exercise (6:70)
Carbamazepine and desmopresson						20b; 25b	Diuretics effects of glibenclamide are opposed by carbamazepine and desmopresson (1:570)
Cimetidine				x		23a; 24b	Glibenclamide concentrations increase (2:163)
Clonidine			x			20b; 25b	Clonidine may dimish the symptoms of hypoglycaemia (2:164)
Cyclosporin				x		16b; 20a; 21a	Increased cyclosporin concentrations with an increased risk of toxicity may occur. Glibenclamide levels may increase, produsing hypoglycaemia (15)
Diflunisal						21a; 20a	Hypoglycaemia with glibenclamide (1:581)
Gemfibrozil		x				23a; 21a	Hypoglycaemic effects of glibenclamide may be increased (13:393)
Glucomannan						22b; 23b	Reduce the absorption of glibenclamide (1:576)
Heparin						16a	Hypoglycaemia occurs with concurrent use (1:577)
Hepatic enzyme inducers (meprobamate phenytoin, rifampicin)			x		x	12	A diminished hypoglycaemic effect may occur (6:70)
Hydrochlorthiazide, glucocorticoids, furosemide and oral contraceptives		x				16a	Impaired glucose tolerance: diminished hypoglycaemia may occur (6:70)
Maprotiline			x			16a	Hypoglycaemia (1:591)
Metolazone						16a	Isolated report: severe hypoglycaemia in a patient on glibenclamide shortly after starting treatment with metalozone (1:580)
Monoamine-oxidase inhibitors		x				27; 16a	Interaction is unpredictable; severe and protracted hypoglycaemia has occurred (6:70)
Naftidrofuryl oxalate						16a	Severe hypoglycaemia during concurrent use (1:581)
Phenylbutazone or oxyphenbutazone		x				16a	Increased hypoglycaemia (1:583)
Piroxicam						23a; 21a	Increase effects of glibenclamide (1:581)
Verapamil			x			23a	Increased glibenclamide concentration following a single dose administration to normal subjects (2:575)
Warfarin		x				13; 25a; 25c	Increased plasma concentrations of both agents; dosage must be adjusted (6:70)
Sulphonylureas							
Anabolic steroids		x				24b; 21a; 23a	May enhance the effect of hypoglycaemic drugs (2:162)

Table 3.13 (continued)

Therapeutic index (drug-drug interaction) Sulphonylureas	Severity 1	2	3	4	5	Message code	Recommendations
Androgen				x		21a; 25a	Hypoglycaemic actions of sulphonylureas may be enhanced (15)
Aspirin, sulphonamides, clofibrate, chloramphenicol, cimetidine, fluconazole, ketoconazole and miconazole		x				23a; 25a	Enhanced hypoglycaemic effect responce to sulphonylureas (6:70)
Captopril			x			13	Increase insulin sensitivity; reduce dosage requirements for antidiabetic drugs (2:162)
Clofibrate			x			23a; 25a	Hypoglycaemic effect enhanced (1:569)
Colestipol			x			25d; 28	Limited information suggests that sulphonylureas may inhibit the response to colestipol (3:205)
Diazoxide		x				25b; 23b	Diazoxide can destablise the patient, resulting in hyperglycaemia (13:959)
Fenfluramine			x			13; 23a	Fenfluramine may enhance the hypoglycaemic activity of antidiabetic treatments (2:166)
Fluvastatin						20a; 21a	Sulphonylurea concentrations may be elevated, increased hypoglyceamic effect (15)
Glucagon			x			6b	Glucagon may result in hyperglycaemia (2:167)
Halofenate		x				23a	Raise sulphonylureas levels (1:577)
Loop diuretics (e,g.etacrynic acid)					x	23b; 25b	Loop diuretics may decrease glucose tolerance, resulting in hyperglycaemia in patients previously well controlled on sulphonylureas (15)
Magnesium salts					x	23a; 21a	Hypoglycaemic effects of sulphonylureas increased (13:968)
Omeprazole				x		23a; 21a	Serum sulphonylurea concentrations may be elevated, increasing hypoglycaemic effects (13:971)
Tricyclic depressants						23a; 25a	Enhance the hypoglycaemic effect of sulphonylureas (3:203)
Thyroid hormones			x			23b; 21b	Thyroid replacement therapy may decrease the effects of hypoglycaemic drugs (2:173)
Food (drug-food interaction)							
Alcohol		x				25a; 21a	Increased risk of hypoglycaemia, and potential for alcohol intolerance leading to flushing, headache, nausea and vomiting (6:70)

Table 3.14: Drug interactions of multivitamin

Patient-factor (drug-patient interaction)	Severity 1	2	3	4	5	Message code	Recommendations
Gender							No effects listed in documents used
Age							
Younger than 6 months						14	Vitamin A: Use not recommended (10:981)
						14	Ascorbic acid: In infants, excessive use causes haemolysis (6:83)
Older than 6 months and younger than 2 years						12	Vitamin A: Use with caution (6:78)
						12	Vitamin D: Hyperreaction with hypercalcaemia and hypercalciura (6:79)
Older than 2 and younger than 6 years						9	Vitamins safe to use (6:78)
Older than 6 and younger than 12 years						9	Vitamins safe to use (6:78)
Older than 12 and younger than 50 years						9	Vitamins safe to use (6:78)
Older than 50 and younger than 70 years						28	Vitamin A: Not specific data available (6:78)
Older than 70 years						9	Vitamin D: No problems (6:79)
						22b	Thiamine: Impaired utilisation - possible increased requirements (12:223)
Blood pressure							No effects listed in documents used
Temperature							No effects listed in documents used
Weight / height / age							No effects listed in documents used
Blood sugar						12	Nicotinamide: Caution with diabetes. Increased glucose (12:168)
Pregnancy							
Vitamin A						14	Avoid excessive use shortly before and during pregnancy. Associated with congenital malformation, growth retardation and early epiphyseal closure in fetus (6:77)
Ascorbic acid						3	Requirements are increased during pregnancy (6:83). To large doses are contraindicated (10:97)
Vitamin D						12	Large doses leads to maternal hypercalcaemia can cause a neonatal hypercalcaemic syndrome (6:79)
Nicotinamide						13	Nicotinamide requirements are increased during pregnancy (6:82)
Lactation							
Vitamin A						12	Present in breast milk (8:1703)
Ascorbic acid							Requirements are increased (6:83)
Vitamin D						12	May cause hypercalcaemia in infants (6:79)
Nicotinamide							Requirements are increased (6:82)

Table 3.14 (continued)

Patient-factor (drug-patient interaction)	Severity 1	2	3	4	5	Message code	Recommendations
Sport involvement						9	Vitamins are safe to use (9:82)
Tobacco							
Ascorbic acid							Requirements are increased (6:83). Nicotine induces tissue desaturation of ascorbic acid (8:1168)
Occupation							No effects listed in documents used
Adverse effects Vitamin A							
Central nervous system							Irritability, drowsiness, vertigo, delirium, headache, coma, increased intracranial pressure (10:981)
Dermatologic							Erythema and peeling skin (10:981)
Gastrointestinal							Vomiting and diarrhoea (10:981)
Hypervitaminosis A							Fatigue, long-bone pain, psychiatric changes, anorexia and abdominal discomfort (6:78)
Ocular							Visual disturbances, papilloedema (10:981). Exophthalmus (6:78)
Ascorbic acid							
Cardiovascular							Flushing (10:97)
Central nervous system							Faintness, dizziness, headache and fatigue (11:70)
Gastrointestinal							Nausea, vomiting, heartburn and diarrhoea (10:97)
Renal							Hyperoxaluria (10:97). Large doses precipitate, cystine, oxalate and renal stones (11:70)
Vitamin D							
Cardiovascular							Hypertension, arrhythmias and hypotension (10:377)
Central nervous system							Drowsiness, irritability, headache, convulsions and somnolence (11:309). Psychosis (10:377)
Dermatologic							Pruritus (10:377)
Endocrine and metabolic							Acidosis, polydipsia (11:309). Hypercholesterolaemia (10:377)
Gastrointestinal							Nausea, vomiting, anorexia, dry mouth, constipation, weight loss, metallic taste (11:309). Dry mouth and pancreatitis (10:377)
Genitourinary							Reversible azotaemia (11:309). Albuminuria and nocturia (10:377)
Hematologic							Anaemia (11:309)

Table 3.14 (continued)

Adverse effects Vitamin D	Severity 1	2	3	4	5	Message code	Recommendations
Miscellaneous							Ectopic calcification (11:309)
Neuromuscular and skeletal							Weakness, muscle and bone pain (10:377). Metastatic calcification (11:309)
Ocular							Photophobia (10:377)
Renal							Polyuria, nephrocalcinosis (10:377). Renal damage (11:309)
Nicotinamide							
Cardiovascular							Flushing, hypotension, tachycardia, syncope, vasovagal attacks (10:685)
Central nervous system							Dizziness and headache (11:595)
Dermatologic							Pruritus, increased sebaceous gland activity, tingling skin and burning (10:685)
Gastrointestinal							Gastrointestinal upset, nausea, vomiting, heartburn and diarrhoea (11:595)
Hepatic							Abnormal liver function tests, jaundice and chronic liver damage (10:685)
Ocular							Blurred vision (11:595)
Thiamine							
Cardiovascular							Cardiovascular collaps and death, warmth (10:916)
Dermatologic							Rash and angioedema (10:916)
Neuromuscular and skeletal							Tingling (10:916)
Medical conditions (drug-disease interaction)							
Viral hepatitis, cirrhosis and other forms of liver disease. Hypervitaminosis A						4b	Vitamin A: Contraindicated (6:77)
Porphyria						3 9	Vitamin A: Contraindicated (10:981) Vitamin A: Use (6:78)
Surgical procedures, hyperthyroidism and burns						9	Vitamin D: Use (6:79) Ascorbic acid: Requirements are increased (6:83)
Diabetes and recurrent renal calculi						14	Ascorbic acid: These patients should not take excessive doses for extended periods of time (11:70)
Renal osteodystrophy with hyperphosphataemia; hypervitaminosis D and hypercalcaemia. Decreased renal function						4b	Vitamin D: Contraindicated (6:79)

Table 3.14 (continued)

Medical conditions (drug-disease interaction)	Severity 1	2	3	4	5	Message code	Recommendations
Liver disease, peptic ulcer, severe hypotension, arterial hemorrhaging, hypersensitivity to nicotinamide						4b 4b	Vitamin D: Contraindicated (11:309) Nicotinamide: Contraindicated (10:527)
Patients with predisposed gout						12	Nicotinamide: Use with caution (11:595)
Chronic renal failure						4b	Vitamin A: Contraindicated (6:77)
Chronic infections						9	Ascorbic acid: Requirements are increased (6:83)
Glucose-6-phosphate dehydrogenase (G6PD) deficiency						13; 12	Ascorbic acid: Risk of hemolytic anaemia (12:243)
Therapeutic index (drug-drug interaction) Vitamin A							
Aminoglycosides					x	21a; 20b; 25b	Therapeutic action of vitamin A may be reduced (13:1125). Neomycin can reduce retinol absorption (17:120)
Cholestyramine, cholestipol, liquid paraffin, large amounts of antacids and sucralfate						22b	Interferes with vitamin A absorption (6:77)
Corticosteroids			x			21a +b	Retinol may worsen or improve wound healing (17:120)
Isotretinoin and etretinate						16a	Additive toxicity (6:77)
Neomycin			x			22b	Reduce absorption of vitamin A from the gastrointestinal tract (1:908)
Oral contraceptives						23a	Raise levels of vitamin A (17:120)
Tetracycline						20a	Risk of intracranial pressure (6:77)
Ascorbic acid							
Aluminium salts						14; 16b	Aluminium antacids should not be given with vitamin C - risk of high aluminium levels (17:124)
Aspirin, iron, phenytoin, convulsant drugs, oestrogen and tetracycline					x	22a; 21a	These drugs induce tissue desaturation of ascorbic acid (8:1168)
Desferrioxamine						23c	High doses of ascorbic acid can cause cardiac disorders with desferrioxamine (1.1:790)
Ferrous sulphate			x			22c; 23c	The absorption of the iron salts may be enhanched by ascorbic acid (16:332)
Fluphenazine						23d	Fall in serum fluphenazine levels and deterioration (1:711)
Oral contraceptives			x			23b	Lower levels of ascorbic acid (1.1:432)
Propranolol					x	20d; 21d	Pharmacologic effects of propranolol may be increased (15)

Table 3.14 (continued)

Therapeutic index (drug-drug interaction) Ascorbic acid	Severity 1	2	3	4	5	Message code	Recommendations
Salicylates					x	22b; 21b	Aspirin reduce ascorbic acid absorption (1:909)
Warfarin					x	23d; 21d	Impaired warfarin response associated with large doses of ascorbic acid. This effect has not been confirmed (2:76)
Vitamin D							
Cholestyramine and liquid paraffin						22a; 21a	Inhibit vitamin D absorption (6:79)
Corticosteroids						21b; 20b	Corticosteroids counteract the effects of vitamin D (17:120)
Digitalis glycosides and verapamil				x		23c; 20c; 21c	Vitamin D increases cardiac arrhythmias (11:309). Therapeutic activity of verapamil may be reduced (15)
Magnesium						22c; 20c	Vitamin D may increase absorption of magnesium (11:309). Increased levels of magensium (17:120)
Phenobarbitone and phenytoin		x				25b; 21b	Prolonged treatment is associated with a reduction of vitamin D activity (6:79)
Phosphate salts						22c	Increased absorption of phosphate. May cause hyperplasplataemia (17:120)
Thiazide diuretics					x	20a	Hypercalcaemia and metabolic alkalosis can develop in patients given vitamin D if they are treated with diuretics (1:885)
Nicotinamide							
Adrenergic-blocking agents						20a	Adrenergic-blocking agents may have an additive vasodilating effect and may cause postural hypotension (11:595)
Clonidine			x			20b	Clonidine may inhibit nicotinamide-induced flushing (3:227)
Lovastatin				x		20c; 21c	Myopathy and rhabdomyolysis have occurred in patients receiving lovastatin and nicotinamide, but a casual relationship has not been established (2:443)
Oral hypoglycaemic agents						23d; 21d	Nicotinamide decrease these drugs effect (11:595)
Salicylates			x			20b; 23a	Aspirin can reduce flushing reaction which occur, but it can increase nicotinamide levels (1:887)
Sulphinpyrazone and probenecid			x			20d; 21d	Nicotinamide may inhibit the uricosuric effect of these drugs (10:528)
Thiamine							
Phenobarbitone sodium, riboflavine, bezylpenicillin						3; 14	Incompatible with thiamine (8:1699)

Table 3.14 (continued)

Food (drug-food interactions)	Severity					Message code	Recommendations
	1	2	3	4	5		
Alcohol			x			24c; 22a	Ascorbic acid may slightly increase the elimination of ethanol (3:555). Alcohol can induce tissue desaturation of ascorbic acid (8:1168)
Food or milk						9	Take nicotinamide with food or milk to avoid nausea, vomiting and diarrhoea (6:82)
Food						9	High carbohydrate diets may increase thiamine requirement (10:916)
Mineral oil					x	20b;21b; 23b	Vitamin A: Reduced therapeutic action (13:1126)

Table 3.15: Drug interactions of diclofenac

Patient-factor (drug-patient interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
Gender							No effects listed in documents used
Age							
Younger than 6 months						3	Not recommended for general analgesic purposes (6:324)
Older than 6 months and younger than 2 years						9	Safe to use (10:313)
Older than 2 and younger than 6 years						9	Safe to use (10:313)
Older than 6 and younger than 12 years						9	Safe to use (10:313)
Older than 12 and younger than 50 years						9	Safe to use (11:252)
Older than 50 and younger than 70 years						9	Safe to use (11:252)
Older than 70 years						12	Use with caution (6:324)
Blood pressure							No effects listed in documents used
Temperature							No effects listed in documents used
Weight / height / age							No effects listed in documents used
Blood sugar							No effects listed in documents used
Pregnancy						14	Diclofenac crosses plasenta. Use not recommended. Use in third trimester, associated with a prolonged gestation period and prolonged labour. Increased risk of antepartum and postpartum bleeding, and premature closure of the ductus arteriosus (6:324)
Lactation						9	Small amounts excreted in milk; not harmful to infants (6:324)
Sport involvement						9	Diclofenac is safe to use (9:113)
Tobacco							No effects listed in documents used
Occupation							No effects listed in documents used
Adverse effects							
Cardiovascular							Congestive heart failure, angina, hypertension, hypotension, arrhythmias and oedema (11:253)
Central nervous system							Dizziness, headache (10:312). Vertigo, drowsiness, fatigue, hallucinations, confusion, depression, emotional lability, psychotic behaviour, asthenia and pyrexia (11:253)
Dermatologic							Rash, pruritus (10:312). Urticaria, angioedema, Stevens-Johnson syndrome, exfoliative dermatitis, ecchymosis, petechiae, purpura and bruising (11:253)

Table 3.15 (continued)

Adverse effects	Severity					Message code	Recommendations
	1	2	3	4	5		
Endocrine and metabolic							Fluid retention (10:312). Hyperglycaemia, hypoglycaemia, hypercaleamia, gynecomastia and hyponatremia (11:253)
Gastrointestinal							Abdominal pain, indigestion, peptic ulcer, gastrointestinal bleeding and perforation, constipation, diarrhoea (10:312). Dyspepsia, heartburn, nausea, flatulence, stomatitis, vomiting, gingival ulcers, pancreatitis, proctitis, paralytic ulcers, colitis, anorexia, weight loss and dry mucus membranes (11:253)
Genitourinary							Azotemia, impotence and dysuria (11:253)
Hematologic							Agranulocytosis, aplastic anaemia, inhibition of platelet aggregation (10:312). Neutropenia, bone marrow suppression and hemorrhage (11:253)
Hepatic							Possible hepatitis (10:312). Cholestatic jaundice (11:253)
Hypersensitivity							Bronchospasm, rashes, pruritis, urticaria and angioedema (6:325)
Miscellaneous							Thirst and sweating (11:253)
Neuromuscular and skeletal							Involuntary muscle movements, muscle weakness and tremors (11:253)
Ocular							With ophthalmic use, itching, tearing, irritation, redness, burning; ocular irritation with use of hydrogel soft contact lenses (10:312). Vision changes, keratitis, anterior chamber reaction and ocular allergy (11:253)
Otic							Tinnitus (10:312)
Renal							Renal impairment, nephrotic-like syndrome (10:312). Polyuria, pyuria, oliguria, anuria and acute renal failure (11:253)
Respiratory							Exacerbation of asthma, dyspnea (11:253)
Medical conditions (drug-disease interaction)							
Hypersensitivity to aspirin or other non-steroid anti-inflammatory drugs active peptic ulceration						1	Absolute contraindicated (6:324)
History of dyspepsia or peptic ulceration; renal or hepatic impairment, atherosclerosis, compromised cardiac function, angina, hypertension, bleeding disorders, asthma, atopy, nasal polyps or urticaria						4b	Relative contraindicated (6:324)
Porphyria						14	Use with extreme caution only (6:324)

Table 3.15 (continued)

Therapeutic index (drug-drug interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
ACE inhibitors, beta-blockers, thiazide diuretics and furosemide		x	x			20d; 21d; 25d	Decreased antihypertensive effects (11:253)
Aminoglycosides		x				20c; 25c	Plasma aminoglycoside concentration may be increased in premature infants (15).
Antihypertensive, angina, cardiac failure or diuretic therapy					x	23d; 21d	Efficiency of these drugs may be markedly attenuated (6:325)
Biphosphonates (atendronate)						20a + c	Risk of gastric ulceration may be increased (15)
Cholestyramine and colestipol			x			22b; 21b	Absorption of diclofenac from the gut is reduced by cholestyramine, and to a lesser extent by colestipol (1:56)
Cimetidine					x	12	Therapeutic action of non-steroid anti-inflammatory drugs may be altered (15)
Cyclosporin		x				16b	May increase nephrotoxicity of cyclosporin (11:253)
Digoxin			x			15a; 16b	Non-steroid anti-inflammatory drugs may exacerbate heart hailure, increase serum digoxin levels. Monitor for toxicity (17:382)
Glucocorticosteroids		x				16a + b	May enhance potential toxicity of both medications (6:324)
Lithium		x				24d; 23c	Diclofenac may decrease renal clearance and increase levels (6:324)
Methotrexate	x					23c; 16b	Non-steroid anti-inflammatory drugs increase levels and toxicity of methotrexate (6:325)
Midasolam						20d; 21d; 25d	Diclofenac reduces both the sedative and hypnotic dosages of midasolam (1:694)
Oral anticoagulants		x				20d; 21d	Enhanced bleeding (6:324)
Other anti-inflammatory agents					x	20a	Potential for ulcerogenicity and other adverse effects may be additive (6:324)
Penicillins, cephalosporins, dipyridamole and valproic acid						20a	May enhance risk of bleeding with non-steroid anti-inflammatory drugs (6:325)
Pentazocine						20a	Grand mal seizures may occur in patients treated with diclofenac and pentazocine (1:57)
Potassium-sparing diuretics						16b	Diclofenac and potassium-sparing diuretics may increase serum potassium (11:253)
Probenecid					x	24d; 25c; 16a	Inhibit renal excretion of non-steroid anti-inflammatory drugs (6:325) and lead to toxicity (17:383)

Table 3.15 (continued)

Therapeutic index (drug-drug interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
Quinolones							Could increase the risk of central nervous system stimulation, e.g. seizures (17:383)
Salicylate					x	23b	Aspirin may reduce plasma diclofenac concentration, but does not appear to interfere with its therapeutic effect (2:583)
Sulphonamides, sulphonylureas, phenytoin, verapamil and nifedipine					x	21c; 16b	Non-steroid anti-inflammatory drugs may displace such agents from plasma proteinbinding sites, increased therapeutic effects and toxicity (6:325)
Sucralfate			x			20b; 21b	Pharmacologic effects of diclofenac may be decreased (15)
Sympathomimetics						20c; 21c	Increased response to sympathomimetics (11:253)
Triamterene				x		20a; 16a	Acute renal failure may occur (15)
Zidovudine						14	There is a risk of haemotoxicity (17:383)
Food (drug-food interaction)							
Alcohol						14	Avoid alcohol use (12:83). Increased risk of gastrointestinal tract bleeding and ulceration (17:382)
Food						22b	Delayed oral absorption with a single dose but not with chronic multiple-dose administration (10:313)

Table 3.16: Drug interactions of reserpine

Patient factor (drug-patient interaction)	Severity 1	2	3	4	5	Message code	Recommendations
Gender							No effects listed in documents used
Age							
Younger than 6 months						14	Dosage not established (6:124)
Older than 6 months and younger than 2 years						14	Dosage not established (6:124)
Older than 2 and younger than 6 years						14	Dosage not established (6:124)
Older than 6 and younger than 12 years						14	Dosage not established (6:124)
Older than 12 and younger than 50 years						9	Safe to use (6:124)
Older than 50 and younger than 70 years						12; 13	Caution: dosage adjustment (17:165)
Older than 70 years						12; 13	Caution: dosage adjustment (17:165)
Blood pressure							Reserpine reduces both cardiac output and peripheral vascular resistance, thus lowering blood pressure (7:791)
Temperature							No effects listed in documents used
Weight / height / age							No effects listed in documents used
Blood sugar							No effects listed in documents used
Pregnancy						14	Avoid use in pregnancy near term as it may cause nasal discharge, lethargy, lethargy, anorexia (17:163), cyanosis and hypothermia in the infant (6:124)
Lactation						12	Caution. Reserpine is excreted into breast milk. Reports of adverse events has not been reported (17:163)
Sport involvement						1	Absolute contraindicated: Reserpine can not be used in sport (9:111)
Tobacco							No effects listed in documents used
Occupation						14	Reserpine causes drowsiness and caution should be taken when driving or performing tasks that require concentration (17:163)
Adverse effects							
Cardiovascular							Bradycardia and hypotension (6:124)
Central nervous system							Dizziness, drowsiness, headache, depression (6:124). Mood changes (17:163). Nightmares (4:163). Occasional psychotic depression can lead to suicide (7:791). Fatigue (11:734)
Dermatologic							Rashes, pruritis (6:124)
Endocrine and metabolic							Sodium (11:734) and fluid retension (6:124)

Table 3.16 (continued)

Adverse effects	Severity					Message code	Recommendations
	1	2	3	4	5		
Gastrointestinal							Diarrhoea, nausea and vomiting (6:124). Gastrointestinal cramps and increased gastric acid secretion (4:163)
Genitourinary							Impotency and urination difficulty (11:734)
Hematologic							Thrombocytopenia (6:124)
Miscellaneous							Dry mouth and lethargy (6:124)
Respiratory							Nasal congestion (6:124)
Medical conditions (drug-disease interaction)							
Epilepsy and Parkinson's disease						2b	Absolute contraindicated (17:165)
History of mental depression						2b	Absolute contraindicated (17:165)
Hypersensitivity to reserpine						2a	Absolute contraindicated (11:734)
Patients receiving electroconvulsive therapy						3	Relative contraindicated (6:124)
Peptic ulcers, gallstones and ulcerative colitis						4b	Absolute contraindicated (17:165)
Phaeochromocytoma						4b	Relative contraindicated (6:124)
Porphyria						9	Reserpine is safe to use (17:163)
Renal insufficiency						4b	Relative contraindicated (11:734)
Therapeutic index (drug-drug interaction)							
Antihypertensives, e.g. propranolol and thiazides						20a; 21a; 13	The combination may cause an increased antihypertensive effect; requiring dose adjustment (17:162)
Anticoagulants			x			28	Little evidence is available to indicate that reserpine affects the hypoprothrombinemic response to oral anticoagulants (2:102)
Central nervous depressants, e.g. barbiturate and thiopental						14; 17b	Avoid the combination (17:162). Reserpine may enhance the central nervous system depression caused by thiopental, resulting in hypotension and bradycardia (16:39)
Digitalis, e.g., digoxin			x			20c; 16b	Reserpine may enhance bradycardia, arrhythmias and hypotension (17:162). Digitalis cardiotoxicity is increased (16:268)
Halothane			x			28	Studies suggested that administration of halothane in patients receiving reserpine may be tolerated without increased risk of hypotension; however, conflicting data are available (16:170)

Table 3.16 (continued)

Therapeutic index (drug-drug interaction)	Severity					Message code	Recommendations
	1	2	3	4	5		
Levodopa			x			21d; 23d	Reserpine may inhibit the therapeutic effect of L-dopa (17:164). This may inhibit the antiparkinsonian effects of L-dopa (2:240)
Monoamine oxidase inhibitors, e.g. phenelzine (MAOIs)		x				21b; 20b	The MAOIs may cause hypertension. Reserpine effect is reversed (17:164). MAOIs may cause hyperpyrexia (6:124)
Quinidine			x			21c; 23c	The antiarrhythmic and cardiodepressant effects of quinidine may be enhanced by the administration of reserpine (16:64)
Sympathomimetics, e.g. dobutamine, dopamine, epinephrine, methoxamine, norepinephrine, metaraminol and ephedrine		x				20c 20d	Reserpine potentiates the pressor response of the direct-acting sympathomimetics which may result in hypertension. The pressor response of the indirect-acting agents is decreased by reserpine (13:993)
Tricyclic antidepressants and other antidepressant medication			x			14; 17b	Reserpine can cause depression and should not be used in patients requiring treatment for depression (17:164)
Food (drug-food interaction)							
Alcohol						1	Avoid the combination (17:162)

CHAPTER 4: RESEARCH METHODOLOGY

4.1 INTRODUCTION

The research methodology for the study was a non-experimental investigation based on existing data of seven Philani Prime Cure® medi centres in South Africa.

To get the overall picture of the occurrence of drug interactions in the seven medi centres a combination of research techniques were used. This will be discussed in section 4.3.2.

The information obtained from the Philani Prime Cure® database, was used to investigate the occurrence of the drug interactions. In this chapter the empirical study, data source, database and research methodology will be discussed.

4.2 GENERAL OBJECTIVE OF THE EMPIRICAL STUDY

The general objective of the study was to investigate the occurrence of drug therapy problems, namely, drug interactions using the database provided by Philani Prime Cure®. The results can assist Philani Prime Cure® in the development of a drug interaction programme. The empirical study was based on an investigation of the occurrence of the drug interactions of ten selected drugs with various variables.

4.3 PHASES OF THE RESEARCH PROJECT

The research project consisted of two phases, namely, the literature phase and the empirical phase.

4.3.1 Phase 1: Literature study

The first phase of the study was to do a thorough literature study of the pharmaceutical care approach and the drug-related or therapy problems. The goals of the literature study (Newman, 1997:89) are listed below:

- Demonstrate a familiarity with a body of knowledge and establish credibility.
- Show the path of prior research and how a current project is linked to it.
- Integrate and summarise what is known about the subject.
- Learn from others and stimulate new ideas.

4.3.1.1 *Specific objectives of the literature study*

The specific objectives of the literature study included the following:

- To define managed pharmaceutical care.

- To illustrate where pharmaceutical care fits into managed pharmaceutical care and define the areas of managed pharmaceutical care
- To define and discuss pharmaceutical care in detail.
- To discuss the different elements of the pharmaceutical care practice (e.g. philosophy of practice, patient care process and practice management).
- To determine the role of the different health care providers in the prevention of drug therapy problems.
- To discuss primary health care.
- To define and discuss the different drug therapy problems.
- To define and discuss drug interactions by examining
  - the classification of drug interactions; and
  - the drugs involved in interactions.
- To discuss the different drug-drug interactions, such as
  - pharmaceutical interactions;
  - pharmacokinetic interactions; and
  - pharmacodynamic interactions.
- To discuss drug-food interactions by investigating
  - the effect of food and medication on each other;
  - factors affecting drug-food interactions; and
  - different types of drug-food interactions.
- To determine the factors affecting drug interactions.
- To discuss iatrogenic illness.
- To discuss the ten selected drugs by referring to
  - classification of the drug;
  - pharmacological properties of the specific drug;
  - mechanism of action;
  - therapeutic uses of each drug; and
  - deficiencies where possible.
- To construct a table with all the potential drug interactions and the adverse reactions of each drug.
- To discuss the mechanism of the drug interactions.

4.3.2 **Phase 2: Empirical study**

The objectives of the empirical study will be discussed.

4.3.2.1 *Specific objectives of the empirical study*

The specific objectives of the empirical study included the following:

- To determine the general information of the patient population during the research period by referring to
  - the total number of patients in the medi centres;
  - the gender distribution of the patients;
  - the age distribution of the patients; and
  - the average, minimum and maximum ages of the patients.
- To investigate the medicine usage patterns of patients of the medi centres during the research period in order to determine
  - the total number of medicine items prescribed in each medi centre;
  - the average number of medicine items prescribed in each medi centre;
  - the total number and percentage of patient visits where one or more medicine items were prescribed; and
  - the occurrence of the ten selected drugs in the medi centres.
- To investigate the medical conditions or disease states in the medi centres according to
  - the total number of medical conditions or disease states per medi centre;
  - the number of medical conditions or disease states diagnosed per patient visit;
  - the average number of medical conditions or disease states diagnosed per visit;
  - the ten most frequently diagnosed medical conditions or disease states diagnosed per patient visit; and
  - the top three medical conditions or disease states for which the ten selected drugs were prescribed.
- To identify and discuss the possible interactions that could occur with the ten selected drugs by considering
  - the age groups interactions; and
  - the drug-drug interactions.
- To determine the medical conditions or disease states where the drug-drug interactions appeared.

(Refer to figure 4.1 for a schematic presentation of the analysis performed on the database).

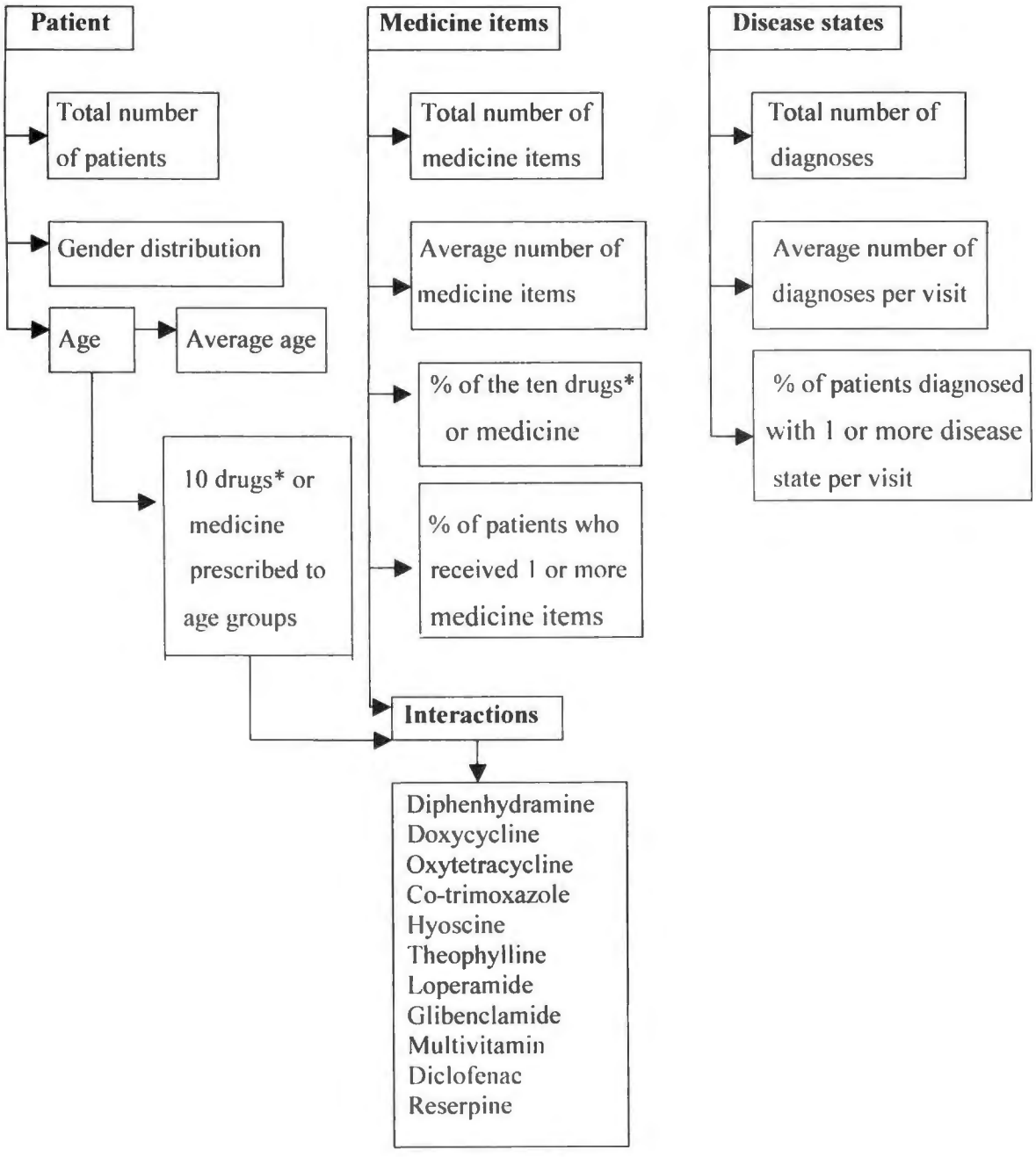

Figure 4.1: Schematic presentation of the analysis done on the database

** In the study there were made use of the words "drugs" or "medicines" to described the drugs selected from the database.*

The above aims are limited to seven randomly chosen Philani Prime Cure® medi centres.

4.3.2.2 *Data collection*

♦ Selection of the top twenty prescribed drugs

Medicine usage report that covered a year period (1 March 2000 to 28 February 2001) were provided by Philani Prime Cure®. The period from which the selected drugs were identified, was for a year (1 March 2000 to 28 February 2001). The data from which the information of the medi centres was obtained, occurred over a six month period (1 January 2000 to 30 June 2000). The two periods overlapped with three months, thus providing the specific data available at the time the research occurred. The unprocessed data were ordered according to frequency of prescription in a descending order, thereby enabling the researcher to identify the top twenty prescribed drugs in the Philani Prime Cure® medi centres. For the purpose of this study, data from seven medi centres were used. These medi centres were randomly chosen from the 53 medi centres to represent all seven provinces where Philani Prime Cure® had medi centres at the time.

The following criteria were used for the selection of the top twenty drugs:

- Only oral medication (e.g. tablets, suspensions, capsules, etc.) were selected. Aerosols, ointments and sprays were excluded.
- Combination medication were divided into different active ingredients and considered as individual drugs.
- If there were two drugs from the same pharmacological group, they were discussed together under the pharmacological group.

A period of six months was used to select the ten drugs to identify possible interactions. These drugs were:

- Diphenhydramine
- Doxycycline → Tetracycline
- Oxytetracycline →
- Co-trimoxazole
- Hyoscine
- Theophylline
- Loperamide
- Glibenclamide
- Multivitamin
- Diclofenac
- Reserpine

As indicated in the list above, doxycycline and oxytetracycline are from the same pharmacological group, namely, tetracyclines. Doxycycline and oxytetracycline will be discussed together as tetracycline in Chapter 3. Their drug interactions will be considered separately. The list given above is not representative of the top ten drugs prescribed by Philani Prime Cure® medi centres, but of the top twenty drugs that were prescribed. A fellow researcher, Me Hester Van der Walt, was already busy with the top ten drugs from her research period. Seven of the drugs used in her research study overlapped with this research period's top twenty drugs. This study therefore consists of the remaining ten drugs that were prescribed during the research period. Table 4.1 shows the medicine usage report that was obtained from the data.

Table 4.1: Medicine usage report.

Pharmacological groups	Generic names	Total of selected drugs**
Antihistamine	Diphenhydramine	31745.83
Tetracycline	Doxycycline	20540.06
	Oxytetracycline	2773.25
Anti-infective agent for systemic use	Co-trimoxazole	17298.05
Cephalosporins*	Cefixime*	16829.37
Antiemetics	Hyoscine	10111.70
Antiasthmatic agent	Theophylline	8601.64
Antidiarrhoels	Loperamide	4110.39
Sulphonylureas	Glibenclamide	3124.54
Vitamins	Multivitamin	3083.05
Anti-inflammatory agent	Diclofenac	2248.10
Antihypertensive agent	Reserpine	1849.62

** Due to problems with this drug, there will be an additional drug discussed, namely, reserpine.*

*** Total of the selected drugs was done according to the prevalence of the drugs in the data supplied by Philani Prime Cure ®.*

Cefixime was identified on the medicine usage report for part of the research period. When the analysis of the medicine usage for the medi centres was done for the specific period (1 March 2000 to 28 February 2001), cefixime was not prescribed at one of the medi centres. The possible reason could be that this drug was excluded during the research period at the medi centres. Thus, the drug was prescribed just for a part of the research period. This could be that cefixime was not prescribed during 1 January 2000 to 30 June

2000. Cefixime could have been prescribed during 1 July 2000 to 28 February 2001. In the place of cefixime, reserpine was the next drug to be identified and discussed.

- Selection of the seven medi centres

This study on the occurrence of drug interactions was conducted on data of seven Philani Prime Cure® medi centres. The central database for the extraction of the data was from all 35 medi centres countrywide. The seven medi centres were randomly selected from the seven provinces where Philani Prime Cure® existed at the time. The seven medi centres used for the purposes of this study were:

- Brits (North West Province)
- Groblersdal (Mpumalanga Province)
- Kwanobuhle (Eastern Cape)
- Parow (Western Cape Province)
- Pietersburg (Northern Province)
- Rosslyn (Gauteng Province)
- Verulam (Kwazulu Natal Province)

Data for these medi centres were extracted for a six months period from 1 January 2000 to 30 June 2000. Only data from 1 January 2000 until 31 December 2000 were available. Due to the extent of the database the decision was made to use only a six-month period of the database to be analysed. A total number of 29441 patient visits were recorded at the seven medi centres over the six month research period (refer to Chapter 5, Table 5.1).

4.3.2.3 *Analysis of the data*

The data analysis was done using the Statistical Analysis System, SAS (SAS institute, 2000). The following criteria were used to analyse the data:

- All medical accessories were excluded. Medicine items were further divided into frequency and the average number of medicine items prescribed per patient visit. The medications that were prescribed in combination with the ten selected drugs, were obtained and the possible interactions could be identified from Chapter 3. The levels 1 to 3 interactions were discussed in detail in Chapter 5, section 5.4.1.
- The age and gender of the patients were also identified. The age groups were obtained from Philani Prime Cure® and in that division used for the analysis. Table 4.2 shows the division of the age groups.

Table 4.2: Age groups division.

Group	Age included
1	Younger than 6 months
2	Older than 6 months and younger than 2 years
3	Older than 2 and younger than 6 years
4	Older than 6 and younger than 12 years
5	Older than 12 and younger than 50 years
6	Older than 50 and younger than 70 years
7	Older than 70 years

- Diagnoses made during the patient visits were divided into procedures and diseases. Procedures that were excluded from this study included dental procedures such as broken teeth, fluoride treatment, dental examination and extraction; occupational health service; substances used while performing procedures such as barium compounds, bromoethane, chloroform and ether, etc.
- Diseases were described according to the frequency, average number and the total number of disease states per patient visit. The 10 most frequently diagnosed disease states were tabulated according to the occurrence of the disease states, gender and the occurrence in the age groups. The different diagnoses where drug interactions occurred were identified and tabulated.

4.3.2.4 *Research instruments*

Research instruments used in the empirical study included: the Philani Prime Cure® database, drug interactions tables and basic statistics.

(i) Philani Prime Cure® database

Due to the extent of the database only the files and fields used in this study will be discussed.

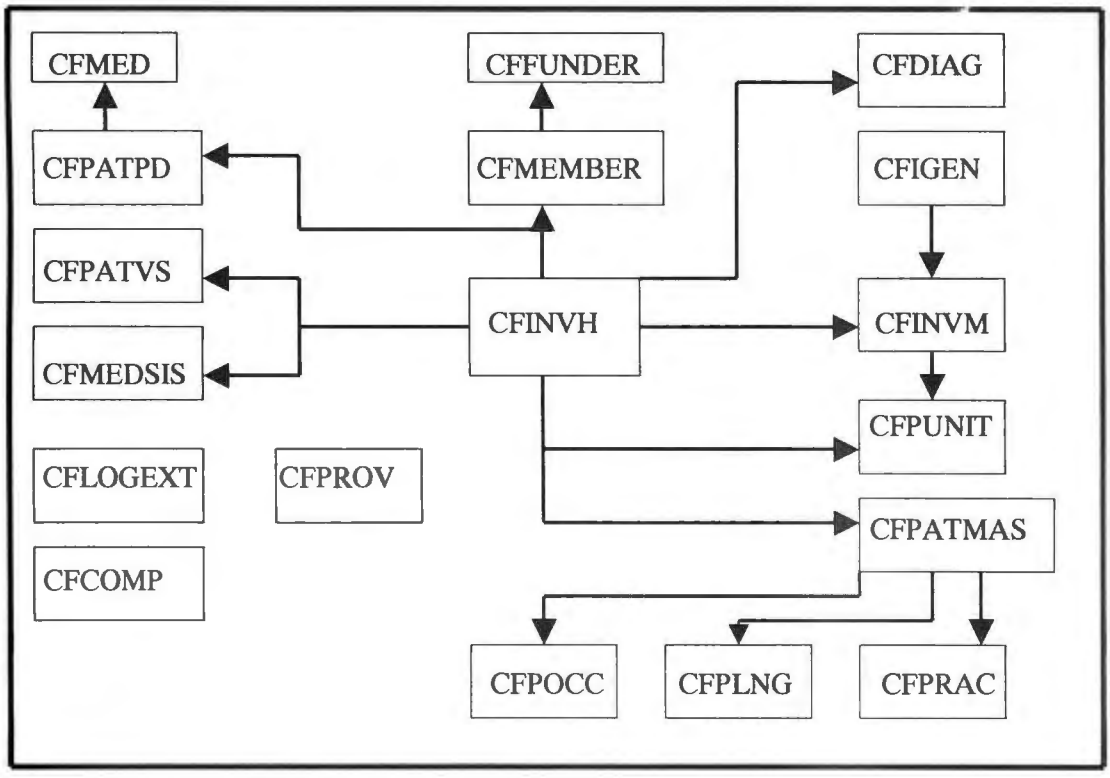

Figure 4.2: Schematic representation of the database.

The following is the description of the keys used in the database (Figure 4.1):

Table 4.3: Keys of the database.

Keys	Description
CFCOMP	Description of event file
CGDIAG	Diagnostic information file
CFFUNDER	Funder information file
CFINVH2	History invoice file
CFINVM	Invoice master file
CFLOGEXT	Log extract file
CFMEDSIS	Medical sister file
CFMEMBER	Patient medical aid member file
CFPATMAS	Patient master file
CFPAPPD	Patient payment detail file
CFPATVS	Visit identification file

Table 4.3 (continued)

CFPLNG	Patient language file
CFPMED	Medical aid record file
CFPOCC	Patient occupation file
CFPRAC	Patient race file
CFPROV	Staff file
CFPUNIT	Unit of measure file
CFIGEN	Generic file

The code, date and debtor fields of the history invoice file were used to gain information regarding the number of patients that visited the seven medi centres during the research period and the medication prescribed to these patients.

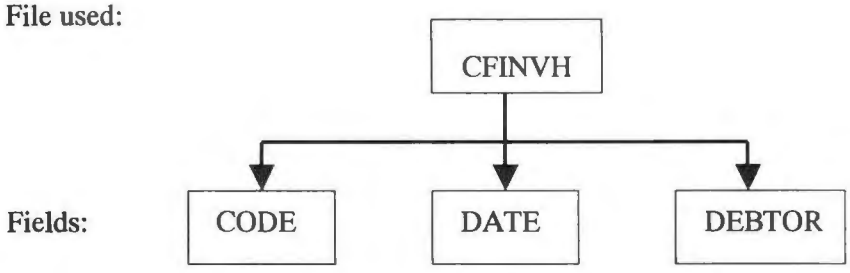

Figure 4.2a: Schematic representation of the database (continued)

- CODE: Stockcode (medication provided to patient). (Used to form inner link with field STK of the file CFINVM).
- DATE: Date of visit to medi centre. This field was used to specify the date of the period for the study (1 January 2000 to 30 June 2000).
- DEBTOR: Patient number issued. Unique to every patient and never changed.

The stockcode, trade name of medication and description fields of the generic file were used to gain information regarding the type of medication prescribed to the patients.

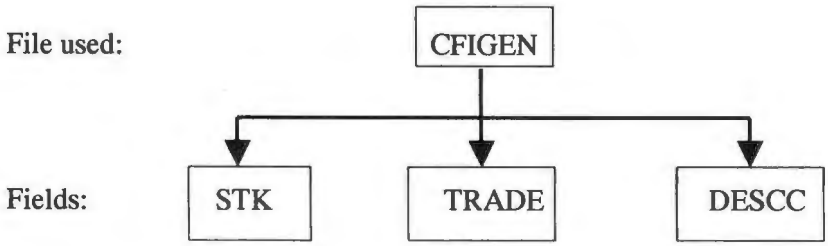

Figure 4.2b: Schematic representation of the database (continued)

- STK: Stockcode
- TRADE: Trade name of medication
- DESCC: Indicated the active ingredient of the medication. This field was used to determine the exact type of medication supplied to the patient in order to perform the study of the drug interactions.

The patient number, patient birth date and gender fields of the patient master file were used to gain information regarding the age and gender of patients that visited the medi centres during the research period.

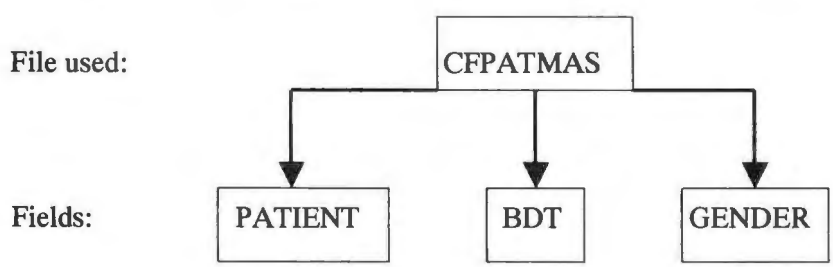

Figure 4.2c: Schematic representation of the database (continued)

- PATIENT: Patient number. The same number as the debtor number in the file CFINVH.
- BDT: Patient birth date. This is an indication of the patient's age.
- GENDER: Indicating whether a patient is male or female.

(ii) Drug interaction tables

Drug interaction tables were constructed and used as research instruments to identify and evaluate the drug interactions that occurred. The process followed in the construction of the tables, as well as the reliability and validity of the tables will be discussed.

- Structure of the drug interaction tables

  For the purpose of this study, specific interactions with the ten selected drugs at the medi centres were tabulated in the research process. Philani Prime Cure® provided the basic structure for the interaction tables according to the information that they require for the incorporation of the drug interactions into their treatment protocols (refer to Chapter 3, section 3.12).

- Description of the drug interaction tables

  The following information was needed to construct the tables:

  ~ The effects of patient variables (e.g. age) and disease states of the patients.

  ~ The concurrent use of food and other medication with the ten selected drugs.

  The information mentioned above was needed to indicate effects on the pharmacodynamic, pharmacokinetic and therapeutic actions of the specific drug. This information was gathered through a comprehensive literature study (refer to Chapter 3).

The clinical significance rating designed by Tatro (2001:xiv) was used to assign severity levels to the drug interactions where it was available. A number was assigned to each drug interaction that indicated the level of the interactions.

Three degrees of severity defined are defined (Tatro, 2001:xiv):

- Major – effects are potentially life threatening or capable of causing permanent damage.
- Moderate – effects may cause deterioration in a patient's clinical status, needing additional treatment.
- Minor – effects are bothersome or unnoticeable, without affecting therapeutic outcome.

According to Tatro (2001:xiv) documentation can determine the degree of confidence that an interaction can cause an altered clinical response. The scale is used to measure the quality and clinical relevance of an interaction. The following documentation levels have been established (Tatro, 2001:xv):

- Established: Proven to occur in well-documented studies.
- Probable: Very likely but not proven clinically.
- Suspected: May occur; some good data; needs more study.
- Possible: Could occur, but data are very limited.
- Unlikely: Doubtful, no good evidence of an altered clinical effect.

Drug interactions assigned documentation levels of "established", "probable" or "suspected" are considered to be reasonably well substantiated and have a significance rating of 1, 2 or 3. Drug

interactions assigned documentation levels of "possible" or "unlikely" are considered to be not substantiated and have significance rating of 4 or 5. The table 4.4 shows the formula for the significance levels.

Table 4.4: Significance levels (Tatro, 2001:xiv).

Significance rating	Severity	Documentation
1	Major	Suspected or greater
2	Moderate	Suspected or greater
3	Minor	Suspected or greater
4	Major/ Moderate	Possible
5	Minor Any	Possible Unlikely

The possible interactions between the selected drugs and the different age groups were also included in the interactions tables. Reliable literature sources were used to obtain the information needed for all the interactions. The source list is shown below.

(iii) Reliability and validity of the tables

The drug interaction tables were constructed from the following sources, namely:

1. STOCKLEY, I.H. 1991. Drug interactions: A source book of drug interactions; their mechanisms, clinical importance and management. 2nd ed. London : Blackwell Scientific Publications. 674p.

1.1. STOCKLEY, I.H. 1999. Drug interactions: A source book of drug interactions; their mechanisms, clinical importance and management. 5th ed. London : Pharmaceutical Press. 948p.

2. HANSTEN, P.D. & HORN, J.R. 1989. Drug interactions: Clinical significance of drug-drug interactions. 6th ed. London : Lea & Febiger. 631p.

3. HANSTEN, P.D. & HORN, J.R. 1990. Drug interactions and Updates. Pennsylvania : Lea & Febiger. 630p.

4. KATZUNG, B.G., *ed.* 1998. Basic and clinical pharmacology. 7 th ed. Connecticut : Appleton & Lange. 1151p.

5. TIERNEY, Jr. L.M., McPHEE, S.J. & PADADAKIS, M.A., *eds.* 1999. Current medical diagnosis and treatment. 38th ed. USA : Appleton & Lange. 1672p.

6. GIBBON, C.J. 2000. South African Medicines Formulary. 5th ed. South Africa : The health and medical publishing group of the South African Medical Association. 537p.

7. HARDMAN, J.G. & LIMBIRD, L.E., *eds.* 1996. Goodman & Gilman's The pharmacological basis of therapeutics. 9th ed. New York : McGraw-Hill. 1905p.

8. REYNOLDS, J.E.F. 1993. Martindale: The extra pharmacopoeia. London : Pharmaceutical Press. 2363p.
9. BOEHRINGER INGELHEIM. 2000. The NOCSA (National Olympic Committee of South Africa) quick guide 2000 to drug-free sport. Infosource. 169p.
10. TAKETOMO, C.K., HODDING, J.H. & KRAUS, D.M. 2001 Pediatric dosage handbook, including neonatal dosing, drug administration & extemporaneous preparations. 7th ed. Cleveland : American Pharmaceutical Association. 1458p.
11. SEMNIA, T.P., BEIZER, J.L. & HIGBEE, M.D. 1997. Geriatric dosage handbook including monitoring, clinical recommendations, and OBRA guidelines. 3rd ed. Cleveland : American Pharmaceutical Association. 968p.
12. PROWSKY, Z.M. 1997. Powers and Moore's food medication interactions. 10th ed. USA. 291p.
13. TATRO, D.S., *ed.* 1998. Drug interaction facts. St. Louis, Mo. : Facts and comparisons Publishing Group. 1226p.
14. TAKETOMO, C.K., HODDING, J.H. & KRAUS, D.M. 1997. Pediatric dosage handbook, including neonatal dosing, drug administration & extemporaneous preparations. 4th ed. Cleveland : American Pharmaceutical Association. 953p.
15. TATRO, D.S., *ed.* 2000. Drug interactions facts on disc V1.0 for Windows®. (*In* Microsoft Windows '97.) [CD-ROM].
16. ZUCCHERO, F.J., HOGAN, M.J. & SCHULTZ, C.D. 1999. Pocket guide to evaluations of drug interactions. 3rd ed. Washington : American pharmaceutical association. 450p.
17. TURNER, L., *ed.* 2001. Daily drug use. Revised edition. South Africa : Tincture press. 629p.
18. TATRO, D.S.,*ed.* 2001. Drug interaction facts. St. Louis, Mo. : Facts and comparisons Publishing Group. 1424p.

4.3.2.5 **Basic statistics**

For the purpose of the study the following basic statistics were used:

- *Average/mean value*

The mean or average of observations in data is defined as the sum of all the observations in the data divided by the number of observations (Kirkwood, 1988:12). The mean is denoted by $\bar{x}$ and is equal to:

$$\bar{x} = \frac{\sum x}{n}$$

Where $\sum x$ represent the sum of the observations and n the total number of observations (Steyn *et al.*, 1998:99).

♦ *Maximum and minimum*

According to Steyn and Ellis (2000:141) the maximum value is the largest observation of collected data and the minimum is the smallest value of the observation in the data.

♦ *Percentage*

Percentage is a proportion of the total observations multiplied by 100 (Reid, 1987:78).

♦ *Standard deviation*

The standard deviation is a measure of variation and is defined as the difference/deviation of the values from the mean value (Reid, 1987:77). The standard deviation is noted as *s* and is calculated as:

$$s = \sqrt{\frac{\sum\left(x - \bar{x}\right)^2}{n-1}}$$

Where *n* is the number of data points and $\sum\left(x - \bar{x}\right)^2$ is the sum of squares of the differences of each value from the mean, $\bar{x}$.

♦ *Chi-square test (x^2)*

Chi-square is a non-parametric statistical method that is used to determine whether the proportion or event rates of two or more groups are different. It is used when data are expressed in frequencies or may by reduced to frequencies. It may be used to test whether a significant difference exists between the observed frequencies in certain categories and what could be expected to occur by change (Jackson, 1981:99).

♦ *Difference between two group means (d-value)*

The effect of size (d) can be defined as the degree to which the phenomenon is present in the population (Cohen, 1988:9-10). The d-value can be calculated as follows (Steyn, 1998:3):

$$d = \frac{x1 - x2}{s1}$$

Where x1 and x2 are the two group means and s1 is the maximum standard deviation of the two groups. The following guidelines were used to evaluate the results:

- d = 0.2: small effect. (These results were non-significant).
- d = 0.3: medium effect. (These results were observable, which may reflect on significant differences).

- d = 0.8: large effect. (The results were significant and of practical importance).

- *Effect size for the relationship between two nominal variables (w-value)*

The following equation is used to calculate the effect size in this situation (Steyn, 1998:8):

$$w = \sqrt{\frac{x^2}{n}}$$

x^2 is the Chi-square value and n the number of observations. The results were interpreted as follows:

- w = 0.1: small effect (These results were non-significant).
- w = 0.3: medium effect. (These results were observable, which may reflect on significant differences).
- w = 0.5: large effect. (These results were significant and of practical importance).

4.4 CHAPTER SUMMARY

The research methodology used in the study was discussed in this chapter with emphasis on the methodology used for the empirical study. The empirical study was discussed in terms of the population group, data collection methods, data analysis, measuring instruments used (e.g. database) and the statistical tests used.

CHAPTER 5: RESULTS

In this chapter the results of the empirical study will be discussed. The results will be analysed in four areas, namely

- general information of patients (e.g. distribution of age, gender, etc.);
- the information of the medicine prescribed;
- the occurrence of the disease states; and
- the possible interactions (e.g. drug-drug interactions, etc.).

5.1 GENERAL INFORMATION OF PATIENTS

The general information of the patients that visited the seven Philani Prime Cure® medi centres during the six-month research period, namely, 1 January 2000 to 30 June 2000, will be discussed as follows:

- ♦ The total number of patients in the medi centres (refer to Table 5.1).
- ♦ The gender distribution of the patients (refer to Table5.2).
- ♦ The age distribution of the patients (refer to Table 5.3).
- ♦ The average, minimum and maximum age of the patients (refer to Table 5.4).

5.1.1 The total number of patients in the medi centres

Table 5.1 shows the total number of patients that visited the medi centres during the six-month research period, namely, 1 January 2000 to 30 June 2000.

Table 5.1: Total number of patients in each medi centre as percentage of the total number of patients that visited the seven medi centres.

Medi centres	Frequency (n = 29441)	% of patients per clinic
Brits	1508	5.12
Groblersdal	4517	15.34
Kwanobuhle	1297	4.41
Parow	7146	24.27
Pietersburg	5027	17.08
Rosslyn	5224	17.74
Verulam	4722	16.04
Total	**29441**	**100.00**

The total number of patients that visited the seven medi centres during the research period was 29441. Parow had the highest number (24.27%, n = 7146) of patients that visited the seven medi centres during the research period. Kwanobuhle had the lowest number of patients (4.41%, n = 1297).

For the purpose of this study the results shown in table 5.1 were used as an indicator of the relative size of the different medi centres. The sizes of the different medi centres were determined according

to the total number of patients that visited the medi centres. Demographic and geographical variables in the areas where the medi centres are situated were not accounted for in this study.

5.1.2 Gender distribution of patients

The results in table 5.2 show the gender distribution of the patients that visited the seven medi centres.

Table 5.2: Gender distribution of patients.

Medi centres	Female frequency (n = 16712)	%*	Male frequency (n = 12601)	%*	G	Total (n = 29313)	w**
Brits	793	52.97	704	47.03	11	**1497**	0.06
Groblersdal	2910	64.52	1600	35.48	7	**4510**	0.30
Kwano	654	51.82	608	48.18	35	**1262**	0.04
Parow	3858	53.99	3287	46.00	1	**7145**	0.10
Pietersburg	2916	58.11	2102	41.89	9	**5018**	0.20
Rosslyn	2755	53.27	2417	46.73	52	**5172**	0.07
Verulam	2826	60.01	1883	39.99	13	**4709**	0.20

** Percentage calculated according to the total number of patients that visited a specific medi centre during the research period.*

G = no gender indicated. These numbers indicate the details that have not been recorded in the medi centres.

*** Difference of practical significance: w > 0.5.*

During the research period, 1 January 2000 to 30 June 2000, female patients were more likely to visit the medi centres. The total number of females that visited the medi centres was 16712 (56.76%). The male patients represented 42.80% (n = 12601) of the total number of patients. In the case of 0.44% (n = 128) of the patients the gender was not indicated. The *Chi-Square test* was performed and the effect size (w) was calculated to determine if there was any practical significant difference between the total number of female and male patients that visited the different medi centres. No practical significant difference between the number of males and females was found during the research period.

5.1.3 Age distribution of patients

Philani Prime Cure® provided the division of the age groups. The age group divisions were discussed in Chapter 4, Table 4.2.

Table 5.3: Age group distribution of patients.

	Age groups															
Medi centres	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**G**	
	n	**%***	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**%***	**n**	**Total B**
Brits	19	2.41	47	3.47	94	4.98	105	6.02	1067	5.48	147	4.21	28	3.95		**1507**
Groblersdal	311	39.5	474	35	420	22.3	326	18.7	2531	13	332	9.51	123	17.4		**4517**
Kwano	24	3.05	83	6.13	139	7.37	116	6.65	792	4.07	126	3.61	20	2.82		**1297**
Parow	101	12.8	167	12.3	371	19.7	382	21.9	4858	25	1072	30.7	194	27.4	1	**7146**
Pietersburg	127	16.1	267	19.7	353	18.7	253	14.5	3548	18.2	395	11.2	84	11.9		**5027**
Rosslyn	125	15.9	188	13.9	272	14.4	266	15.3	3591	18.4	659	18.9	123	17.4		**5224**
Verulam	81	10.3	128	9.45	238	12.6	296	17	3083	15.8	760	21.8	136	19.2		**4722**
Total A	**788**	**100**	**1354**	**100**	**1887**	**100**	**1744**	**100**	**19470**	**100**	**3491**	**100**	**708**	**100**	**1**	**29440**
% ♦	**2.68**		**4.59**		**6.41**		**5.92**		**66.13**		**11.9**		**2.4**		**0**	**100**

Total A is the total number of patients in each age group in all seven medi centres.

Total B is the total number of patients of each individual medi centre.

** Percentage calculated according to the number of patients in each age group in all seven medi centres (total A).*

♦ Percentage calculated according to number of patients in the different age groups in all seven medi centres (n = 29440) (total B).

As shown in table 5.3 age group 5 (12-50 years) represents 66.13% (n = 19470) of the patients that visited the medi centres. It could be that this age group represents the working and economically active class of the society and Philani Prime Cure® may have contracts with companies to provide medical care to these patients. The age group with the smallest number of patients is age group 7 (older than 70 years), which represents 2.4% (n = 708) of the total population.

5.1.4 The average, minimum and maximum age of the patients

Table 5.4 illustrates the average, minimum and maximum age of the patients that visited the seven medi centres during the research period.

Table 5.4: The average, minimum and maximum age.

Medi centres	N	Mean age (years)	Standard deviation	Minimum age (years)	Maximum age (years)
Brits	1508	30.7	17.25	0.03	86.7
Groblersdal	4517	24.5	19.61	0.002	98.8
Kwanobuhle	1297	26.7	18.53	0.15	88.1
Parow	7146	32.8	18.23	0.24	98.7
Pietersburg	5027	28.1	16.86	0.04	93.9
Rosslyn	5224	32.2	17.73	0.02	95.2
Verulam	4722	32.4	18.77	0.005	99.0

The mean, minimum and maximum ages are calculated in years. The minimum age of the patients varies between 0.002 (Groblersdal) and 0.24 (Parow) years. The maximum age of the patients varies between 86.7 (Brits) and 99 years (Verulam). The average age of the patients varies between 24.5 ±

19.61 years and 32.8 ± 18.23 years in the different medi centres. The patients that visited the Parow medi centre had the highest mean age of 32.8 ± 18.23 years and the lowest mean age was at Groblersdal (24.5 ± 19.61 years) (refer to Table 5.4).

Table 5.5: Statistical d-values as indication of the differences of practical significance between the average ages of patients in the different medi centres.

Medi centres	Brits	Groblersdal	Kwanobuhle	Parow	Pietersburg	Rosslyn	Verulam
Brits		0.32	0.21	0.12	0.15	0.08	0.09
Groblersdal	0.32		0.11	0.42	0.18	0.39	0.4
Kwanobuhle	0.21	0.32		0.33	0.08	0.29	0.3
Parow	0.12	0.42	0.33		0.25	0.03	0.02
Pietersburg	0.15	0.18	0.08	0.25		0.22	0.24
Rosslyn	0.08	0.39	0.29	0.03	0.22		0.01
Verulam	0.09	0.40	0.30	0.02	0.24	0.01	

Difference of practical significance is d>0.8.

According to table 5.5 the d-value calculated (refer to Chapter 4, section 4.3.2.5) shows that there was no difference of practical significance found between the average ages of patients that visited the medi centres during the research period.

5.2 INFORMATION OF THE MEDICINE PRESCRIBED

The medicine prescribed over the six-month research period, in the seven medi centres will be discussed under the following headings:

- The total number of the medicine items prescribed in each medi centre (refer to Table 5.6).
- The average, minimum and maximum number of medicine items prescribed (refer to Table 5.7).
- The total number and percentage of patient visits where one or more medicine items were prescribed (refer to Table 5.9).
- The occurrence of the ten selected drugs in the different medi centres (refer to Table 5.10).

5.2.1 The total number of medicine items prescribed in each medi centre

The following table illustrates the total number of medicine items that was prescribed to patients in the different medi centres during the six-month research period.

Table 5.6: Total number of medicine items prescribed to the patients that visited the medi centres.

Medi centres	Total number of medicine items prescribed (n = 131081)	%*
Brits	9804	7.48
Groblersdal	20177	15.39
Kwanobuhle	6781	5.17
Parow	27233	20.78
Pietersburg	22513	17.17
Rosslyn	24770	18.90
Verulam	19803	15.11
Total	**131081**	**100.00**

** Percentage calculated according to the total number of medicine items prescribed (n = 131081).*

As indicated in Table 5.6 a total of 131081 medicine items were prescribed to 29441 patients that visited the seven medi centres during the six-month research period (refer to Table 5.1). Parow had the most medication prescribed during this research period (20.78%, n = 27233). It concurs with Table 5.1 that shows that Parow has the highest number of patients that visited the medi centres during the research period. Kwanobuhle has the smallest number of medicine items prescribed (5.17%, n = 6781).

5.2.2 The average, minimum and maximum number of medicine items prescribed to patients

The average, minimum and maximum number of medicine items prescribed per prescription will be illustrated in table 5.7.

Table 5.7: The average, minimum, maximum number of the medicine items prescribed per patient visit over the research period in the seven selected medi centres.

Medi centres	Total number of prescriptions	Mean	Standard deviation	Median	Minimum	Maximum
Brits	3312	2.95	1.34	3	1	12
Groblersdal	5677	3.55	1.14	4	1	8
Kwanobuhle	1968	3.45	1.47	3	1	10
Parow	8466	3.22	1.33	3	1	9
Pietersburg	6162	3.65	1.29	4	1	10
Rosslyn	7502	3.30	1.37	3	1	11
Verulam	5455	2.87	2.02	3	0	11

Table 5.7 reveals that the average number of medicine items prescribed varies between 2.87 ± 2.02 and 3.65 ± 1.29 medicine items per patient visit. Brits has the maximum number of medicine items prescribed per patient visit namely 12 items. No minimum number of items was prescribed at Verulam medi centre.

Table 5.8: Statistical d-values as indication of the differences of practical significance between the average number of medicine items prescribed in the medi centres.

Medi centres	Brits	Groblersdal	Kwanobuhle	Parow	Pietersburg	Rosslyn	Verulam
Brits		0.45	0.34	0.20	0.52	0.26	0.05
Groblersdal	0.45		0.07	0.25	0.08	0.18	0.34
Kwanobuhle	0.34	0.07		0.16	0.14	0.10	0.29
Parow	0.20	0.25	0.16		0.32	0.06	0.17
Pietersburg	0.52	0.08	0.14	0.32		0.26	0.39
Rosslyn	0.26	0.18	0.10	0.06	0.26		0.21
Verulam	0.05	0.34	0.29	0.17	0.39	0.21	

Difference of practical significance is d>0.8.

According to Table 5.8 the d-value calculated (refer to Chapter 4, section 4.3.2.5) shows that there was no difference of practical significance found between the average number of medicine items prescribed at the medi centres during the research period.

5.2.3 The total number and percentage of patient visits where one or more medicine item were prescribed

As illustrated in table 5.9 Brits is the only medi centre were 12 items where prescribed per patient visit and Verulam and Rosslyn have 11 items that were prescribed.

Table 5.9: Total number and percentage of prescriptions where one or more medicine items were prescribed.

		Items per visit												
Medi centres		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total A**
Brits	**n**	474	814	996	623	276	98	24	4	2	0	0	1	**3312**
	%*	14.3	24.6	30.1	18.8	8.33	2.96	0.72	0.12	0.06	0	0	0.03	
Groblersdal	**n**	281	630	1712	1970	911	148	23	2					**5677**
	%*	4.95	11.1	30.2	34.7	16.1	2.61	0.40	0.04					
Kwanobuhle	**n**	168	325	593	477	247	98	37	15	6	2			**1968**
	%*	8.54	16.5	30.1	24.2	12.6	4.98	1.88	0.76	0.30	0.10			
Parow	**n**	835	1764	2466	2035	966	311	78	9	2				**8466**
	%*	9.86	20.8	29.1	24.0	11.4	3.67	0.92	0.11	0.02				
Pietersburg	**n**	242	811	1854	1863	896	356	109	24	6	1			**6162**
	%*	3.93	13.2	30.1	30.2	14.5	5.78	1.77	0.39	0.10	0.02			
Rosslyn	**n**	734	1409	2137	1868	934	307	92	14	4	2	1		**7502**
	%*	9.78	18.8	28.5	24.9	12.5	4.10	1.23	0.19	0.05	0.03	0.01		
Verulam	**n**	374	954	1408	1289	775	400	189	56	6	3	1		**5455**
	%*	6.86	17.5	25.8	23.6	14.2	7.33	3.46	1.03	0.11	0.05	0.02		

** Percentage calculated according to the total number of prescriptions prescribed during the patients' visits to the medi centres.*

Total A = the total number of prescriptions at each medi centre.

As indicated in table 5.9 the patients received a maximum of 12 medicine items per visit (Brits) and a minimum of 1 medicine item per patient visit. The highest percentage of patients received between 2 and 4 medicine items per patient visit (Brits = 73.3%, Groblersdal = 76%, Kwanobuhle = 70.8%, Parow = 73.9%, Pietersburg = 73.5%, Rosslyn = 72.2% and Verulam = 66.9%).

5.2.4 The occurrence of the ten selected drugs in the medi centres

The ten selected drugs will be discussed according to their occurrence in the medi centres. As illustrated in Table 5.10 oxytetracycline is discussed as part of the ten selected drugs because doxycycline and oxytetracycline were from the same pharmacological group, namely, tetracycline (refer to Chapter 4, section 4.3.2.2).

Table 5.10: The occurrence of the ten selected drugs.

	The ten selected drugs											
Medi centres	**Diphenhydramine**	**Doxycycline**	**Oxytetracycline**	**Co-trimoxazole**	**Hyoscine**	**Theophylline**	**Loperamide**	**Glibenclamide**	**Multivitamin**	**Diclofenac**	**Reserpine**	**Total B**
Brits	955	204	34	377	69	39	69	37	121	414	1	**2320**
Groblersdal	1528	514	3	1969	50	125	37	78	676	411	90	**5481**
Kwanobuhle	612	106	21	184	51	103	36	20	100	243	7	**1483**
Parow	1250	541	10	1228	156	628	251	140	1048	1381	60	**6693**
Pietersburg	1444	666	22	884	143	464	91	85	880	936	21	**5636**
Rosslyn	1436	298	31	1060	170	531	151	175	498	794	6	**5150**
Verulan	933	161	32	680	503	439	157	110	324	1219	88	**4646**
Total A	**8158**	**2490**	**153**	**6382**	**1142**	**2329**	**792**	**645**	**3647**	**5398**	**273**	**31409**

Total A: Total of the individual drugs in all the medi centres.

Total B: Total of the ten drugs in each medi centre.

Table 5.11: Percentage of the ten selected drugs in the medi centres.

Ten selected drugs	Total of the individual drugs in all the medi centres	%*
Diphenhydramine	8158	25.97
Doxycycline	2490	7.93
Oxytetracycline	153	0.49
Co-trimoxazole	6382	20.32
Hyoscine	1142	3.64
Theophylline	2329	7.42
Loperamide	792	2.52
Glibenclamide	645	2.05
Multivitamin	3647	11.61
Diclofenac	5398	17.19
Reserpine	273	0.87
Total	**31409**	**100.00**

** Percentage calculated according to the total number of the ten individual drugs in all the medi centres (n = 31409).*

According to Table 5.10 and Table 5.11 the ten selected drugs amounted to 31409 (23.96%) of the total medication prescribed (n = 131081). The drug that is most prescribed in the seven medi centres is diphenhydramine (25.97%, n = 8158). The drug that shows the lowest prescription rate is oxyteteracycline (0.49%, n = 153). Oxytetracycline is placed second only because oxytetracycline and doxycycline are from the same pharmacological group, namely tetracycline. In this sense, reserpine is the least prescribed of these ten drugs (0.87%, n = 273).

Table 5.12: Percentage that the ten selected drugs represent of the total number of medicine items prescribed in the individual medi centres.

Medi centres	Total number of medicine items prescribed	Frequency**	%*
Brits	9804	2320	23.66
Groblersdal	20177	5481	27.16
Kwanobuhle	6781	1483	21.87
Parow	27233	6693	24.58
Pietersburg	22513	5636	25.03
Rosslyn	24770	5150	20.79
Verulam	19803	4646	23.46
Total	**131081**	**31409**	

** Percentage calculated according to the total number of medicine items prescribed in each individual medi centre.*

** *Frequency according to Total B-column of Table 5.10.*

As shown in Table 5.12 the ten selected drugs represented between 20.79% (Rosslyn) and 27.16% (Groblersdal) of the total number of medicine items prescribed in the individual medi centres.

Table 5.13: The percentage that the individual drugs contributed to the total number of medicine items (n = 131081) prescribed in all seven medi centres.

Drug names	Frequency	%*
Diphenhydramine	8158	6.22
Doxycycline	2490	1.90
Oxytetracycline	153	0.12
Co-trimoxazole	6382	4.87
Hyoscine	1142	0.87
Theophylline	2329	1.78
Loperamide	792	0.60
Glibenclamide	645	0.49
Multivitamin	3647	2.78
Diclofenac	5398	4.12
Reserpine	273	0.21
Total	**31409**	**23.96**

* *Percentage was calculated according to the total number of medicine items prescribed (n = 131081).*

The results in Table 5.13 indicate that diphenhydramine maintains the highest prescription rate in the medi centres (n = 8158). This is representative of 6.22% of the total number of medicine items prescribed (n = 131081) to patients that visited the seven medi centres during the research period. The drug the least prescribed in the medi centres is reserpine (n = 273, 021%). Refer to Chapter 4, section 4.3.2.2 for the discussion of oxytetracycline and reserpine. Table 5.12 shows what portion the ten selected drugs represent of the total number of medicine items prescribed in each medi centre and Table 5.13 shows what the ten selected drugs contributed to the total number of medicine items prescribed in all seven medi centres.

5.3 INFORMATION ON THE MEDICAL CONDITIONS OR DISEASE STATES DIAGNOSED DURING THE RESEARCH PERIOD

The information of all the medical conditions or disease states diagnosed in the medi centres will be discussed according to

- the total number of medical conditions or disease states diagnosed per medi centre (refer to Table 5.14);

- the total number of medical conditions or disease states diagnosed per patient visit (refer to Table 5.15);
- the average number of medical conditions or disease states diagnosed per patient visit (refer to Table 5.16);
- the ten most frequently diagnosed medical conditions or disease states per patient visit (refer to Table 5.18); and
- the top three medical conditions or disease states for which the ten selected drugs were prescribed in the seven medi centres (refer to Table 5.19 to 5.29).

5.3.1 Total number of medical conditions or disease states diagnosed per medi centre

Table 5.14 shows the number of medical conditions or disease states diagnosed in each of the seven medi centres during the six-month research period.

Table 5.14: The total number of medical conditions or disease states diagnosed in each of the seven medi centres.

Medi centres	Freqeuncy (n = 57455)
Brits	5690
Groblersdal	7815
Kwanobuhle	3041
Parow	11100
Pietersburg	10079
Rosslyn	12800
Verulam	6930
Total	**57455**

As indicated in Table 5.14 the total number of medical conditions or disease states diagnosed were 57455, over the research period in all seven medi centres. The medi centres with the most disease states diagnosed was Rosslyn with 12800 medical conditions or disease states (5224 patients visited Rosslyn). The results presented in table 5.14 include antenatal follow-ups, antenatal booking visits, family planning and general examination.

5.3.2 Number of medical conditions or disease states diagnosed per patient visit

Table 5.15: Percentage of patient visits where one or more medical conditions or disease states were diagnosed.

Number of medical conditions or disease states	Medi centres													
	Brits		Groblersdal		Kwanobuhle		Parow		Pietersburg		Rosslyn		Verulam	
	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*	n	%*
1	1974	56.2	4137	71.5	1372	66.1	6971	78.3	3508	56.2	4173	53.5	4394	78.9
2	1053	29.9	1320	22.8	495	23.8	1681	18.9	1875	30.1	2514	32.2	1014	18.2
3	361	10.3	296	5.11	172	8.28	237	2.66	655	10.5	898	11.5	147	2.64
4	101	2.88	35	0.60	30	1.44	14	0.16	155	2.49	187	2.40	13	0.23
5	19	0.54	2	0.03	6	0.29			33	0.53	30	0.38	3	0.05
6	2	0.06			1	0.05			7	0.11	0	0		
7	1	0.03			1	0.05			3	0.05	1	0.01		
8	0	0							1	0.02				
9	1	0.03												
Total	**3512**	**100**	**5790**	**100**	**2077**	**100**	**8903**	**100**	**6237**	**100**	**7803**	**100**	**5571**	

** Percentage calculated according to the total number of patient visits to each medi centre.*

As shown in table 5.15 the majority of the patients were diagnosed with one medical condition or disease state per patient visit (Brits = 56.2%, Groblersdal = 71.5%, Kwanobuhle = 66.1%, Parow = 78.3%, Pietersburg = 56.2%, Rosslyn = 53.5% and Verulam = 78.9%). In Brits (96.4%) and Parow (99%) of the patient visits with three or fewer medical conditions or disease states were diagnosed. Only at Brits (0.06%), Kwanobuhle (0.05%), Parow (0.07%) and Rosslyn (0.02%) were patients diagnosed with more than six medical conditions or disease states per patient visit.

5.3.3 The average number of medical conditions or disease states per patient visit

Table 5.16: Average number of disease states.

Medi centres	Total number of patient visits	Mean	Standard deviation	Median	Minimum	Maximum
Brits	3512	1.62	0.85	1	1	9
Groblersdal	5790	1.35	0.61	1	1	5
Kwanobuhle	2077	1.46	0.75	1	1	7
Parow	8903	1.25	0.49	1	1	4
Pietersburg	6237	1.62	0.84	1	1	8
Rosslyn	7803	1.64	0.81	1	1	7
Verulam	5571	1.24	0.51	1	1	5

According to table 5.16 the average number of medical conditions or disease states per patient visit varies between 1.24 ± 0.51 medial conditions or disease states at Verulam and 1.64 ± 0.81 medical conditions or disease states at Rosslyn. A minimum of one medical condition or disease state was made in all seven medi centres. A maximum of 9 medical conditions or disease states per patient visit was made at Brits medi centre.

Table 5.17: Statistical d-values as indication of the practically significant difference between the average number of medical conditions or disease states diagnosed per patient visit in the seven medi centres.

Medi centres	Brits	Groblersdal	Kwanobuhle	Parow	Pietersburg	Rosslyn	Verulam
Brits		0.32	0.19	0.43	0	0.02	0.45
Groblersdal	0.32		0.15	0.16	0.32	0.36	0.18
Kwanobuhle	0.19	0.15		0.28	0.19	0.22	0.29
Parow	0.43	0.16	0.28		0.44	0.48	0.02
Pietersburg	0	0.32	0.19	0.44		0.02	0.45
Rosslyn	0.02	0.36	0.22	0.48	0.02		0.49
Verulam	0.45	0.18	0.29	0.02	0.45	0.49	

Difference of practical significance is d>0.8.

According to table 5.17 there were no practically significant differences (refer to Chapter 4, section 4.3.2.5) between the average number of medical conditions or disease states diagnosed per patient visit in the seven medi centres during the research period.

5.3.4 Medical conditions or disease states diagnosed in the medi centres per patient visit

The ten most frequently diagnosed medical conditions or disease states are listed from the highest to lowest frequency in table 5.18.

Table 5.18: The most frequently diagnosed medical conditions or disease states.

	Brits		
	Medical conditions or disease states	**n**	**%***
1	Viral: influenza	565	9.93
2	Hypertension: new non-complicated	248	4.36
3	Arthralgia	213	3.74
4	Urinary tract infection	187	3.29
5	Subacute sinusitis	157	2.76
6	Cough	154	2.71
7	Tonsillitis	139	2.44
8	Backache: general considerations	119	2.09
9	Peptic ulceration	118	2.07
10	Severe tooth cavity	103	1.81
			♠35.20
	Groblersdal		
	Medical conditions or disease states	**n**	**%***
1	Upper respiratory tract	609	7.79
2	Hypertension: new non-complicated	473	6.05
3	Viral: influenza	442	5.66
4	Acute cystitis: non-pregnant	424	5.43
5	Pelvic inflammatory disease	289	3.70
6	Infection: Acute cystitis: pregnant	278	3.56
7	Infection: bronchitis: acute	278	3.56
8	Cough	148	1.89
9	Tonsillitis	148	1.89
10	Cystitis	144	1.84
			♠41.37
	Kwanobuhle		
	Medical conditions or disease states	**n**	**%***
1	Infection: bronchitis: acute	303	9.96
2	Viral: influenza	199	6.54
3	Upper respiratory tract	149	4.90
4	Hypertension: new non-complicated	132	4.34
5	Gastroenteritis	83	2.73
6	Low back pain	68	2.24
7	Acute sinusitis	52	1.71
8	Arthralgia	50	1.64
9	Gastritis: uncomplicated	49	1.61
10	Scabies	49	1.61
			♠37.28

Table 5.18 (continued)

	Parow		
	Medical conditions or disease states	**n**	**%***
1	Viral: influenza	1532	13.80
2	Urinary tract infection	431	3.88
3	Muscle pains	419	3.77
4	Arthralgia	418	3.76
5	Infection: bronchitis: acute	399	3.59
6	Low back pain	371	3.34
7	Gastroenteritis	370	3.33
8	Otitis media	283	2.55
9	Gastritis: uncomplicated	270	2.43
10	Acute sinusitis	204	1.84
			♠42.29
	Pietersburg		
	Medical conditions or disease states	**n**	**%***
1	Viral: influenza	584	5.79
2	Lower abdominal pain	495	4.91
3	Upper respiratory tract	475	4.71
4	Urinary tract infection	446	4.42
5	Lower respiratory infections	334	3.31
6	Cough	304	3.02
7	Headache: migraine	229	2.27
8	Muscle pains	218	2.16
9	Deep hands and feet burns	209	2.07
10	Low back pain	173	1.72
			♠34.38
	Rosslyn		
	Medical conditions or disease states	**n**	**%***
1	Viral: influenza	1013	7.91
2	Upper respiratory tract	652	5.09
3	Hypertension: new non-complicated	589	4.60
4	Infection: acute cystitis: pregnant	360	2.81
5	Muscle pains	357	2.79
6	Urinary tract infections	312	2.44
7	Acute cystitis: non-pregnant	282	2.20
8	Episodic weakness	253	1.98
9	Muscle trauma	237	1.85
10	Weakness	223	1.74
			♠33.41

Table 5.18 (continued)

	Verulam		
	Medical conditions or disease states	**n**	**%***
1	Upper respiratory tract	553	7.98
2	Arthralgia	386	5.57
3	Viral: influenza	334	4.82
4	Urinary tract infections	239	3.45
5	Infection: bronchitis: acute	203	2.93
6	Tonsillitis	183	2.64
7	Gastritis: uncomplicated	174	2.51
8	Acute tonsillitis	151	2.18
9	Cough	131	1.89
10	Impetigo	114	1.65
			♠35.62

** Percentage calculated according to the total number of medical conditions or disease states diagnosed per medi centre during the research period (refer to Table 5.12).*

♠ Percentage that the top ten medical conditions or disease states represent of the total number of medical conditions or disease states diagnosed in each medi centre (refer to Table 5.12).

According to table 5.18 influenza viral infections occurred under the top three medical conditions or disease states in the seven medi centres. That influenza viral infections ranged among the top three medical conditions or disease states is acceptable because the research period was partly in the winter months. During this period the influenza virus could lead to many infections. Throughout the seven medi centres one form or another of an upper respiratory tract infection occurred (e.g. cough, bronchitis, acute sinusitis). These medical conditions or disease states occurred in different combinations in the seven medi centres. Parow medi centre had the greatest variety of medical conditions or disease states (42.29%) diagnosed at a medi centre.

Tables 5.19 to 5.29 contain a summary of the top most three medical conditions or disease states for which the ten selected drugs were prescribed in each of the seven medi centres. The medical conditions or disease states were selected according to the frequency of diagnoses during the research period. As illustrated in the following tables, the top three medical conditions or disease states represent 25% or more of the total number of medical conditions or disease states diagnosed at each medi centre.

Table 5.19: Top 3 indications (medical conditions or disease states) for diphenhydramine in the individual medi centres.

DIPHENHYDRAMINE			
Nr	**Medical conditions or disease states**	**n**	**%***
BRITS			
1	Viral: Influenza	500	29.99
2	Cough	146	8.76
3	Infection: bronchitis: acute	88	5.28
		734	**44.03**
GROBLERSDAL			
1	Upper respiratory tract	409	19.26
2	Viral: Influenza	322	15.16
3	Infection: bronchitis: acute	243	11.44
		974	**45.86**
KWANOBUHLE			
1	Infection: bronchitis: acute	250	26.97
2	Viral: Influenza	133	14.35
3	Upper respiratory tract	115	12.41
		498	**♣53.73**
PAROW			
1	Viral: Influenza	835	49.58
2	Infection: bronchitis: acute	125	7.42
3	Upper respiratory tract	74	4.39
		1034	**♣61.39**
PIETERSBURG			
1	Viral: Influenza	408	16.13
2	Upper respiratory tract	342	13.52
3	Lower respiratory infections	259	10.24
		1009	**39.89**
ROSSLYN			
1	Viral: Influenza	661	26.42
2	Upper respiratory tract	421	16.83
3	Cough	108	4.32
		1190	**47.57**
VERULAM			
1	Upper respiratory tract	293	24.32
2	Viral: Influenza	189	15.68
3	Infection: bronchitis: acute	94	7.8
		576	**47.8**

** Percentage calculated according to the total number of medical conditions or disease states, for which diphenhydramine was prescribed during the research period (excluding antenatal follow-up, antenatal booking visit, family planning and general examination).*

♣ Indications where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states for which diphenhydramine was prescribed.

♠ Indications where the top three disease states represent less than 25% of the total number of disease states for which diphenhydramine was prescribed.

As indicated in table 5.19 the percentage of the top three medical conditions or disease states for which diphenhydramine was prescribed represents more than 25% for Brits (44.03%), Groblersdal (45.86%), Pietersburg (39.89%), Rosslyn (47.57%) and Verulam (47.80%). There were only two medi centres where the top three disease states represent more than 50% of the total number of disease states, namely, Kwanobuhle (53.73%) and Parow (61.39%). According to Gibbon (2000:467) and Taketomo *et al.* (2001:328) there is none of the top three disease states where diphenhydramine is not indicated.

Table 5.20: Top 3 indications (medical conditions or disease states) for doxycycline in the individual medi centres.

DOXYCYCLINE			
Nr	**Medical conditions or disease states**	**n**	**%***
BRITS			
1	Pelvic inflammatory disease	65	19.4
2	Lower abdominal pain	48	14.33
3	Urethral discharge	17	5.07
		130	**38.8**
GROBLERDAL			
1	Pelvic inflammatory disease	238	34.64
2	Chronic prostatitis	34	4.95
3	Infection: salpingitis	33	4.80
		305	**44.39**
KWANOBUHLE			
1	Pelvic inflammatory disease	31	18.67
2	Lower abdominal pain	10	6.02
	STD: bacterial urethritis	10	6.02
3	Gastroenteritis	9	5.42
	STD: urethritis in men	9	5.42
		69	**41.55**
PAROW			
1	Pelvic inflammatory disease	134	19.39
2	Infection: salpingitis	65	9.41
3	Vulvovaginitis: bacterial	61	8.83
		260	**37.63**
PIETERSBURG			
1	Lower abdominal pain	352	31.65
2	Vaginal discharge	87	7.82
3	Urethral discharge	63	5.67
		502	**45.14**
ROSSLYN			
1	Pelvic inflammatory disease	94	18.54
2	STD: urethritis in men	74	14.60
3	Cervix: cervicitis	34	6.71
		202	**39.85**

Table 5.20 (continued)

	VERULAM		
1	Infection: vulvovaginitis	18	8.57
	Pelvic inflammatory disease	18	8.57
2	STD: bacterial urethritis	14	6.67
3	Bacterial vulvovaginitis	8	3.81
	Candida: vaginitis	8	3.81
	Cough	8	3.81
	Gonorrhoea	8	3.81
	Lower abdominal pain	8	3.81
		90	**42.86**

* *Percentage calculated according to the total number of medical conditions or disease states, for which doxycycline was prescribed during the research period (excluding antenatal follow-up, antenatal booking visit, family planning and general examination).*

♣ *Indications where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states where doxycycline was prescribed.*

♠ *Indications where the top three medical conditions or disease states represent less than 25% of the total number of medical conditions or disease states where doxycycline was prescribed.*

It is evident from table 5.20 that the top three medical conditions or disease states where doxycycline was prescribed represent more than 25% of all the medical conditions or disease states for which the drug was prescribed during the research period. There are no medical conditions or disease states that are contraindicated for the use of doxycycline among the top three disease states (Gibbon, 2000:259). As indicated in Table 5.20 lower abdominal pain is one of the top three medical conditions or disease states at Brits and Pietersburg. Doxycycline is not usually used for the treatment of lower back pain, but doxycycline can treat urinary tract infections caused by *Klebsiella* organisms (Dollery, 1999:T67; Kapusnik-Uner *et al.*, 1996:1128) (refer to Chapter 3, section 3.2.4.) Lower back pain can therefore be a symptom of urinary tract infection.

Table 5.21: Top three indications (medical conditions or disease states) for oxytetracycline in the individual medi centres.

	OXYTETRACYCLINE		
Nr	**Medical conditions or disease states**	**N**	**%***
	BRITS		
1	Peptic ulceration	11	17.19
2	Subacute sinusitis	6	9.38
3	Tension headache	5	7.81
	Severe tooth cavity	5	7.81
		27	**42.19**

Table 5.21 (continued)

GROBLERDAL			
1	Acne vulgaris: severe	2	66.67
2	Lymphogranuloma venereum	1	33.33
		3	**♣100.00**
KWANOBUHLE			
1	Acne vulgaris: severe	7	18.92
2	Acne vulgaris: moderate: comedon	6	16.22
3	Acne vulgaris: mild	4	10.81
		17	**45.95**
PAROW			
1	Acne vulgaris: moderate: papules	4	28.57
2	Severe tooth cavity	3	21.43
3	Acne vulgaris: severe	1	7.14
		8	**♠57.14**
PIETERSBURG			
1	STD: bacterial urethritis	6	22.22
2	Urethral discharge	4	14.81
3	Bacterial vulvovaginitis	3	11.11
		13	**48.14**
ROSSLYN			
1	STD: urethritis in men	8	14.81
2	Vaginal discharge	7	12.96
3	Acne vulgaris: severe	4	7.41
		19	**35.18**
VERULAM			
1	Acne vulgaris: moderate: comedon	7	18.92
2	Acne vulgaris: moderate: cystic	5	13.51
	Acne vulgaris: severe	5	13.51
3	Acne vulgaris: moderate: papules	4	10.81
		21	**♠56.75**

* *Percentage calculated according to the total number of medical conditions or disease states, for which oxytetracycline was prescribed during the research period (excluding antenatal follow-up, antenatal booking visit, family planning and general examination).*

♣ *Indications where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states for which oxytetracycline was prescribed.*

♠ *Indications where the top three medical conditions or disease states represent less than 25% of the total number of medical conditions or disease states for which oxytetracycline was prescribed.*

According to table 5.21 there are three medi centres where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states diagnosed in the research period. These medi centres are Groblersdal (100%), Parow (57.14%) and Verulam (56.75%). The percentage of Groblersdal is 100% because the frequency differs from 2 and 1 implying that all the medical conditions or disease states can be counted under the top three disease states. 'No medical conditions or disease states are contraindicated for the use of oxytetracycline (Gibbon, 2000:259). There is none of the medi centres with less than 25% of the total number of

medical conditions or disease states where oxytetracycline was prescribed. In Table 5.21 tension headache and severe tooth cavity were indicated in the top three medical conditions or disease states at Brits and Parow. The patients suffering from the tension headache could have had an infection for which oxytetracycline was prescribed. The tension headache was probably the patient's primary symptom and reason for visiting the medi centres. In the Philani Prime Cure® database this information of the patient's symptoms could not be traced. It can also not be determined for which specific medical condition or disease state a specific drug was prescribed. Severe tooth cavity could take place because of a possible infection and therefore the oxytetracycline was prescribed to treat the infection. Refer to Chapter 3, section 3.2.4, for the indications for oxytetracycline.

Table 5.22: Top three indications (medical conditions or disease states) for co-trimoxazole in the individual medi centres.

CO-TRIMOXAZOLE			
Nr	**Medical conditions or disease states**	**n**	**%***
	BRITS		
1	Viral: Influenza	117	18.03
2	Urinary tract infection	95	14.64
3	Cough	21	3.24
		233	**35.91**
	GROBLERSDAL		
1	Upper respiratory tract	335	12.01
2	Acute cystitis: female	317	11.36
3	Viral: Influenza	288	10.32
		940	**33.69**
	KWANOBUHLE		
1	Viral: Influenza	46	16.73
2	Gastroenteritis	38	13.82
3	Upper respiratory tract	26	9.45
		110	**40.00**
	PAROW		
1	Urinary tract infection	352	20.21
2	Gastroenteritis	259	14.87
3	Viral: Influenza	209	12.00
		820	**47.08**
	PIETERSBURG		
1	Urinary tract infection	198	13.40
2	Upper respiratory tract	164	11.10
3	Lower respiratory infections	148	10.01
		510	**34.51**
	ROSSLYN		
1	Urinary tract infection	258	12.01
2	Acute cystitis: female	238	11.07
3	Upper respiratory tract	123	5.72
		619	**28.8**

Table 5.22 (continued)

VERULAM			
1	Urinary tract infection	194	20.55
2	Upper respiratory tract	73	7.73
3	Infection: viral gastroenteritis	59	6.25
		326	**34.53**

** Percentage calculated according to the total number of medical conditions or disease states, for which co-trimoxazole was prescribed during the research period (excluding antenatal follow-up, antenatal booking visit, family planning and general examination).*

♣ *Indications where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states for which co-trimoxazole was prescribed.*

♠ *Indications where the top three medical conditions or disease states represent less than 25% of the total number of medical conditions or disease states for which co-trimoxazole was prescribed.*

As indicated in table 5.22 all the top three medical conditions or disease states in the medi centres represent more than 25% of the total number of medical conditions or disease states where co-trimoxazole was prescribed during the research period. The top three disease states are all indicated for the use of co-trimoxazole (Gibbon, 2000:265). Co-trimoxazole is used for prophylaxis and treatment of abscesses and the treatment for respiratory tract infections (e.g., viral influenza). Refer to Chapter 3, section 3.3.4, for the therapeutic uses of co-trimoxazole.

Table 5.23: Top three indications (medical conditions or disease states) for hyoscine in the individual medi centres.

HYOSCINE			
Nr	**Medical conditions or disease states**	**n**	**%***
BRITS			
1	Spastic colon	19	13.77
2	Colic	18	13.04
3	Non-specific diarrhoea	5	3.62
	Constipation	5	3.62
		47	**34.05**
GROBLERSDAL			
1	Pain: dysmenorrhoea	9	13.24
2	Spastic colon	8	11.76
3	Pelvic inflammatory disease	7	10.29
		24	**35.29**
KWANOBUHLE			
1	Gastroenteritis	17	22.67
2	Gastritis: uncomplicated	10	13.33
3	Colic	6	8.00
		33	**44.00**

Table 5.23 (continued)

PAROW			
1	Gastroenteritis	79	38.92
2	Gastritis: uncomplicated	18	8.87
3	Non-specific diarrhoea	15	7.39
		112	**♣55.18**
PIETERSBURG			
1	Pain: dysmenorrhoea	54	22.22
2	Colic	22	9.05
3	Non-specific diarrhoea	12	4.94
	Lower abdominal pain	12	4.94
	Urinary tract infection	12	4.94
		112	**46.09**
ROSSLYN			
1	Pain: dysmenorrhoea	33	11.26
2	Urinary tract infection	18	6.14
3	Lower abdominal pain	17	5.80
		68	**♠23.2**
VERULAM			
1	Urinary tract infection	86	15.03
2	Gastritis: uncomplicated	83	14.51
3	Infection: viral gastroenteritis	48	8.39
		217	**37.93**

** Percentage calculated according to the total number of medical conditions or disease states, for which hyoscine was prescribed during the research period (excluding antenatal follow-up, antenatal booking visit, family planning and general examination).*

♣ Indications where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states for which hyoscine was prescribed.

♠ Indications where the top three medical conditions or disease states represent less than 25% of the total number of medical conditions or disease states for which hyoscine was prescribed.

As shown in table 5.23 the top three disease states where hyoscine was prescribed represent less than 25% of the total number of medical conditions or disease states which occurred in Rosslyn (23.2%). Parow was the only medi centre where the top three medical conditions or disease states represented more than 50% of the total number of medical conditions or disease states where hyoscine was prescribed. In all the other medi centres the top three disease states represent more than 30% of the total number of medical conditions or disease states where hyoscine was prescribed. The medical conditions or disease states are all indicated for the use of hyoscine (Gibbon, 2000:123). In Table 5.23 pelvic inflammatory disease and urinary tract infections occurred under the top three medical conditions or disease states in Groblersdal, Rosslyn and Verulam. According to Katzung (1998:112) hyoscine can be used for the relief of cramps occurring at pelvic and urinary infections. The main problem of the patients who visited the medi centres was pelvic inflammatory disease or urinary tract infections. Hyoscine was probably prescribed for the relief of some of the symptoms.

Table 5.24: Top three indications (medical conditions or disease states) for theophylline in the individual medi centres.

THEOPHYLLINE			
Nr	**Medical conditions or disease states**	**n**	**%***
BRITS			
1	Infection: bronchitis: acute	8	14.81
2	Infection: bronchopneumonia	5	9.26
3	Viral: Influenza	4	7.41
		17	**31.48**
GROBLERSDAL			
1	Infection: bronchitis: acute	75	54.35
2	# Hypertension	11	7.97
3	Cough	5	3.62
	Viral: Influenza	5	3.62
		96	**♣69.56**
KWANOBUHLE			
1	Infection: bronchitis: acute	41	29.29
2	Upper respiratory tract	15	10.71
	Viral: Influenza	15	10.71
3	# Hypertension	5	3.57
	Infection: bronchiolitis	5	3.57
		76	**♣57.85**
PAROW			
1	Viral: Influenza	237	33.33
2	Infection: bronchitis: acute	189	26.58
3	Cough	34	4.78
		460	**♣64.69**
PIETERSBURG			
1	Upper respiratory tract	137	19.66
2	Viral: Influenza	83	11.91
3	Cough	69	9.90
		289	**41.47**
ROSSLYN			
1	Viral: Influenza	210	25.36
2	Upper respiratory tract	100	12.08
3	Infection: bronchitis: acute	93	11.23
		403	**48.67**
VERULAM			
1	Upper respiratory tract	106	22.55
2	Infection: bronchitis: acute	73	15.53
3	Viral: Influenza	41	8.72
		220	**46.8**

** Percentage calculated according to the total number of medical conditions or disease states, for which theophylline was prescribed during the research period (excluding antenatal follow-up, antenatal booking visit, family planning and general examination).*

♣ Indications where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states for which theophylline was prescribed.

♠ Indications where the top three medical conditions or disease states represent less than 25% of the total number of medical conditions or disease states for which theophylline was prescribed.

 # Theophylline is not indicated for the disease state according to sources listed in Chapter 4.

As shown in table 5.24 there are three medi centres where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states where theophylline were prescribed. The medi centres are Groblersdal (69.56%), Kwanobuhle (57.85%) and Parow (64.69%). According to Gibbon (2000:458) hypertension is contraindicated with the use of theophylline. The medications taken by the patients who suffer from hypertension (e.g., propranolol) reduce the clearance of theophylline and toxicity can occur (Stockley, 1991:776). Groblersdal and Kwanobuhle have hypertension as one of the top three disease states. According to Table 5.24 viral influenza infection occurred as one of the top three medical conditions or disease states at all seven medi centres. According to Gibbon (2000:458) theophylline is primarily used for the relief of bronchospasm. The patients with influenza viral infection could have been treated for asthma. Their main problem was the viral infection. A limitation of the database is that medication is not separated according to the medical condition or disease state. The database does not allow the distinction between the treatment for the main medical condition or disease state and treatment of a symptom associated with the disease.

Table 5.25: Top three indications (medical conditions or disease states) for loperamide in the individual medi centres.

LOPERAMIDE			
Nr	**Medical conditions or disease states**	**n**	**%**
BRITS			
1	Non-specific diarrhoea	41	34.45
2	# Gastroenteritis	13	10.92
3	Chronic diarrhoea	9	7.56
		63	**+52.93**
GROBLERSDAL			
1	Non-specific diarrhoea	11	22.92
2	# Gastroenteritis	10	20.83
3	Chronic diarrhoea	3	6.25
	Pelvic inflammatory disease	3	6.25
		27	**+56.25**
KWANOBUHLE			
1	# Gastroenteritis	27	50
2	Gastritis: uncomplicated	4	7.41
3	Non-specific diarhhoea	3	5.56
		34	**+62.97**
PAROW			
1	# Gastroenteritis	188	55.62
2	Viral: Influenza	34	10.06
3	Non-specific diarhhoea	33	9.76
		255	**+75.44**

Table 5.25 (continued)

PIETERSBURG			
1	Non-specific diarrhoea	24	12.77
2	Acute diarrhoea	23	12.23
	Deep perineal burns	23	12.23
3	# Gastroenteritis	22	11.70
		92	**48.93**
ROSSLYN			
1	# Infection: viral gastroenteritis	63	20.79
2	Non-specific diarrhoea	37	12.21
3	# Gastroenteritis	20	6.60
		120	**39.6**
VERULAM			
1	# Infection: viral gastroenteritis	56	26.17
2	# Gastroenteritis	44	20.56
3	Non-specific diarrhoea	17	7.94
		117	**♣54.67**

** Percentage calculated according to the total number of medical conditions or disease states, for which loperamide was prescribed during the research period (excluding antenatal follow-up, antenatal booking visit, family planning and general examination).*

♣ Indications where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states for which loperamide was prescribed.

♠ Indications where the top three medical conditions or disease states represent less than 25% of the total number of medical conditions or disease states for which loperamide was prescribed.

 # Loperamide is not indicated for the disease state according to sources listed in Chapter 4.

In table 5.25 all the medi centres, except Pietersburg and Rosslyn, the top three medical conditions or disease states represented more than 50% of the total number of disease states where loperamide was prescribed. The percentage of the medi centres differs from 52.93% (Brits) to 75.44% (Parow). At all the medi centres one or two of the disease states show contraindications to the use of loperamide. These disease states are diarrhoea of an infective origin (e.g. gastroenteritis and viral gastroenteritis) (Gibbon, 2000:59). In Table 5.25 pelvic inflammatory disease, influenza infection and deep perineal burns were identified as part of the top three medical conditions or disease states. Loperamide is not indicated in Table 5.25 for one of the above mentioned disease states or medical conditions. It is possible that the patient was diagnosed with more than one medical condition or disease state. The medication cannot be separated according to the medical conditions or disease states. The possibility that the same patient was diagnosed with a viral infection and diarrhoea is possible. The database does not allow this distinction and above mentioned statement can thus not be confirmed. This shortcoming of the database places a definite limitation on the analytical capability of the system and should receive due attention.

Table 5.26: Top three indications (medical conditions or disease states) for glibenclamide in the individual medi centres.

GLIBENCLAMIDE			
Nr	**Medical conditions or disease states**	**n**	**%**
BRITS			
1	Diabetes mellitus: type 2: follow-up	24	28.92
2	Hypertension	13	15.66
3	Diabetes mellitus: type 2: new diagnosis	7	8.43
		44	**♣53.01**
GROBLERSDAL			
1	Diabetes mellitus: type 2: follow-up	18	19.78
2	Diabetes mellitus: non-insulin dependant	12	13.19
3	Diabetes mellitus: type 2: new diagnosis	11	12.09
		41	**45.06**
KWANOBUHLE			
1	Diabetes mellitus: type 2: follow-up	5	13.51
	Diabetes mellitus: type 2: new diagnosis	5	13.51
	Hypertension	5	13.51
2	Diabetes mellitus: non-insulin	2	5.41
	Heart failure: cardiomyopathy	2	5.41
	Osteoarthritis	2	5.41
3	Acne vulgaris: mild	1	2.70
		22	**♣59.46**
PAROW			
1	Diabetes mellitus: non-insulin dependant	59	29.35
2	Diabetes mellitus: type 2: follow-up	34	16.92
3	Diabetes mellitus: type 2: new diagnosis	12	5.97
		105	**♣52.24**
PIETERSBURG			
1	Diabetes mellitus: non-insulin dependant	51	27.57
2	Diabetes mellitus: type 2: follow-up	24	12.97
3	Osteoarthritis	10	5.41
		85	**45.95**
ROSSLYN			
1	Diabetes mellitus: non-insulin dependant	82	19.34
2	Diabetes mellitus: type 2: follow-up	72	16.98
3	Hypertension	65	15.33
		219	**♣51.65**
VERULAM			
1	Diabetes mellitus: non-insulin dependant	32	24.62
2	Diabetes mellitus: non-insulin	19	14.62
3	Arthralgia	15	11.54
		66	**♣50.78**

** Percentage calculated according to the total number of medical conditions or disease states, for which glibenclamide was prescribed during the research period (excluding antenatal follow-up, antenatal booking visit, family planning and general examination).*

♣ Indications where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states for which glibenclamide was prescribed.

♠ *Indications where the top three medical conditions or disease states represent less than 25% of the total number of medical conditions or disease states for which glibenclamide was prescribed.*

As shown in table 5.26 the top three disease states that represent more than 50 % of the total number of medical conditions or disease states where glibenclamide was prescribed occurred in Kwanobuhle (59.46%), Parow (52.24%), Rosslyn (51.65%) and Verulam (50.78%). There is none of the top three medical conditions or disease states that are contraindicated for the use of glibenclamide (Gibbon, 2000:70). In Table 5.26 hypertension, osteoarthritis, acne vulgaris and heart failure were indicated under the top three medical conditions or disease states in the medi centres. As discussed earlier, the possibility that the patient was diagnosed with more than one medical condition or disease state is still to be seen. The patient could easily be diagnosed with diabetes and receive glibenclamide as treatment and at the same time suffer from hypertension or one of the other disease states mentioned. The limitation of the database does not permit the analysis of this possibility.

Table 5.27: Top three indications (medical conditions or disease states) for multivitamin in the individual medi centres.

MULTIVITAMIN			
Nr	**Medical conditions or disease states**	**n**	**%***
BRITS			
1	Viral: Influenza	26	12.87
2	Weakness	13	6.44
3	Tonsillitis	10	4.95
		49	**24.26**
GROBLERSDAL			
1	Infection: acute cystitis: pregnant	98	13.23
2	Upper respiratory tract	78	10.53
3	Tonsillitis	34	4.59
		210	**28.35**
KWANOBUHLE			
1	Infection: bronchitis: acute	19	13.67
2	Viral: Influenza	10	7.19
3	Gastroenteritis	9	6.47
		38	**27.33**
PAROW			
1	Viral: Influenza	455	36.34
2	Infection: bronchitis: acute	112	8.95
3	Upper respiratory tract	59	4.71
		626	**50.00**
PIETERSBURG			
1	Viral: Influenza	107	7.21
2	Episodic weakness	88	5.93
3	Lower abdominal pain	64	4.31
		259	**♠17.45**

Table 5.27 (continued)

ROSSLYN			
1	Episodic weakness	228	22.37
2	Upper respiratory tract	97	9.52
3	Viral: Influenza	81	7.95
		406	**39.84**
VERULAM			
1	Upper respiratory tract	34	8.19
2	Viral: Influenza	31	7.47
3	Arthralgia	28	6.75
		93	**♠22.41**

* *Percentage calculated according to the total number of medical conditions or disease states, for which multivitamin was prescribed during the research period (excluding antenatal follow-up, antenatal booking visit, family planning and general examination).*

♣ *Indications where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states for which multivitamin was prescribed.*

♠ *Indications where the top three medical conditions or disease states represent less than 25% of the total number of medical conditions or disease states for which multivitamin was prescribed.*

As illustrated in table 5.27 the top three medical conditions or disease states that represent less than 25% of the total number of medical conditions or disease states where multivitamin was prescribed occurred in Pietersburg (17.45%) and Verulam (22.41%). The other medi centres had more than 25% of the total number of medical conditions or disease states where multivitamin was prescribed. The medical conditions or disease states that were indicated as one of the top three indications for multivitamin was not contraindicated for the use of multivitamin (referring to Chapter 3, section 3.8.1.4, 3.8.2.3, 3.8.3.3, 3.8.4.3 and 3.8.5.3.) The patients were diagnosed with these medical conditions or disease states and probably requested a multivitamin. The possibility could not be proved because of the limitation of the database.

Table 5.28: Top three indications (medical conditions or disease states) for diclofenac in the individual medi centres.

DICLOFENAC			
Nr	**Medical conditions or disease states**	**n**	**%**
BRITS			
1	Backache: general	86	11.57
2	Arthralgia	78	10.50
3	Mild/moderate dental abscess	54	7.27
		218	**29.34**

Table 5.28 (continued)

GROBLERSDAL			
1	# Hypertension	81	14.29
2	Chronic prostatitis	36	6.36
3	Acute cystitis: female	28	4.95
	Osteoathritis	28	4.95
		173	**30.55**
KWANOBUHLE			
1	Low back pain	35	9.21
2	Viral: Influenza	34	8.95
3	# Hypertension	27	7.11
		96	**25.27**
PAROW			
1	Muscle pains	303	19.31
2	Arthralgia	188	11.98
3	Low back pain	171	10.90
		662	**42.19**
PIETERSBURG			
1	Muscle pains	177	10.55
2	Low back pain	144	8.59
3	Backache: general	134	7.99
		455	**27.13**
ROSSLYN			
1	Muscle pains	209	14.08
2	# Hypertension	87	5.86
3	Muscle: trauma	86	5.80
		382	**25.74**
VERULAM			
1	Arthralgia	234	14.66
2	Upper respiratory tract	206	12.91
3	Viral: Influenza	118	7.39
		558	**34.96**

** Percentage calculated according to the total number of medical conditions or disease states, for which diclofenac was prescribed during the research period (excluding antenatal follow-up, antenatal booking visit, family planning and general examination).*

♣ Indications where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states for which diclofenac was prescribed.

♠ Indications where the top three medical conditions or disease states represent less than 25% of the total number of medical conditions or disease states for which diclofenac was prescribed.

 # Diclofenac is not indicated for the medical conditions or disease state according to sources listed in Chapter 4.

Hypertension is the only disease state in the top three medical conditions or disease states that is contraindicated for the use of diclofenac (Gibbon, 2000:324). In table 5.28 it shows that Groblersdal, Kwanobuhle and Rosslyn have hypertension as one of their top three medical conditions or disease states. According to Gibbon (2000:325) the efficiency of the antihypertensive therapy is markedly

attenuated. All the medi centres have more than 25% of the total number of medical conditions or disease states that were diagnosed where diclofenac was prescribed. In Table 5.28 influenza infection and upper respiratory tract infection were part of the top three medical conditions or disease states. As with hypertension, these two medical conditions occurred because the patients were probably diagnosed with one or more medical condition or disease state. Diclofenac is indicated for the relief of pain and could be given for pain with the infections. Refer to Chapter 3, section 3.9.4, for the therapeutic use of diclofenac.

Table 5.29: Top three indications (medical conditions or disease states) for reserpine in the individual medi centres.

RESERPINE			
Nr	**Medical conditions or disease states**	**n**	**%**
	BRITS		
1	Hypertension	1	50.00
2	# Peptic ulceration	1	50.00
		2	**+100.00**
	GROBLERSDAL		
1	Hypertension	56	47.46
2	Acute cystitis: female	5	4.24
	Diabetes mellitus: type 2: follow-up	5	4.24
	Low back pain	5	4.24
3	Diabetes mellitus: type 2: new diagnosis	4	3.39
	Viral: Influenza	4	3.39
		79	**+66.96**
	KWANOBUHLE		
1	Chronic gout	3	27.27
	Hypertension	3	27.27
2	Fungal infection: tinea cruris	2	18.18
3	Arthralgia	1	9.09
	Diabetes mellitus: non-insulin dependent	1	9.09
	Diabetes mellitus: insulin dependant	1	9.09
		11	**+100.00**
	PAROW		
1	Viral: Influenza	8	13.56
2	Urinary tract infection	6	10.17
3	Muscle pains	5	8.47
		19	**32.2**
	PIETERSBURG		
1	Bites: dog	5	14.71
2	Hypertension	4	11.76
3	Diabetes mellitus: type 2: follow-up	2	5.88
	Diabetes mellitus: non-insulin dependent	2	5.88
	Lower abdominal pain	2	5.88
	Urinary tract infection	2	5.88
		17	**49.99**

Table 5.29 (continued)

ROSSLYN			
1	Hypertension	6	46.15
2	Diabetes mellitus: type 2: follow-up	3	23.08
3	Acute cystitis: female	2	15.38
		11	**♣84.61**
VERULAM			
1	Arthralgia	10	13.16
2	Diabetes mellitus: non-insulin dependent	9	11.84
3	Bites: dog	4	5.26
	# Peptic ulceration	4	5.26
		27	**35.52**

* *Percentage calculated according to the total number of medical conditions or disease states, for which reserpine was prescribed during the research period (excluding antenatal follow-up, antenatal booking visit, family planning and general examination).*

♣ *Indications where the top three medical conditions or disease states represent more than 50% of the total number of medical conditions or disease states for which reserpine was prescribed.*

♠ *Indications where the top three medical conditions or disease states represent less than 25% of the total number of medical conditions or disease states for which reserpine was prescribed.*

#Reserpine is not indicated for the medical conditions or disease state according to sources listed in Chapter 4.

Peptic ulceration is contraindicated when using reserpine (Turner, 2001:165). According to Benowitz (1998:163) reserpine increases gastric acid secretion and patients with peptic ulceration must not use reserpine. The effect of reserpine on peptic ulcers forms a part of the toxicity of reserpine. Peptic ulceration forms part of the top three medical conditions or disease states in Brits and Verulam medi centres. In table 5.29 the top three medical conditions or disease states that represent more than 50% of the total number of medical conditions or disease states where reserpine was prescribed were in Brits (100%), Kwanobuhle (100%) and Rosslyn (84.61%). Brits and Kwanobuhle have a percentage of 100% because the frequency differ from 1 (Brits) and from 3 to 1 (Kwanobuhle) implying that all the disease states can be counted under the top three medical conditions or disease states.

In Table 5.29 the following medical conditions or disease states were identified as part of the top three indications for reserpine. These medical conditions or disease states were diabetes mellitus, low back pain, chronic gout, dog bites, urinary tract infection, cystitis, fungal infection, influenza infection and muscle pains. The patients were probably diagnosed with more than one medical condition or disease state, for example the patient suffers from hypertension (indication for reserpine) and had an urinary infection. The database does not allow for the separation of the different diagnoses and it seems as if reserpine was prescribed for the above mentioned medical conditions or disease states.

5.4 INFORMATION ON DIFFERENT INTERACTIONS THAT OCCURRED DURING THE RESEARCH PERIOD

The interactions discussed consist of the following:

- The interactions that occurred between the ten selected drugs and the different age groups (refer to Tables 5.30 and 5.31).
- The number of different types of drug-drug interactions that occurred with the ten selected drugs (refer to Table 5.32).
- The number of drug-drug interactions identified on prescriptions according to the significance levels (refer to Tables 5.33 and 5.34).
- Different drug-drug interactions with significance levels 1 to 3 that occurred with the ten selected drugs (refer to Table 5.35).
- The medical conditions or disease states where the drug-drug interactions appeared (refer to section 5.4.3 and Appendix A).

5.4.1 Interactions that occurred between the ten selected drugs and the different age groups

In table 5.30 the total number of patients in the different age groups, that received one or more of the selected drugs is summarised.

Table 5.30: The total number of patients in the different age groups that received the selected ten drugs.

	Selected drugs										
Age groups	**Diphenhydramine**	**Doxycycline**	**Oxytetracycline**	**Co-trimoxazole**	**Hyoscine**	**Theophylline**	**Loperamide**	**Glibenclamide**	**Multivitamin**	**Diclofenac**	**Reserpine**
	N										
1	163	0	0	296	0	99	0	0	61	0	0
2	561	1	0	645	2	133	0	0	331	3	0
3	958	2	0	670	2	188	4	0	472	7	0
4	775	2	1	381	18	176	33	0	276	28	0
5	4792	2308	142	3406	899	1311	652	293	2084	3350	93
6	698	160	9	769	116	332	88	293	319	1282	136
7	157	12	1	203	22	80	13	58	94	260	44
Total	**8104**	**2485**	**153**	**6370**	**1059**	**2319**	**790**	**644**	**3637**	**4930**	**273**

N = Total number of patients in the different age groups that received the selected drugs during the research period.

Table 5.31: Age group distribution.

Groups	Age included
1	Younger than 6 months
2	Older than 6 months and younger than 2 years
3	Older than 2 and younger than 6 years
4	Older than 6 and younger than 12 years
5	Older than 12 and younger than 50 years
6	Older than 50 and younger than 70 years
7	Older than 70 years

Table 5.32: Percentage of the patients in the different age groups that received the selected drugs.

	Selected drugs										
	Diphenhydramine	Doxycycline	Oxytetracycline	Co-trimoxazole	Hyoscine	Theophylline	Loperamide	Glibenclamide	Multivitamin	Diclofenac	Reserpine
Age groups	%										
1	2.01	0	0	4.65	0	4.27	0	0	1.68	0	0
2	6.92	0.04	0	10.1	0.19	5.74	0	0	9.10	0.06	0
3	11.8	0.08	0	10.5	0.19	8.11	0.51	0	13.0	0.14	0
4	9.56	0.08	0.65	5.98	1.70	7.59	4.18	0	7.59	0.57	0
5	59.1	92.9	92.8	53.5	84.9	56.5	82.5	45.5	57.3	68.0	34.1
6	8.61	6.44	5.88	12.1	11.0	14.3	11.1	45.5	8.77	26.0	49.8
7	1.94	0.48	0.65	3.19	2.08	3.45	1.65	9.0	2.58	5.27	16.1
Total	100	100	100	100	100	100	100	100	100	100	100

** Percentage calculated according to the total number of patients that received the selected drugs during the research period.*

According to tables 5.30 and 5.32 age group 5 (older than 12 and younger than 50 years) had the most patients that received the ten selected drugs. Most of the patients received diphenhydramine (n = 8104).

- **Diphenhydramine**

The following age groups cannot use diphenhydramine, namely age group one (younger than 6 months), two (older than 6 months and younger than 2 years), six (older than 50 and younger 70 years) and seven (older than 70 years). Age groups one (n = 163, 2.01%), two (n = 561, 6.92%), six (n = 698, 8.61%) and seven (n = 157, 1.94%) had interactions with diphenhydramine (refer to Tables

5.30 and 5.32). According to Gibbon (2000:467) diphenhydramine's use is not recommended to children under the age of two years. Diphenhydramine in patients two years and younger can cause central nervous system stimulation, which includes seizures, hallucinations and dystonic reactions (Gibbon, 2000:467). The elderly patients in group six (older than 50 and younger than 70 years) and seven (older than 70 years) are more prone to the anticholinergic effects of antihistamine. Diphenhydramine has high sedative and anticholinergic properties, so it may not be considered the antihistamine of choice for use in the elderly (Semla *et al.*, 1998:272). Diphenhydramine must be used with caution and lower doses are recommended for patients older than 50 years (Gibbon, 2000:467). Age groups three, four and five can use diphenhydramine, thus, patients older than 2 years and younger than 50 years of age are safe to use diphenhydramine (Semla *et al.*, 1998:272).

♦ **Doxycycline and oxytetracycline**

Doxycycline and oxytetracycline will be discussed together as they are both from the same pharmacological group, namely, tetracycline. The following age groups cannot use doxycycline, namely, age groups two (older than 6 months and younger than 2 years), three (older than 2 years and younger than 6 years), four (older than 6 years and younger than 12 years) and seven (older than 70 years). Age groups two (n = 1, 0.04%), three (n = 2, 0.08%), four (n = 2, 0.08%) and seven (n = 12, 0.48%). The following age groups that cannot use oxytetracycline are age groups four (n = 1, 0.65%) (older than 6 years and younger than 12 years) and seven (n = 1, 0.65%) (older than 70 years) (refer to Tables 5.30 and 5.32). According to Taketomo *et al.* (2001:349) and Gibbon (2000:259) doxycycline and oxytetracycline are contraindicated to children under the age of eight. Doxycycline and oxytetracycline can cause retardation in skeletal development, permanent discoloration of the teeth and enamel hypoplasia in children younger than 8 years of age (Taketomo *et al.*, 1998:264). Doxycycline and oxytetracycline are contraindicated for the frail or elderly patients. The elderly patients are more susceptible to the hepatotoxic and antianabolic effects of doxycycline (Gibbon, 2000:259).

According to Taketomo *et al.* (1998:264) doxcycline is safe to be used by patients older that 12 years and younger than 70 years. Doxycycline was not prescribed during the research period to age group one (younger than 6 months), but these patients cannot use doxycycline as already explained. Oxytetracycline was not prescribed to the following age groups during the research period, namely, age groups one to three (younger than 6 years), five (older than 12 years and younger than 50 years) and six (older than 50 years and younger than 70 years).

♦ **Co-trimoxazole**

The following age groups cannot use co-trimoxazole, namely age groups one (younger than 6 months) and seven (older than 70 years). Age group one had 296 (4.65%) and age group seven had 203

(3.19%) interactions with co-trimoxazole (refer to Tables 5.30 and 5.32). According to Gibbon (2000:264) co-trimoxazole is contraindicated for infants of 1 to 2 months. These patients are at risk of kernicterus. The elderly appear to be at risk of adverse effects of co-trimoxazole (Gibbon, 2000:266). Elderly patients can have an increased risk of problems with their renal function, thus the dosage must be adjusted accordingly (Semla *et al.*,1998:226). The patients with age ranging from older than 6 months and younger than 70 years can use co-trimoxazole (Taketomo *et al.*, 1998:197).

♦ **Hyoscine**

The age groups that cannot use hyoscine are age groups two (older than 6 months and younger than 2 years) and seven (older than 70 years). Age groups two had 2 (0.19%) and age group seven had 22 (2.08%) interactions with hyoscine (refer to Tables 5.30 and 5.32). According to Taketomo *et al.* (2001:498) the use of hyoscine is not recommended for children. According to Gibbon (2000:123) hyoscine causes anticholinergic side effects in the elderly patients. According to Semla *et al.* (1998:426) the anticholinergic effects (e.g. tachycardia, confusion, respiratory depression) of hyoscine are too severe for these two age groups. According to Table 5.30 hyoscine was not prescribed in regard to age group one (younger than 6 months). The age groups three to six (older than 2 years and younger than 70 years) can use hyoscine (Taketomo *et al.*, 1998:380).

♦ **Theophylline**

The age groups where it is not safe to use theophylline are age groups one (younger than 6 months), six (older than 50 years and younger than 70 years) and seven (older than 70 years). Age groups one (n = 99, 4.27), six (n = 332, 14.3%) and seven (n = 22, 3.45%) had interactions with theophylline (refer to Tables 5.30 and 5.32). According to Gibbon (2000:459) theophylline must be used with caution in neonates. The hepatic metabolism of theophylline is decreased in neonates and thus leading to toxicity of theophylline (Taketomo *et al.*, 1998:708). Behavioural and cognitive functions in children may be affected adversely (Gibbon, 2000:459). According to Gibbon (2000:459) the elderly patients are at risk of increased toxicity of theophylline, because of decreased plasma clearance. Lower initial doses are recommended because the elderly have slower hepatic clearance (Semla *et al.*, 1998:799). Patients older than 6 months and younger than 50 years of age can use theophylline (Taketomo et al., 1998:708).

♦ **Loperamide**

The age groups that cannot use loperamide are age groups three (older than 2 years and younger than 6 years), four (older than 6 years and younger than 12 years) and seven (older than 70 years). Age groups three (n = 4, 0.51%), four (n = 33, 4.18%) and seven (n = 13, 1.65%) had interactions with loperamide (refer to Tables 5.30 and 5.32). According to Gibbon (2000:59) loperamide causes sedation and dehydration. The use of loperamide is not recommended for children. Loperamide is

contraindicated for elderly patients (Gibbon, 2000:59). According to Semla *et al.* (1998:498) the elderly are particularly sensitive to fluid and electrolyte loss. This generally results in lethargy, weakness and confusion. Repletion and maintenance of electrolytes and water are essential in the treatment of diarrhoea. Drug therapy must be limited in elderly patients in order to avoid toxicity of loperamide. According to Table 5.30 loperamide was not prescribed to patients in age groups one (younger than 6 months) and two (older than 6 months and younger than 2 years). Loperamide can be used by patients from the age of 12 years and younger than 70 years.

♦ **Glibenclamide**

The only age group that cannot use glibenclamide is age group seven (n = 58, 9.0%) (older than 70 years) (refer to Tables 5.30 and 5.32). According to Tierney *et al.* (1999:1129) glibenclamide must be avoided in elderly patients. According to Semla *et al.* (1998:388) age, hepatic and renal impairment are independent factors of hypoglycaemia, thus, dosage titration should be made at weekly intervals. This makes the treatment of type II diabetes difficult. It depends on the patients' functional and cognitive status and how well they recognise hypoglycaemic or hyperglycaemic symptoms. According to Table 5.30 glibenclamide was not prescribed to age groups one (younger than 6 months) to four (older than 6 months and younger than 12 years). According to Gibbon (2000:69) age groups five (older than 12 years and younger than 50 years) and six (older than 50 years and younger than 70 years) can use glibenclamide to treat type II diabetes mellitus.

♦ **Multivitamins**

The age groups where the use of multivitamin is not recommended are age groups one (n = 61, 1.68%) (younger than 6 months), two (n = 331, 9.1%) (older than 6 months and younger than 2 years) and seven (n = 94, 2.58%) (older than 70 years) (refer to Tables 5.30 and 5.32). According to Gibbon (2000:83) and Taketomo *et al.* (2001:981) multivitamins are not recommended for use in infants, especially vitamin A and C. The infants could experience haemolysis. According to Gibbon (2000:78-79) vitamins A and D must be used with caution for children between six and twelve months of age. A hypersensitivity reaction with hypercalcaemia and hypercalciuria can occur in infants. According to Prowsky (1997:223) elderly patients have an increased requirement for thiamine. The age groups three to six (patients older than 2 years and younger than 70 years) can use multivitamins (Gibbon, 2000:81).

♦ **Diclofenac**

Age group seven (n = 260, 5.27%) (older than 70 years) is the only group that cannot use diclofenac (refer to Tables 5.30 and 5.32). According to Gibbon (2000:324) diclofenac must be used with caution in elderly patients. The lowest effective dose must be used with elderly patients. The renal function decline with age must be considered. Central nervous effects such as confusion, agitation

and hallucination are generally seen in high dose situations, but the elderly may demonstrate these adverse effects at lower doses than younger adults (Semla *et al.,* 1998:254). According to Table 5.30 diclofenac was not prescribed to age group one (younger than 6 months). The age groups two to six (patients older than 6 months and younger than 70 years) can use diclofenac but not age group seven (Taketomo *et al.,* 1998:236).

♦ **Reserpine**

The age groups that must use reserpine with caution are age groups six (older than 50 years and younger than 70 years) and seven (older than 70 years). According to Turner (2001:165) reserpine must be used with caution in the elderly because the dosage needs adjustment. The elderly have an increased sensitivity for the central nervous system effects (e.g., drowsiness, headache) and hypotensive effects of reserpine (Gibbon, 2000:124). According to Table 5.30 reserpine was not prescribed to age groups one to four (younger than 6 months and younger than 12 years). Reserpine is indicated for age group five (older than 12 years and younger than 50 years) (Gibbon, 2000:124). Age group five (n = 93, 34.1%) is the only age group that can use reserpine for the treatment of hypertension (refer to Chapter 3, section 3.10.4).

5.4.2 **Drug-drug interactions that occurred during the research period**

The total number of different interactions that occured between the identified ten selected drugs and other drugs, for the seven medi centres, is displayed in table 5.33.

Table 5.33: The number of different types of interactions that occurred with the selected drugs in each of the medi centres.

Medi centre	Diphenhydramine	Doxycycline	Oxytetracycline	Co-trimoxazole	Hyoscine	Theophylline	Loperamide	Glibenclamide	Vultivitamin	Diclofenac	Reserpine	Total number of different types of interactions per medi centre
	Number of different types of interactions											
Brits	4	7	3	5	5	7	5	6	7	12	0	**61**
Groblersdal	4	8	0	6	2	7	5	6	5	13	3	**59**
Kwanobuhle	3	3	2	3	4	6	4	5	2	12	0	**53**
Parow	2	13	2	4	3	10	4	7	8	11	3	**89**
Pietersburg	3	5	0	3	4	9	5	8	10	9	1	**66**
Rosslyn	4	6	1	3	4	14	4	10	10	12	1	**69**
Verulam	3	6	2	2	4	10	4	8	6	15	2	**62**
Total of interactions	**23**	**48**	**10**	**26**	**26**	**63**	**31**	**50**	**48**	**84**	**10**	**459**

According to Table 5.33 Parow medi centre proved to have the greatest variety of different types of drug-drug interactions (n = 89) and Kwanobuhle has the smallest number of different types of drug-drug interactions (n = 53) during the research period. The drug that had the highest presentation of different types of drug-drug interactions was diclofenac, with a total of 84 interactions.

The drug-drug interactions that can occur between the ten selected drugs and other drugs were discussed in Chapter 3. Drug interactions were rated on a scale of significance levels from 1 to 5, where level 1 is the most severe interaction that can occur, and level 5 the least severe (minor) and unlikely interactions to occur. Level 2 indicates a moderate suspected interaction and level 3 indicates a minor suspected interaction. The interactions discussed in this chapter occurred in levels 1 to 3. Level 6 is used to indicate that there is no level of significance indicated in the references that were used to construct the drug interaction tables in Chapter 3. In these cases further investigation is necessary.

Table 5.34: Total number of drug-drug interactions identified on prescriptions according to the significance levels.

Significance level	Diphenhydramine	Doxycycline	Oxytetracycline	Co-trimoxazole	Hyoscine	Theophylline	Loperamide	Glibenclamide	Multivitamin	Diclofenac	Reserpine	Total
	Different types of interactions											
1	0	234	12	0	0	16	0	0	0	0	0	**262**
2	0	15	1	1	0	190	0	81	0	280	8	**576**
3	0	25	5	27	0	71	0	71	465	0	5	**669**
4	0	107	5	0	202	83	0	12	2	0	0	**411**
5	0	55	1	0	0	540	0	40	93	1140	0	**1869**
6	7832	7	1	360	231	36	897	91	189	944	74	**10662**

Table 5.35 shows the total number of drug-drug interactions of levels 1 to 6.

Table 5.35: Number of significance level 1 to 6 interactions as percentage of the total number of medicine items (n = 131081) prescribed and of the total number of drug-drug interactions that occurred during the research period (n = 14449).

Significance level	Number of interactions	%*	%♣
1	262	0.19	1.81
2	576	0.44	3.99
3	669	0.51	4.63
4	411	0.31	2.84
5	1869	1.43	12.94
6	10662	8.13	73.79
Total	**14449**	**11.01**	**100.00**

** Percentage (%*) calculated according to the total number of medicine items (n = 131081) prescribed during the research period.*

♣ Percentage (%♣) calculated according to the total number of drug-drug interactions (n = 14449) that occurred during the research period.

According to table 5.35 level 6 interactions outnumber the remaining significance levels. It represented 8.13% of the total number of medicine items prescribed and 73.79% (n = 10662) of the total number of drug-drug interactions. As no significance level was given in the literature used for the purpose of this study, the level 6 interactions were not taken into consideration when discussing the drug-drug interactions.

For the purpose of this study only drug-drug interactions with significance levels 1 to 3 will be discussed in more detail, because interactions with significance levels of 4 and 5 are not substantiated, having documentation levels of possible and unlikely (Tatro, 1998:xvii). Table 5.36 indicates the different drug-drug interactions that occurred in the seven medi centres according to significance levels 1 to 3.

Table 5.36: Identified drug-drug interactions with significance levels 1 to 3.

Level	Drug-drug interactions	Brits	Groblersdal	Kwanobuhle	Parow	Pietersburg	Rosslyn	Verulam	Total A	%
1	Doxycycline - Antacids	5	9	2	18	14	19	8	75	0.52
	Doxycycline - Penicillins	0	0	0	2	127	28	1	158	1.09
	Doxycycline - Digoxin	1	0	0	0	0	0	0	1	0.007
	Oxytetracycline - Antacids	9	0	0	1	0	0	0	10	0.07
	Oxytetracycline - Penicillins	0	0	0	2	0	0	0	2	0.01
	Theophylline - Cimetidine	0	0	1	2	1	5	7	16	0.11

Table 5.36 (continued)

Level	Drug-drug interactions	Brits	Groblersdal	Kwanobuhle	Parow	Pietersburg	Rosslyn	Verulam	Total A	%
2	Doxycycline - Oral contraceptives	0	1	0	5	0	0	0	6	0.04
	Doxycycline - Calcium	0	1	0	2	0	2	2	7	0.05
	Doxycycline - Phenytoin	0	0	1	0	0	0	0	1	0.007
	Doxycycline - Carbamazepine	1	0	0	0	0	0	0	1	0.007
	Oxytetracycline - Oral contraceptives	0	0	1	0	0	0	0	1	0.007
	Co-trimoxazole - Phenobarbitone	0	1	0	0	0	0	0	1	0.007
	Theophylline - Carbamazepine	0	0	0	0	0	1	0	1	0.007
	Theophylline - Furosemide	0	5	0	3	0	2	4	14	0.1
	Theophylline - Quinolone antibiotics	1	1	0	6	2	2	1	13	0.09
	Theophylline - Macrolide antibiotics	0	11	9	33	33	47	16	149	1.03
	Theophylline - Beta-blockers	1	0	0	0	3	0	0	4	0.03
	Theophylline - Oral contraceptives	0	0	0	4	0	0	0	4	0.03
	Theophylline - Allupirinol	0	0	0	1	0	0	0	1	0.007
	Theophylline - Thyroid hormones	0	0	0	0	0	3	0	3	0.02
	Theophylline - Calcium channel blockers	0	0	0	0	0	1	0	1	0.007
	Glibenclamide - Aspirin	1	0	0	1	1	3	0	6	0.04
	Glibenclamide - Corticosteroids	0	3	1	0	1	0	1	6	0.04
	Glibenclamide - Hydrochlorothiazide	0	0	0	0	29	0	40	69	0.48
	Diclofenac - Thiazide diuretics	30	50	8	3	0	82	78	251	1.74
	Diclofenac - Beta-blockers	2	1	3	10	2	8	3	29	0.2
	Reserpine - Sympatomimmetics	0	7	0	0	0	0	1	8	0.06
3	Doxycycline - Cimetidine	2	4	0	6	3	9	1	25	0.17
	Oxytetracycline - Cimetidine	4	0	0	0	0	1	0	5	0.03
	Co-trimoxazole - Digoxin	1	5	0	2	0	4	0	12	0.08
	Co-trimoxazole - Oral contraceptives	4	6	1	4	0	0	0	15	0.1
	Theophylline - Antacids	2	0	1	15	0	22	12	52	0.36
	Theophylline - Bensodiasepines	1	4	2	0	0	8	0	15	0.1
	Theophylline - Loperamide	0	0	0	0	0	0	4	4	0.03
	Glibenclamide - Antacids	0	1	3	8	1	9	4	26	0.18
	Glibenclamide - Captopril	6	0	10	4	4	9	6	39	0.27
	Multivitamin - Corticosteroids	1	0	0	8	1	1	0	11	0.08
	Multivitamin - Salicylates	13	25	7	169	165	23	52	454	3.14
	Reserpine - Digoxin	0	4	0	0	0	0	0	4	0.03
	Reserpine - Tricyclic antidepressants	0	0	0	1	0	0	0	1	0.007
	Total B	**85**	**139**	**47**	**310**	**387**	**289**	**241**	**1501**	**10.38**

Total A: Total number of specific interactions in all the medi centres.

Total B: Total number of interactions of levels 1 to 3 as presented at the individual medi centres.

** Percentage calculated according to the total number of drug-drug interactions (n = 14449) identified (refer to Table 5.35).*

The percentage of the interactions identified with significance levels 1 to 3, represented 10.38% of all the identified interactions (n = 14449) that occurred with the ten selected drugs (refer to Table 5.35).

♦ **Level 1 interactions**

Doxycycline and antacids

The level 1 interaction between doxycycline and antacids occurred on 75 prescriptions, which is 0.52% of all the identified interactions (refer to Table 5.36). According to Stockley (1991:213) the therapeutic effectiveness of tetracycline antibiotics (e.g. doxycycline) can be reduced or even abolished with the concurrent use of antacids that contain aluminium, bismuth, calcium and magnesium. The antibiotic forms an insoluble chelate with the antacid. There is a decrease in doxycycline's anti-infective response. According to Tatro (1998:1005) the tetracycline antibiotic and the antacids must not be administrated simultaneously; they must be administrated at least three to four hours apart. This level one interaction occurred at all the medi centres (refer to Table 5.36).

Doxycycline and penicillins

The level 1 interaction between doxycycline and penicillins occurred on 158 of the prescriptions, which is 1.09% of all the identified interactions (refer to Table 5.36). According to Hansten and Horn (1989:238) tetracycline administration may impair the efficiency of the penicillin therapy. The pharmacological and therapeutic actions of penicillins are reduced. The bacteriostatic action of doxycycline may withhold part of the micro-organism from the bactericidal activity of the penicillins (Tatro, 1998:816). This interaction occurred at Parow (n = 2), Pietersburg (n = 127), Rosslyn (n = 28) and Verulam (n = 1) (refer to Table 5.36).

Doxycycline and digoxin

The level 1 interaction between doxycycline and digoxin occurred on 1 prescription, which is 0.007% of all interactions (refer to Table 5.36). According to Semnia *et al.* (1997:290) the digoxin concentration may be increased when given simultaneously with diclofenac and this leads to toxicity of digoxin. Brits medi centre (n = 1) is the only centre where the interaction occurred.

Oxytetracycline and antacids

The level 1 interaction between oxytetracycline and antacids occurred on 10 prescriptions, which is 0.07% of all the interactions (refer to Table 5.36). Refer to the level 1 interaction between doxycycline and antacids. It is the same for oxytetracycline and antacids. This interaction occurred at Brits (n = 9) and Parow (n = 1) (refer to Table 5.36).

Oxytetracycline and penicillins

The level 1 interaction between oxytretacycline and penicillins occurred on 2 prescriptions, which is 0.01% of all the interactions (refer to Table 5.36). Refer to the level 1 interaction between doxycycline and penicillins. It is the same for oxytetracycline and penicillins. Parow medi centre is the only centre where the interaction occurred (n = 2) (refer to Table 5.36).

Theophylline and cimetidine

The level 1 interaction between theophylline and cimetidine occurred on 16 prescriptions, which is 0.11% of all the interactions (refer to Table 5.36). According to Gibbon (2000:458) the theophylline biotransformation is significantly diminished when given with cimetidine. This results in raised theophylline levels. According to Hansten and Horn (1989:395) cimetidine inhibits the hepatic metabolism of theophylline. This inhibition may cause cimetidine to bind to theophylline and form a complex that interrupts the metabolism (Zucchero *et al.,* 1999:334). Thus the elimination of theophylline is decreased and the therapeutic actions are increased. This interaction occurred at Kwanobuhle (n = 1), Parow (n = 2), Pietersburg (n = 1), Rosslyn (n = 5) and Verulam (n = 7) (refer to Table 5.36).

- **Level 2 interactions**

Doxycycline and oral contraceptives

The level 2 interaction between doxycycline and oral contraceptives occurred on 6 prescriptions, which is 0.04% of all interactions (refer to Table 5.36). According to Gibbon (2000:259) the efficacy of the oral contraceptives are reduced and additional contraception is advisable. Doxycycline may suppress the intestinal flora, which normally provide the hydrolytic enzymes essential for enterohepatic recirculation of certain contraceptive steroid conjugases. This may lead to decreased contraceptive plasma levels (Tatro, 1998:312). Groblersdal (n = 1) and Parow (n = 5) are the only medi centres where this interaction occurred (refer to Table 5.36).

Doxycycline and calcium

The level 2 interaction between doxycycline and calcium occurred on 7 prescriptions, which is 0.05% of all the interactions (refer to Table 5.36). According to Reynolds (1993:1186) doxycycline has a loss in activity when combined with calcium. The absorption of doxycycline decreases through the chelate that forms with the calcium (Gibbon, 2000:259). The anti-infective response of doxycycline is decreased (Tatro, 1998:1007). The interaction occurred at Groblersdal (n = 1), Parow (n = 2), Rosslyn (n = 2) and Verulam (n = 2) (refer to Table 5.36).

Doxycycline and phenytoin

The level 2 interaction between doxycycline and phenytoin occurred on 1 prescription, which is 0.007% of all the interactions (refer to Table 5.36). According to Gibbon (2000:259) the serum levels of doxycycline may be reduced. Doxycycline is metabolised by hepatic conjugation, a process that is inducible (Cytochrome P450-enzymes). This stimulation of hepatic microsomal enzymes by phenytoin induced the metabolism of doxycycline. The displacement of doxycycline from plasma proteins may also contribute to this phenomenon (Tatro, 1998:454). Kwanobuhle is the only medi centre where this interaction occurred (n = 1) (refer to Table 5.36).

Doxycycline and carbamazepine

The level 2 interaction between doxycycline and carbamazepine occurred on 1 prescription, which is 0.007% of all interactions (refer to Table 5.36). According to Gibbon (2000:259) the serum levels of doxycycline can be reduced. The metabolism of doxycycline is through hepatic conjugation (Cytochrome P450-enzymes). The stimulation of the hepatic enzymes by carbamazepine induces the metabolism of doxycycline. Doxycycline can be displaced from plasma protein and this can contribute to the phenomenon (Tatro, 1998:454). Brits was the only medi centre where the interaction occurred (n = 1) (refer to Table 5.36).

Oxytetracycline and oral contraceptives

The level 2 interaction between oxytetracycline and oral contraceptives occurred on 1 prescription, which is 0.007% of all interactions (refer to Table 5.36). Refer to the level 2 interactions between doxycycline and oral contraceptives, because they are the same for oxytetracycline and oral contraceptives. The interaction only occurred at Brits medi centre (n = 1) (refer to Table 5.36).

Co-trimoxazole and phenobarbitone

The level 2 interaction between co-trimoxazole and phenobarbitone occurred on 1 prescription, which is 0.007% of all interactions (refer to Table 5.36). According to Gibbon (2000:266) the prolonged concurrent use of the two drugs may aggravate the folate antagonism that occurs and the risk of megaloblastic anaemia is increased. The serum concentration of phenobarbitone is increased and this produces an increase in the pharmacological and toxic effects of the phenobarbitone (Tatro, 1998:599). Groblersdal is the only medi centre where the interaction occurred (n = 1) (refer to Table 5.36).

Theophylline and carbamazepine

The level 2 interaction between theophylline and carbamazepine occurred on 1 prescription, which is 0.007% of all interactions (refer to Table 5.36). According to Stockley (1991:778) the serum levels of theophylline and carbamazepine can fall during concurrent use. There is a possible mutual induction

of the hepatic metabolism of these drugs (Tatro, 1998:1023). This interaction occurred only at Rosslyn (n = 1) (refer to Table 5.36).

Theophylline and furosemide

The level 2 interaction between theophylline and furosemide occurred on 14 prescriptions, which is 0.10% of all interactions (refer to Table 5.36). According to Hansten and Horn (1990:343) a single dose of furosemide can increase the theophylline concentration. Furosemide may reduce the volume of distribution of theophylline and increase its serum concentration. Theophylline can be displaced from the serum proteins and the clearance of theophylline can be increased (Zucchero *et al.*, 1999:336). This interaction occurred at Groblersdal (n = 5), Parow (n = 3), Rosslyn (n = 2) and Verulam (n = 4) (refer to Table 5.36).

Theophylline and quinolone antibiotics

The level 2 interaction between theophylline and quinolone antibiotics (e.g. enoxacin) occurred on 13 prescriptions, which is 0.09% of all interactions (refer to Table 5.36). The levels of theophylline are increased, therefore the theophylline dosage must be halved to avoid toxicity. Norfloxacin can cause serious toxicity and pipemidic acid interacts to a lesser extent with theophylline (Stockley, 1991:796). The quinolone antibiotics inhibit the hepatic metabolism of theophylline (Tatro, 1998:1050). The interaction occurred at all the medi centres except at Kwanobuhle (refer to Table 5.36).

Theophylline and macrolide antibiotics

The level 2 interaction between theophylline and macrolide antibiotics (e.g. erythromycin) occurred on 149 prescriptions, which is 1.03% of all interactions (refer to Table 5.36). According to Stockley (1991:790) triacetyloleandomycin increases the theophylline levels, leading to theophylline toxicity if the dosage is not reduced. Claritromycin, roxithromycin and spiramycin only cause modest changes or do not interact with theophylline at all. Macrolide antibiotics inhibit the metabolism of theophylline (Tatro, 1998:1044). This interaction occurred at all the medi centres except at Brits (refer to Table 5.36).

Theophylline and beta-blockers

The level 2 interaction between theophylline and beta-blockers occurred on 4 prescriptions, which is 0.03% of all interactions (refer to Table 5.36). Propranolol reduces the clearance of theophylline (Stockley, 1991:776). According to Stockley (1991:776) non-selective beta-blockers (e.g. nadolol and propranolol) cause bronchospasm in asthmatic patients and selective beta-blockers (e.g. atenolol, bisoprolol and metoprolol) must be used with caution. According to Tatro (1998:1021) theophylline elimination is reduced in the presence of non-selective beta-blockers and the effect of theophylline is

reduced. Brits (n = 1) and Pietersburg (n = 3) are the only medi centres where the interaction occurred (refer to Table 5.36).

Theophylline and oral contraceptives

The level 2 interaction between theophylline and oral contraceptives occurred on 4 prescriptions, which is 0.03% of all interactions (refer to Table 5.36). Theophylline levels are raised to some extent, but no toxicity has been noticed when oral contraceptives and theophylline are given simultaneously (Stockley, 1991:779). Oral contraceptives decrease the oxidative degradation of theophylline by the cytochrome enzyme system (Tatro, 1998:1025), thus theophylline's elimination is decreased. Parow is the only medi centre where this interaction occurred (n = 4) (refer to Table 5.36).

Theophylline and allopurinol

The level 2 interaction between theophylline and allopurinol occurred on 1 prescription, which is 0.007% of all interactions (refer to Table 5.36). According to Stockley (1991:771) the effects of theophylline may be increased with the concurrent use of allopurinol, therefore a risk of theophylline toxicity (Zucchero *et al.*, 1999:331). Tatro (1998:1017) mentioned that allopurinol may impair the liver degradation of theophylline. Parow (n = 1) is the only medi centre where the interaction occurred (refer to Table 5.36).

Theophylline and thyroid hormones

The level 2 interaction between theophylline and thyroid hormones occurred on 3 prescriptions, which is 0.02% of all interactions (refer to Table 5.36). The initiation of thyroid replacement therapy in patients receiving theophylline may reduce the theophylline levels. The rate of theophylline elimination tends to increase in hyperthyroidism and decrease in hypothyroidism (Hansten & Horn, 1989:515). The administration of theophylline can increase in a patient with thyroid hormone replacement therapy (Hansten & Horn, 1989:515). The interaction occurred only at Rosslyn medi centre (n = 3) (refer to Table 5.36).

Theophylline and calcium channel blockers

The level 2 interaction between theophylline and calcium channel blockers occurred on 1 prescription, which is 0.007% of all interactions (refer to Table 5.36). According to Stockley (1991:777) the concurrent use of theophylline and calcium channel blockers seem to have no adverse effects on the control of asthma, despite the small or modest changes in serum theophylline levels reported with diltiazem, felodipine, nifedipine and verapamil. Calcium channel blockers inhibit the hepatic metabolism of theophylline (Hansten & Horn, 1990:71). This interaction occurred only at Rosslyn medi centre (n = 1) (refer to Table 5.36).

Glibenclamide and aspirin

The level 2 interaction between glibenclamide and aspirin occurred on 6 prescriptions, which is 0.04% of all interactions (refer to Table 5.36). Aspirin and glibenclamide in combination result in an enhanced hypoglycaemic effect (Gibbon, 2000:70). Aspirin reduces the basal plasma glucose levels and enhance insulin secretion (Tatro, 1998:975). The inhibition of the prostaglandin synthesis may inhibit the acute insulin responses to glucose. Thus the actions of the glibenclamide may be enhanced (Tatro, 2000). This interaction occurred at Brits (n = 1), Parow (n = 1), Pietersburg (n = 1) and Rosslyn (n = 3) (refer to Table 5.36).

Glibenclamide and corticosteroids

The level 2 interaction between glibenclamide and corticosteroids occurred on 6 prescriptions, which is 0.04% of all interactions (refer to Table 5.36). According to Hansten and Horn (1989:165) corticosteroids have intrinsic hyperglycaemic activity. According to Reynolds (1993:810) the hypoglycaemic effects of glibenclamide are diminished when given with corticosteroids. Thus the corticosteroids decrease the activity of glibenclamide. This interaction occurred at Groblerdal (n = 3), Kwanobuhle (n = 1), Pietersburg (n = 1) and Verulam (n = 1) (refer to Table 5.36).

Glibenclamide and hydrochlorothiazide

The level 2 interaction between glibenclamide and hydrochlorothiazide occurred on 69 prescriptions, which is 0.48% of all interactions (refer to Table 5.36). According to Tatro (2000) the diuretics may decrease insulin tissue sensitivity, decrease insulin secretion or increase potassium loss, thus causing hyperglycaemia. There is an impaired glucose tolerance with this combination of drugs and the hypoglycaemic effect of glibenclamide is diminished (Gibbon, 2000:70). Pietersburg (n = 29) and Verulam (n = 40) are the only medi centres where the interaction occurred (refer to Table 5.36).

Diclofenac and thiazide diuretics

The level 2 interaction between diclofenac and thiazide diuretics occurred on 251 prescriptions, which is 1.74% of all the interactions (refer to Table 5.36). The antihypertensive effects of the thiazide diuretics are decreased by diclofenac (Semnia *et al.,* 1997:253). Thus the efficiency of the diuretics is markedly attenuated (Gibbon, 2000:325). This interaction occurred at all the medi centres except Pietersburg (refer to Table 5.36).

Diclofenac and beta-blockers

The level 2 interaction between diclofenac and beta-blockers occurred on 45 prescriptions, which is 0.20% of all interactions (refer to Table 5.36). The antihypertensive effects of the beta-blockers are decreased by diclofenac (Semnia *et al.,* 1997:253). Thus the efficiency of the beta-blockers is

markedly attenuated (Gibbon, 2000:325). This interaction occurred at all the medi centres (refer to Table 5.36).

Reserpine and sympathomimetics

The level 2 interaction between reserpine and sympathomimetics occurred on 8 prescriptions, which is 0.06% of all interactions (refer to Table 5.36). Reserpine potentiates the pressor response of the direct-acting sympathomimetics, which may result in hypertension. The pressor response of the indirect-acting agents is decreased by reserpine. Reserpine depletes the stores of catecholamines, increasing the receptor sensitivity to the direct-acting sympathomimetics while antagonising the effects of the indirect-acting agents, which release norepinephrine from the neurons (Tatro, 1998:993). Groblersdal (n = 7) and Verulam (n = 1) are the only medi centres where this interaction occurred (refer to Table 5.36).

♦ **Level 3 interactions**

Doxycycline and cimetidine

The level 3 interaction between doxycycline and cimetidine occurred on 25 prescriptions, which is 0.17% of all interactions (refer to Table 5.36). According to Zucchero *et al.* (1999:205) further research is needed for the interaction between doxycycline and cimetidine. The dissolution of the capsule form of doxycycline depends on the gastric acidity, and cimetidine raises the gastric pH. Thus the efficiency of doxycycline can be decreased. The interaction occurred at all the medi centres except Kwanobuhle (refer to Table 5.36).

Oxytetracycline and cimetidine

The level 3 interaction between oxytetracycline and cimetidine occurred on 5 prescriptions, which is 0.03% of all interactions (refer to Table 5.36). Refer to the level 3 interaction of doxycycline and cimetidine. The same interaction occurs between oxytetracycline and cimetidine. Brits (n = 4) and Rosslyn (n = 1) are the only medi centres where the interaction occurred (refer to Table 5.36).

Co-trimoxazole and digoxin

The level 3 interaction between co-trimoxazole and digoxin occurred on 12 prescription, which is 0.08% of all the interactions (refer to Table 5.36). According to Gibbon (2000:266) the levels of digoxin can be increased by co-trimoxazole through the digoxin excretion that is reduced by co-trimoxazole. Thus the possibility of digoxin toxicity is increased. The interaction occurred at Brits (n = 1), Groblersdal (n = 5), Parow (n = 2) and Rosslyn (n = 4) (refer to Table 5.36).

Co-trimoxazole and oral contraceptives

The level 3 interaction between co-trimoxazole and oral contraceptives occurred on 15 prescriptions, which is 0.10% of all the interactions (refer to Table 5.36). According to Gibbon (2000:266) the efficiency of the contraceptives is reduced and additional contraception is advisable. The oestrogen levels in the body rise due to sulphamethoxazole (in the combination of co-trimoxazole). The drug is concentrated with the liver enzymes, which handles the metabolism and the clearance of the oestrogen (Stockley, 1999:425). Thus sulphametoxazole inhibits the enzyme system that metabolises the oestrogen (Zucchero *et al.*, 1999:204). This interaction occurred at Brits (n = 4), Groblersdal (n = 6), Kwanobuhle (n = 1) and Parow (n = 4) (refer to Table 5.36).

Theophylline and antacids

The level 3 interaction between theophylline and antacids occurred on 52 prescriptions, which is 0.36% of all interactions (refer to Table 5.36). According to Zucchero *et al.* (1999:332) antacids can change the pH and increase theophylline absorption. Factors such as gastrointestinal fluid pH may influence the degradation and/or absorption of some slow release theophylline formulations. This interaction occurred at Brits (n = 2), Kwanobuhle (n = 1), Parow (n = 15), Rosslyn (n = 22) and Verulam (n = 12) (refer to Table 5.36).

Theophylline and bensodiasepines

The level 3 interaction between theophylline and bensodiasepines occurred on 15 prescriptions, which is 0.10% of all interactions (refer to Table 5.36). According to Tatro (2000) the sedative effects of bensodiasepines may be antagonised by theophylline. The antagonism occurs through competitive binding to the intracerebral adenosine receptors by theophylline. This interaction occurred at Brits (n = 1), Groblersdal (n = 4), Kwanobuhle (n = 2) and Rosslyn (n = 8) (refer to Table 5.36).

Theophylline and loperamide

The level 3 inteaction between theophylline and loperamide occurred on 4 prescriptions, which is 0.03% of all interactions (refer to Table 5.36). According to Stockley (1991:789) loperamide delays the absorption of theophylline from a sustained-release preparation. The effectiveness of theophylline is decreased. Verulam (n = 4) is the only medi centre where this interaction occurred (refer to Table 5.36).

Glibenclamide and antacids

The level 3 interaction between glibenclamide and antacids occurred on 26 prescriptions, which is 0.18% of all interactions (refer to Table 5.36). According to Hansten and Horn (1990:202) the antacids increase the concentration of glibenclamide. The antacids appear to increase the absorption of the glibenclamide, but the clinical importance of their effect has not been established (Neuvonen &

Kivistö, 1991:218). This interaction occurred at all the medi centres except at Brits (refer to Table 5.36).

Glibenclamide and captopril

The level 3 interaction between glibenclamide and captopril occurred on 39 prescriptions, which is 0.27% of all interactions (refer to Table 5.36). The captopril causes an increase in insulin sensitivity and the dosage of the antidiabetic drugs (e.g. glibenclamide) must be reduced (Hansten & Horn, 1989:162). This interaction occurred at all the medi centres except Groblersdal (refer to Table 5.36).

Multivitamin and corticosteroids

The level 3 interaction between multivitamins and corticosteroids occurred on 11 prescriptions, which is 0.08% of all interactions (refer to Table 5.36). Vitamin A may worsen or improve the wound healing that is a therapeutic effect of corticostreroids. The corticosteroids may counteract the effects of vitamin D (Turner, 2001:120). This interaction occurred at Brits (n = 1), Parow (n = 8), Pietersburg (n = 1) and Rosslyn (n = 1) (refer to Table 5.36).

Multivitamin and salicylates

The level 3 interaction between multivitamins and salicylates occurred on 454 prescriptions, which is 3.14% of all interactions (refer to Table 5.36). The salicylates can reduce the flushing reactions that occur with nicotinamide, but it can also increase the nicotinamide levels (Stockley, 1991:887). This interaction occurred at all the medi centres (refer to Table 5.36).

Reserpine and digoxin

The level 3 interaction between reserpine and digoxin occurred on 4 prescriptions, which is 0.03% of all interactions (refer to Table 5.36). Reserpine can enhance the bradicardia, arrthythmias and hypotension that are caused by digoxin (Turner, 2001:162). Digoxin cardiotoxicity is increased (Zucchero *et al.,* 1999:268). Groblersdal is the only medi centre where the interaction occurred (refer to Table 5.36).

Reserpine and tricyclic antidepressant

The level 3 interaction between reserpine and tricyclic antidepressants occurred on 1 prescription, which is 0.007% of all interactions (refer to Table 5.36). According to Turner (2001:164) reserpine can cause depression and should not be used in patients that require treatment for depression. When reserpine and tricyclic antidepressants are combined there is a release of norepinephrine into the synapse where the antidepressants inhibit their uptake (Zucchero *et al.,* 1999:145). The depletion of the norepinephrine stores leads to the sedation and depression (Stockley, 1999:362). Parow is the only medi centre where this interaction occurred (n = 1) (refer to Table 5.36).

5.4.3 Medical conditions or disease states diagnosed where drug-drug interactions appeared

A statistical analysis was performed in order to identify the different medical conditions or disease states where drug-drug interactions occurred. The current Philani Prime Cure® system identifies possible drug-drug interactions in the same protocol, but not between drugs in different protocols. The identification of these drug-drug interactions is important, as one patient can be diagnosed with more than one disease state at the same time and therefore be treated with combinations of medication. Appendix A reveals the different disease states where drug-drug interactions were identified.

5.5 CHAPTER SUMMARY

In this chapter the results of the empirical study were discussed according to the research objectives discussed in Chapter 4, section 4.3.2.1. The conclusions and recommendations that can be drawn from these results in Chapter 5 will be discussed in Chapter 6. The limitations will be discussed in the following chapter.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

In this chapter the conclusions, recommendations and limitations will be discussed. These aspects will be discussed according to the specific objectives as stated in Chapters 1 and 4. Limitations and the recommendations of this study will be discussed in sections 6.3 and 6.4. Sections 6.1.1 to 6.1.15 will conclude the specific objectives of the literature review.

6.1 LITERATURE REVIEW

6.1.1 Managed pharmaceutical care

The first objective of the literature review was to define managed pharmaceutical care.

Managed pharmaceutical care is the role of pharmacy to improve the quality of care and the control of the utilisation of health care resources. The aim of managed pharmaceutical care is to identify, prevent and resolve medicine-related problems in a cost-effective way (refer to section 2.1).

6.1.2 Pharmaceutical care and the other research fields in pharmacy practice

The second objective of the literature review was to show how pharmaceutical care fits into managed pharmaceutical care and defines the areas of managed pharmaceutical care.

Figure 2.1 in Chapter 2 shows an overall integration of the different areas of managed pharmaceutical care. The different areas of managed pharmaceutical care were briefly discussed. The main area of focus of this study was on pharmaceutical care. The other areas that were discussed included outcomes management, disease management, drug utilisation review, pharmacoeconomics and pharmacoepidemiology (refer to sections 2.1.1 to 2.1.6).

The general conclusion to be made from pharmaceutical care was that the pharmaceutical care provider must take responsibility for the provision of care and the therapy of the patients (refer to section 2.1.1). Pharmaceutical care is the responsibility of achieving definite outcomes that improve a patient's quality of life (Hepler & Strand, 1990:539). Outcomes management includes procedures that can improve pharmaceutical care results, through modifying the pharmaceutical practice in response of the data obtained with the outcomes management procedures (refer to section 2.1.2). Disease management is a system designed to optimise outcomes within a specific population for a specific disease or treatment. Pharmaceutical care focuses on all the drug-related needs of a patient (refer to section 2.1.3). A drug utilisation review is used to establish the medical appropriateness of pharmaceutical care providers giving medication to patients for a certain disease state. The purpose of a drug utilisation review is to improve the quality of life, containment of medical costs and the identification of fraud and abuse (refer to section 2.1.4). Pharmacoeconomics is a division of

outcomes management and is used to analyse the drug therapy that is provided through pharmaceutical care. Pharmacoenonomics enables the profession to delineate which pharmaceutical care services are cost-effective so as to improve efficiency in providing patient care (refer to section 2.1.5). Pharmacoepidemiology provides information about the health and cost outcomes of drugs and other services to large numbers of people (refer to section 2.1.6).

6.1.3 **Pharmaceutical care**

The third objective of the literature review was to define and discuss pharmaceutical care.

There are numerous people and pharmaceutical organisations that define pharmaceutical care as they see fit. Pharmaceutical care can be described as the direct, responsible provision of medication-related care. The focus point of pharmaceutical care is to improve the patient's quality of life. Pharmaceutical care can be seen as the identification, solving and preventing of drug-related problems of the individual patient. The main point is that the provider of pharmaceutical care must take responsibility for pharmaceutical care and the advice he/she provides to a patient (refer to section 2.1.1.1 to 2.1.1.5).

6.1.4 **Different elements of pharmaceutical care**

The fourth objective of the literature review was to discuss the different elements of the pharmaceutical care practice.

The different elements of the pharmaceutical care practice are the philosophy of practice, the patient care process and the practice management system (refer to section 2.3). The philosophy of practice is to establish the acts associated with pharmaceutical care (refer to section 2.3.1). The patient care process was discussed in more detail than the other two divisions. The patient care process is where the pharmacist interacts with the patient and establishes a therapeutic relationship. The three steps of the patient care process (e.g. assessment step, care plan, and follow-up evaluation) were discussed in section 2.3.2. These steps form the heart of pharmaceutical care. For pharmaceutical care to be successfully implemented there must be an efficient and effective practice management system in place (section 2.3.3).

6.1.5 **Role of the different health care providers**

The fifth objective of the literature review was to determine the role of the different health care providers in the prevention of drug therapy problems.

The most important health care providers can be one of the following, namely a pharmacist, a nurse or a physician. In section 2.4.2 the different roles and functions of the pharmacist were discussed. The

provision of pharmaceutical care by a pharmacist was emphasised by the Pharmacy Act (53/1974) and this is also the viewpoint of the South African Pharmacy Council. The nurse has two kinds of functions, namely dependent or independent functions. Dependent functions are where the nurse needs a prescription from a physician to perform the required task such as intravenous feeding. Independent functions are those functions for which she takes responsibility, e.g. administration of medicine (Vlok, 1999:49). The various roles of nurses were briefly discussed in section 2.4.3. The physician has two responsibilities, namely to the community and to the individual. In both situations the physician must diagnose disease states, prescribe medical therapy and give advice on health-related problems. The role of the physician is discussed in section 2.4.4.

6.1.6 **Primary health care**

The sixth objective of the literature review was to discuss primary health care.

Primary health care is essential care and all patients are entitled to one or other form of health care. When primary health care can be provided, pharmaceutical care is possible. The pharmacist's responsibility for primary health care is to promote health care, assist in the training and education of patients and rural health care workers (refer to section 2.5).

6.1.7 **Drug therapy problems**

The seventh objective of the literature review was to define and discuss different drug therapy problems.

A drug therapy problem can be defined as any undesirable event experienced by a patient because of the drug therapy. Drug therapy problems can cause considerable harm to a patient as discussed in section 2.6.2. Nine different drug therapy problems were identified and discussed. These drug therapy problems include untreated indication, improper drug selection, subtherapeutic dosage, failure to receive drugs, overdose, adverse drug reactions, using drugs without indication, drug interactions and treatment failures. Drug interaction, the main research point of this study, forms part of drug therapy problems. By identifying drug therapy problems (using pharmaceutical care) a patient's quality of life can be improved.

6.1.8 **Drug interactions**

The eighth objective of the literature review was to discuss drug interactions according to the classification of drug interactions and drugs involved in interactions.

The classification of drug interactions was discussed as addition, inhibition and potentiation of effects. Addition of effects occur when drugs with similar pharmacological effects are administered

concurrently. Inhibition occurs when a substance prevents a drug from exerting its action and producing its full effect in a patient. Potentiation of effects means the enhancement of the effect of a drug by another substance (refer to section 2.8). The drugs involved in interactions were discussed as precipitant and object drugs. The clinical importance of drug interactions cannot always be determined, but it is possible to predict which types of drugs are likely to be involved in drug interactions. For this reason precipitant and object drugs was discussed (refer to section 2.9).

6.1.9 **Different drug-drug interactions**

The ninth objective of the literature review was to discuss the different drug-drug interactions such as pharmaceutical, pharmacodynamic and pharmacokinetic interactions.

The three different kinds of interactions were pharmaceutical, pharmacokinetic and pharmacodynamic interactions. Pharmaceutical interactions are related to the physiochemical properties of a drug and are studied in more detail by pharmaceutical research (refer to section 2.10.1). Pharmacokinetic interactions occur when the drug alters the absorption, distribution and excretion of another drug (refer to section 2.10.2). Pharmacodynamic interactions include the interactions that occur through the alternation of response sensitivity of a drug (refer to section 2.10.3). The pharmacokinetic and pharmacodynamic interactions were the basis of the identified drug-drug interactions in this study.

6.1.10 **Drug-food interactions**

The tenth objective of the literature review was to discuss drug-food interactions.

Drugs and food can affect each other when given simultaneously. The drug and/or food kinetics can be affected and were discussed in section 2.11.1. Drug-food interactions occur when the effect of the drug alone is altered when given with food. The factors affecting drug-food interactions were listed in Table 2.6, section 2.11.2. These factors affecting drug-food interactions are physiological stress, chronic disease, hepatic dysfunction, renal dysfunction and malabsorption of drugs. For the purpose of this study interactions between tobacco smoke and certain drugs and alcohol-drug interactions were also classified as drug-food interactions (refer to section 2.11.3). The general conclusion is not to smoke tobacco when receiving drug therapy.

6.1.11 **Factors affecting drug interactions**

The eleventh objective of the literature review was to determine the factors affecting drug interactions.

The physiologic factors affecting drug interactions are age (e.g. elderly and paediatric patients), body weight, gender, genetics, the administration time of medications, tolerance and body temperature

(refer to section 2.12.1 to 2.12.7). Age is one of the important factors affecting drug interactions, because the metabolism and excretions of drugs in different age groups are not similar. These differences in metabolism and excretion of drugs were discussed in section 2.12.1. The other factors affecting drug interactions were discussed in section 2.12.2 to 2.12.7.

6.1.12 **Iatrogenic illness**

The twelfth objective of the literature review was to discuss iatrogenic illness.

Iatrogenic illness means an illness caused by an error in diagnosis or treatment. The pharmacist must have the knowledge of the factors that can be a risk for the patient and place the patients in harm's way of an iatrogenic illness. The factors that can lead to an iatrogenic illness were discussed in section 2.13.1 to 2.13.3. These factors that can lead to an iatrogenic illness are age, gender and disease states (e.g., renal failure, liver disease, porphyria).

6.1.13 **Ten selected drugs**

The thirteenth objective of the literature review was to discuss the ten selected drugs according to classification, pharmacological properties, the mechanism of action, therapeutic uses and deficiencies where possible, for each of the ten drugs.

This objective was thoroughly discussed in Chapter 3, sections 3.1 to 3.10. These sections were discussed to understand the ten drugs that were selected to identify possible drug interactions in Chapter 5. These ten drugs included diphenhydramine, tetracycline (doxycycline and oxytetracycline), co-trimoxazole, hyoscine, theophylline, loperamide, glibenclamide, multivitamin, diclofenac and reserpine.

6.1.14 **Drug interaction tables**

The fourteenth objective of the literature review was to construct tables with all the potential drug interactions and the adverse effects of each selected drug.

Tables 3.7 to 3.16 discussed the drug interactions of each drug separately. Every possible interaction was listed in the tables (e.g., drug-food, drug-drug and drug-disease interactions.) These tables were used to discuss the interactions that were identified on the Philani Prime Cure® database (refer to Chapter 5, section 5.4.2) during the empirical study.

6.1.15 **Mechanisms of drug-drug interactions**

The fifteenth objective of the literature review was to discuss the mechanisms of the drug interactions.

The mechanisms of action of the possible drug interactions, constructed in Tables 3.7 to 3.16 were discussed in section 3.11. These mechanisms of drug interactions were discussed to understand how the drug interactions occurred. The main mechanisms of these drug interactions were focused on pharmacokinetic (e.g. altered absorption, distribution and metabolism of the administrated drugs) and pharmacodynamic (e.g. drugs administrated with opposing pharmacological effects) effects of the drug interactions. Certain mechanisms were not discussed because the mechanisms were not known and need more research to understand the drug interactions. These drug interactions with unknown mechanisms were listed in Tables 3.1 to 3.6.

6.2 **EMPIRICAL REVIEW**

The specific objectives of the empirical review will be discussed in sections 6.2.1 to 6.2.5.

6.2.1 **General information of the patients**

The first objective of the empirical review was to determine the general information of the patient population that visited the medi centres during the research period.

The seven medi centres were visited by a total of 29441 patients (refer to section 5.1.1, Table 5.1). The gender distribution of the patients was 16712 females and 12601 males. The *Chi-Square test* was performed and there was no practical significant difference between the number of female and male patients in the seven medi centres (refer to section 5.1.2.) The age group distribution of patients was illustrated in table 5.3, section 5.1.3. Age group 5 (older than 12 years and younger than 50 years) represented 66.13% of the patients that visited the seven medi centres. The average age of the patients varied between 24.56 ± 19.61 years and 32.8 ± 18.23 years in the seven medi centres. There was no difference of practical significance between the average ages of the patients in the different medi centres (refer to section 5.1.4, Table 5.5).

6.2.2 **Medicine usage patterns**

The second objective of the empirical review was to investigate the medicine usage patterns of patients during the research period in the seven medi centres.

The total number of medicine items prescribed was 131081 (refer to section 5.2.1, Table 5.6). The average number of medicine items varied between 2.87 ± 2.02 (Verulam) and 3.65 ± 1.29 (Pietersburg) medicine items per patient visit or prescription (refer to section 5.22, Table 5.7). There was no difference of practical significance between the average number of medicine items prescribed

in the seven medi centres (refer to Table 5.8). The maximum number of medicine items prescribed for one patient visit was twelve items and the minimum number of medicine items was one item (refer to section 5.2.3, Table 5.9). The ten selected drugs (diphenhydramine, tetracycline (e.g., doxycycline and oxytetracycline), co-trimoxazole, hyoscine, theophylline, loperamide, glibenclamide, multivitamin, diclofenac, reserpine) amounted to 31409 (23.96%) of the total number of medicine items prescribed in all seven medi centres (refer to section 5.2.4, Table 5.10). Table 5.13 shows the contributions the ten selected drugs made to the total number of medicine items prescribed in all seven medi centres. These ten selected drugs form part of the top twenty most prescribed drugs during the research period in all the medi centres. The drug that was the most prescribed of the ten selected drugs was diphenhydramine (n = 8158, 6.22% of all the medicine items prescribed during the research period).

6.2.3 **Medical conditions or disease states**

The third objective of the empirical review was to investigate the medical conditions or disease states diagnosed during the research period.

The total number of medical conditions or disease states diagnosed per medi centres was 57455 (refer to section 5.3.1, Table 5.14). One medical condition or disease state was diagnosed for most of the patient visits (refer to section 5.3.2, Table 5.15). The average number of medical conditions or disease states diagnosed per patient visit was between 1.24 ± 0.51 (Verulam) and 1.64 ± 0.81 (Rosslyn) medical conditions or disease states (refer to section 5.3.3, Table 5.16). There were no practical significant differences between the average number of medical conditions or disease states diagnosed per patient visit in the different medi centres (refer to Table 5.17). The ten most frequent diagnosed medical conditions or disease states amounted to the following at the medi centres, namely at Brits (35.28%), Groblersdal (41.37%), Kwanobuhle (37.28%), Parow (42.29%), Pietersburg (34.38%), Rosslyn (33.41%) and Verulam (35.62%) (refer to section 5.3.5, Table 5.18). The top three medical conditions or disease states for which the ten selected drugs were prescribed in the seven medi centres, were summarised in Table 5.19 to 5.29. Viral influenza infection was the only medical condition or disease state that occurred at all seven medi centres. The general conclusion that could be made was that there were just a few of the disease states that were not indicated for the use of the ten selected drugs. The following drugs had medical conditions or disease states that were not indicated, namely theophylline (e.g. in patients that also experience hypertension), loperamide (e.g. in patients that also experience diarrhoea of infective origin), diclofenac (e.g. in patients that also experience hypertension) and reserpine (e.g. in patients that experience peptic ulceration).

6.2.4 **Drug interactions**

The fourth objective of the empirical review was to identify and discuss the drug interactions that occurred with ten selected drugs.

There were two kinds of interactions, namely drug-age and drug-drug interactions. The results of the first type of drug interactions with the different age groups are illustrated in Tables 5.30 and 5.31, section 5.4.1. The most frequent drug-age interactions occurred with diphenhydramine (19.48% of all drug-age interactions) and multivitamin (13.36% of all drug-age interactions). The drug-age group interaction of diphenhydramine occurred when diphenhydramine was prescribed to patients younger than two years and to patients older than 50 years. The prescribing of multivitamin to patients younger than two years and patients older than 70 years led to the drug-age interaction of multivitamin. From these results it can be concluded that the health care team at the medi centres must be more alert towards the prescribing of drugs to patients of the different age groups. Thus more care must be taken when prescribing drugs to patients. The possible interactions were discussed in this section and, where possible, reasons for the interactions were given.

The second type of interaction that occurred was drug-drug interaction as discussed in section 5.4.2. The total number of different interactions showed that Parow medi centre had the most different types of drug interactions (n = 89) (refer to Table 5.33). There were different significant levels of drug interactions (level 1 to 5). Certain drug interactions had no indicated level of interaction and therefore level 6 was used to categorise these interactions. Table 5.34 illustrates the total number of drug-drug interactions on presciptions according to their significance levels. Level 5 had the most drug-drug interactions (n = 1869) and it represented 1.43% of the total number of medicine items prescribed during the research period. Only levels 1 to 3 of the drug interactions were discussed in section 5.4.2. Levels 4 and 5 were not discussed because these interactions are not substantiated and likely to occur. Table 5.36 illustrates the drug-drug interactions with significance levels 1 to 3 (Tatro, 1998:xv). Level 1 drug interactions represented 0.19% of the total number of medicine items prescribed during the research period. Level 2 drug interactions represented 0.44% and level 3 drug interactions represented 0.51% of the total number of medicine items prescribed during the research period. The level 1 drug interactions occurred most frequently with doxycycline (n = 234). The drug-drug interactions occurred between doxycycline and antacids (n = 75), between doxycycline and penicillins (n = 158) and between doxycycline and digoxin (n = 1) (refer to Table 5.36). Level 2 drug interactions occurred mostly with theophylline (n = 190 interactions), glibenclamide (n = 81 interactions) and diclofenac (n = 280 interactions). The drug-drug interactions between theophylline occurred with carbamazepine (n = 1), furosemide (n = 14), quinolone antibiotics (n = 13), macrolide antibiotics (n = 149), beta-blockers (n = 4), oral contraceptives (n = 4), allopurinol (n = 1), thyroid hormones (n = 3) and calcium channel blockers (n = 1) (refer to Table 5.36). The drug-drug

interactions occurred between glibenclamide and aspirin (n = 6), corticosteroids (n = 6) and hydrochlorothiazide (n = 69). The drug-drug interactions of diclofenac occurred with thiazide diuretics (n = 251) and beta-blockers (n = 29). Level 3 drug interactions occurred most frequently with theophylline (n = 71), glibenclamide (n = 65) and multivitamin (n = 465). The drug-drug interactions with theophylline occurred with antacids (n = 52), bensodiasepine (n = 15) and loperamide (n = 4). The glibenclamide drug-drug interactions occurred with antacids (n = 26) and captopril (n = 39). The drug-drug interactions of multivitamin occurred between multivitamin and corticosteroids (n = 11) and salicylate (n = 454) (refer to Table 5.36). The occurrence and effects of these drug-drug interactions were discussed in Chapter 5, section 5.4.2. Section 5.4.2 is a summary of the drug interaction tables (refer to Tables 3.7 to 3.16) and the mechanism of drug interactions in section 3.11.

6.2.5 **Medical conditions or disease states according to drug-drug interactions**

The fifth objective of the empirical review was to determine the medical conditions or disease states where the drug-drug interactions occurred.

The medical conditions or disease states that were diagnosed where the drug-drug interactions occurred were summarised in Table A1 to A40 in Appendix A. As indicated in Appendix A, there were several drug-drug interactions of which the diagnoses of the medical conditions or disease states were not indicated on the Philani Prime Cure® database. Thus several drug-drug interactions did not have the diagnoses indicated. For example, the interaction between glibenclamide and hydrochlorthiazide had 69 interactions in total, but there were 17 missing diagnoses and thus in 52 cases the medical conditions or disease states were indicated on the database. The health care team at the medi centres must take note to indicate the medical condition or disease state of each patient, so that accurate patient profiles can be kept. There were several interactions that only occurred once in the medi centres, e.g. interactions between oxytetracycline and oral contraceptives, interactions between doxycycline and phenytoin, just to name a few.

The medical conditions or disease states where doxycycline and antacids (level 1 drug-drug interactions) were prescribed, were pelvic inflammatory disease and heartburn. The medical conditions or disease states where doxycycline and penicillin (level 1 drug-drug interactions) were prescribed, were mainly pelvic inflammatory disease and lower abdominal pain. Viral influenza infections were the most diagnosed medical condition or disease state where the theophylline and cimetidine level 1 drug-drug interaction occurred. Doxycycline and oral contraceptives or calcium (level 2 drug-drug interactions) were simultaneously prescribed for the treatment of pelvic inflammatory disease. The level 2 drug-drug interactions of theophylline and quinolone or macrolide antibiotics were prescribed for the following medical conditions or disease states, namely acute

bronchitis infection and upper respiratory tract infections. The combination of glibenclamide and aspirin or hydrochlorothiazide led to the level 2 drug-drug interactions when patients with diabetes mellitus required drug therapy. Hypertension and muscle pains were the medical conditions or disease states where diclofenac and thiazide diuretics, that lead to the level 2 drug-drug interactions, were prescribed together.

6.3 LIMITATIONS AND SHORTCOMINGS OF THE STUDY

The following limitations and shortcoming of the study must be considered when evaluating the results and conclusions:

- The duration of drug treatment is not revealed in the database.
- Certain information of patient history (e.g. smoking and drinking habits, occupation and sport involvement) was not included in the database and could be considered in the analysis.
- It was not possible to determine whether the prescriber followed the treatment protocol or if the prescriber deviated from the recommended treatment protocols.
- All diagnoses and protocols on the database were assumed to be correct.
- The database could not supply the diagnosis for which a certain drug was prescribed in cases where more than one diagnosis was made during a single patient visit.
- Interactions were not included in the database provided, and alternative routes had to be followed.
- The database could not identify the medical condition or disease states where a drug-drug interaction occurred between more than two drugs simultaneously.
- The inability to identify the origin (prescribers) of the prescriptions where the drug interactions occurred.
- The study did not attempt to evaluate the cost implications of the drug interactions that occurred.
- A retrospective study was performed and therefore the clinical relevance of the drug interactions could not be evaluated.

6.4 RECOMMENDATIONS

The following recommendations can be made as a result of this study and will aim to facilitate improved management of drug interactions in Philani Prime Cure® medi centres:

- The importance of patient variables and patient history record keeping should be reconsidered and measures should be implemented to ensure that this information is recorded and continuously updated for all patients. All members of Philani Prime Cure® health team should be aware of the importance of this issue.

- The vital importance of the consideration of drug therapy problems, especially drug interactions, in the treatment of patients, as well as the available information regarding the management of the interactions should be emphasised in all the Philani Prime Cure® medi centres.
- The drug interaction tables (refer to Chapter 3, section 3.12) containing the recommendations and effects of these drug interactions must be incorporated into the treatment protocols and the database of Philani Prime Cure®.
- The treatment protocols for medical conditions or disease states identified with the drug-drug interactions (refer to Appendix A) need to re-evaluated in order to prevent drug interactions that occur between drugs in different protocols.
- Where only one medical condition or disease state was identified with a drug-drug interaction, it implies that the interaction occurred between the drugs used in the same treatment protocols. The re-evaluation of these treatment protocols will be necessary.
- Further study is needed on the mechanisms of drug interactions that are not clearly stated in the literature.

The following recommendations for further research can be formulated:

- Perform similar studies to determine the possible interactions that may occur with all the remaining drugs available in Philani Prime Cure® medi centres.
- Perform studies on all the other patient variables (variables not included in this study) in order to identify other potential drug interactions.
- Conduct studies to investigate the cost implications of drug interactions.
- Perform studies to investigate the seasonal variation in the occurrence of viral influenza infections.

6.5 CHAPTER SUMMARY

In this chapter the conclusions of the study were discussed. The limitations and shortcomings of this study were discussed in section 6.3. The recommendations made to improve the database of Philani Prime Cure® medi centres were discussed in section 6.4. Thereby the objectives of this study were met and discussed.

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Appendix A: Medical conditions or disease states diagnosed where drug-drug interactions occurred

Table A1: The number of medical conditions or disease states where doxycycline and antacids were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Heartburn	Urinary tract infections	Lower abdominal pain			1
	Heartburn	Urethral discharge				1
	Urethral discharge	Peptic ulceration				1
	Cough	Constipation	Heartburn	Lower abdominal pain		1
	Pelvic inflammatory disease	Gastritis: uncomplicated				1
Groblersdal	Pelvic inflammatory disease					2
	Pelvic inflammatory disease	Heartburn				1
	Infection: viral: warts					1
	Peptic ulceration	Infection: salpingitis				1
	Heartburn	Atopic dermatitis				1
	Heartburn	Syphilis: primary lesion				1
	Pelvic infalmmatory disease	Peptic ulceration				1
	Pelvic inflammatory disease	Gastritis: uncomplicated				1
Kwanobuhle	Gastroenteritis					1
	Diabetes mellitus: insulin	Nausea: non-specific	Infection: lobar pneumonia	Constipation		1
Parow	Vulvovaginitis: bacterial	Gastritis: uncomplicated				1
	Cough					1
	Gastritis: uncomplicated	Lower respiratory infections				1
	Gastritis: uncomplicated	Pelvic inflammatory disease				4
	Lower respiratory infections	Heartburn	Conjunctiva: allergic conjunctivitis			1
	Gastritis: uncomplicated	Pelvic inflammatory disease	Anaemia: iron deficiency			1

Table A1 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	Viral: Influenza					2
	Gastritis: uncomplicated	STD: urethritis in men				2
	Vulvovaginitis: bacterial	Gastritis: uncomplicated	Diabetes mellitus: type 2: follow-up			1
	Gastritis: uncomplicated	Acne vulgaris: mild				2
	STD: urethritis in men					1
	Gastritis: uncomplicated	Infection: salpingitis				1
Pietersburg	Heartburn	Vaginal discharge				1
	Gastritis: uncomplicated	Lower abdominal pain				4
	Lower abdominal pain	Peptic ulceration	Shoulder pain			1
	Lower abdominal pain	Peptic ulceration	Backache: general	Severe tooth cavity		1
	Lower abdominal pain	Peptic ulceration				3
	Heartburn	Lower abdominal pain	Urinary tract infections			1
	Gastritis: uncomplicated	Epididymo orchitis				1
	Gastritis: uncomplicated	Vaginal discharge				1
	Lower abdominal pain	Peptic ulceration	Deep hand and feet burns	Headache: migraine		1
Rosslyn	Osteoarthritis	Esophageal reflux	Urinary tract infections			1
	Muscle pains	Gastritis: uncomplicated	Infection: vulvovaginitis			1
	Muscle pains	Gastritis: uncomplicated	Cervix: cervicitis			1
	Gastritis: uncomplicated	Cervix: cervicitis				5
	STD: bacterial urethritis					1
	Pelvic inflammatory disease	Peptic ulceration				1
	Esophageal reflux	Pelvic inflammatory disease				1
	Gastritis: uncomplicated	Pelvic inflammatory disease	Constipation			1
	Pelvic inflammatory disease	Reflux oesophagitis				1
	Pelvic inflammatory disease	Reflux oesophagitis	Acute cystitis: female			1

Table A1 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Rosslyn	Cervix: cervicitis	Esophageal reflux				2
	Cervix: cervicitis	Esophageal reflux	Muscle pains			1
	Pelvic inflammatory disease	Esophageal reflux	Vulvovaginitis: candida			1
	Gastritis: uncomplicated	Lower abdominal pain				1
Verulam	Vaginal discharge					1
	Candida: vaginitis	Gastritis: uncomplicated				1
	Lower abdominal pain					1
	Reflux oesophagitis	Lymphogranuloma venereum				1
	Fallopian tubes: acute					1
	Gastritis: uncomplicated	Vulvovaginitis: candida				1
	Renal calculi					1
	Reflux oesophagitis	Pelvic inflammatory disease				1
					Subtotal	75
					No diagnosis indicated	0
					Total	75

Table A2: The number of medical conditions or disease states where doxycycline and penicillin were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	Viral: Influenza	Otitis media				1
	Infection: bronchitis: acute					1
Pietersburg	STD: bacterial urethritis					4
	Urethral discharge					10
	Larynx: chronic laryngitis					1
	STD: bacterial urethritis	Infection: acute cystitis: male	Otitis media			1
	Low back pain	Lower abdominal pain				1

Table A2 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Pietersburg	Lower abdominal pain	Bites: dog				1
	Hypertension	Chancroid				1
	Lower abdominal pain					32
	STD: bacterial urethritis	Necrotic ulcerative gingivitis	Infection: bronchitis: acute			1
	Lower abdominal pain	Urinary tract infections				5
	Urinary tract infections					3
	Lower abdominal pain	Deep hands and feet burns	Headache: migraine			4
	Lower abdominal pain	Diffuse myalgias				1
	Lower abdominal pain	Stings: wasp				1
	Muscle pains	Lower respiratory infections	Lower abdominal pain			1
	Acute cystitis: female	Acute pharyngitis				1
	Lower abdominal pain	Severe tooth cavity	Backache: general			1
	Cutaneuos abscess	Vaginal discharge				1
	Infection: acute cystitis: male					3
	Deep burns	Acute pharyngitis	Urethral discharge			1
	Diabetes mellitus: non-insulin dependant	Vaginal discharge				1
	Lower abdominal pain	Lymphadenopathy				1
	Bruises and abrasions	Perianal: abscess				1
	Vulvovaginitis: bacterial	Chancroid				1
	Urinary tract infections	Urethral discharge				1
	Chancroid					1
	Lower abdominal pain	Gastritis: uncomplicated				1
	Lower abdominal pain	Gastritis: uncomplicated	Dysentry: Shigella			1
	Lower abdominal pain	Episodic weakness	Urticaria: acute	Upper respiratory tract		1
	Vaginal discharge					7
	Lower abdominal pain	Severe tooth cavity	Backache: general	Pain: dysmenorrhoea		1

Table A2 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Pietersburg	Urinary tract infections	Urethral discharge	Lower respiratory infections			1
	Lower abdominal pain	Cough				1
	Urinary tract infections	Muscle: trauma	STD: urthritis: male			1
	Lower abdominal pain	Viral: influenza				1
	Lower abdominal pain	Genital ulcers				1
	Cough	Vaginal discharge				1
	Gynaecology: menorrhagia	Lower abdominal pain				1
	Diabetes mellitus: non-insulin dependant	Lower abdominal pain				3
	Lower abdominal pain	Conjunctiva: allergic				1
	Lower abdominal pain	Nausea: non-specific				1
	Lower abdominal pain	Episodic weakness				2
	Lower abdominal pain	Neck pain				1
	Lower abdominal pain	Lower respiratory infections				1
	Urinary tract infection	Tonsillitis				1
	Episodic weakness	Vaginal discharge	Low back pain			1
	Lower abdominal pain	Acute cystitis: female				1
	Deep hands and feet burns	Headache: migraine	Genital ulcers			1
	Genital ulcers					1
	Lower abdominal pain	Vaginal discharge				1
	Wax	Acute cystitis: female				1
	Vaginal discharge	Urinary tract infection				2
	Vaginal discharge	Urinary tract infection	Deep hands and feet burns	Headache: migraine		1
	Infection: acute cystitis: male	STD: bacterial urethritis				2
	STD: urthritis: male					1
	Acute sinusitis	Urethral discharge				1
	Muscle pains	STD: bacterial urethritis				1

Table A2 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Pietersburg	Urethral discharge	Penis: impotence: erectile				1
	Deep hands and feet burns	Headache: migraine	Vaginal discharge			1
	Vaginal discharge	Colon: acute diarrhoea	Otitis media			1
	Lower abdominal pain	Brochial asthma				1
	Lower abdominal pain	Constipation				1
Rosslyn	Epididymo orhitis					5
	Infection: acute cystitis: male	STD: urthritis: male	Genital ulcers			1
	Osteoarthritis	Esophageal reflux	Urinary tract infection			1
	STD: urthritis: male	Upper respiratory tract				1
	STD: urthritis: male					9
	Epididymo orhitis	Muscle pains				1
	STD: urthritis: male	Aphthous stomatitis	Cheilitis: angular	Viral: Influenza		1
	STD: bacterial urethritis					2
	STD: urthritis: male	Weakness				1
	Muscle pains	Viral: Influenza	STD: bacterial urethritis			1
	Superficial burns	Candida: balanitis	Colon: constipation	Infection: acute cystitis: male	STD: urthritis: male	1
	Candida: balanitis	Infection: acute cystitis: male	STD: urthritis: male			1
	STD: urthritis: male	Urinary tract infection				1
	STD: urthritis: male	General: fibromyalgia				1
	Abscess: groin					1
Verulam	Tuberculosis					1
					Subtotal	**158**
					No diagnosis indicated	**0**
					Total	**158**

Table A3: The number of medical conditions or disease states where doxycycline and digoxin was prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Hypertension					1
					Subtotal	1
					No diagnosis indicated	0
					Total	1

Table A4: The number of medical conditions or disease states where oxytetracycline and antacids were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Peptic ulceration					2
	Peptic ulceration	Rheumatoid arthritis				1
	Peptic ulceration	Severe tooth cavity	Tension headache			1
	Peptic ulceration	Severe tooth cavity	Tension headache	Depression		1
		bronchopneumonia				
	Peptic ulceration	Shoulder pain				1
	Peptic ulceration	Stress disorder: ptsd				1
	Peptic ulceration	Stress disorder: acute				1
Parow	Peptic ulceration	Viral: influenza				1
					Subtotal	10
					No diagnosis indicated	0
					Total	10

Table A5: The number of medical conditions or disease states where oxytetracycline and penicillin were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	Severe tooth cavity	Acne vulgaris: moderate				1
	Severe tooth cavity					1
					Subtotal	2
					No diagnosis indicated	0
					Total	2

Table A6: The number of medical conditions or disease states where theophylline and cimetidine were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Kwanobuhle	Superficial hands and feet burns	Scabies	Esophageal reflux	Infection: bronchitis: acute		1
Parow	Viral: Influenza					1
	Gastritis: uncomplicated	Cough				1
Pietersburg	Viral: Influenza	Peptic ulceration				1
Rosslyn	Gastritis: uncomplicated	Upper respiratory tract				1
	Viral: Influenza	Peptic ulceration				1
	Rheumatoid arthritis	Infection: bronchitis: acute				1
	Viral: Influenza	Esophageal reflux	Atopic dermatitis			1
	Viral: Influenza	Peptic ulceration	Infection: viral			1
Verulam	Peptic ulceration	Cough				1
	Gastritis: uncomplicated					1
	Urinary tract infections					1
	Gastritis: uncomplicated	Upper respiratory tract				1
	Tonsillitis: acute					1
	Infection: bronchitis: acute					1
	Gastritis: uncomplicated	Infection: bronchitis: acute				1
					Subtotal	**16**
					No diagnosis indicated	**0**
					Total	**16**

Table A7: The number of medical conditions or disease states where doxycycline and oral contraceptives were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Groblersdal	General examination	Pelvic inflammatory disease				1
Parow	Family planning: depo provera	Pelvic inflammatory disease				1

Table A7 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	Family planning: depo provera	Pelvic inflammatory disease	Colon: constipation			1
	Pelvic inflammatory disease					1
	Esophageal reflux	Infection: salpingitis				1
	Family planning: depo provera	Vulvovaginitis: bacterial				1
					Subtotal	**6**
					No diagnosis indicated	**0**
					Total	**6**

Table A8: The number of medical conditions or disease states where doxycycline and calcium were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Groblersdal	Cramps	Pelvic inflammatory disease				1
Parow	Fungal infection: tinea					1
	Pelvic inflammatory disease	Low back pain	Cramps			1
Rosslyn	Menopause	Lower abdominal pain				1
	Amenorrhoea	Cervix: cervicitis	Weakness	Muscle pains		1
Verulam	Pelvic inflammatory disease					1
	Nephrotic syndrome					1
					Subtotal	**7**
					No diagnosis indicated	**0**
					Total	**7**

Table A9: The number of medical conditions or disease states where doxycycline and phenytoin were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Kwanobuhle	Varicose ulcers	Acute prostatitis	Epilepsy: general seizures			1
					Subtotal	1
					No diagnosis indicated	0
					Total	1

Table A10: The number of medical conditions or disease states where doxycycline and carbamazepine was prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Epilepsy: general seizures	Fungal infection: tinea unguium	Malaria			1
					Subtotal	1
					No diagnosis indicated	0
					Total	1

Table A11: The number of medical conditions or disease states where oxytetracycline and oral contraceptives were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Kwanobuhle	Acne vulgaris: moderate	Pregnancy: prophylaxsis				1
					Subtotal	1
					No diagnosis indicated	0
					Total	1

Table A12: The number of medical conditions or disease states where co-trimoxazole and phenobarbitone was prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Groblersdal	Epilepsy: general seizures	Upper respiratory tract				1
					Subtotal	1
					No diagnosis indicated	0
					Total	1

Table A13: The number of medical conditions or disease states where theophylline and carbamazepine were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Rosslyn	Epilepsy: treatment	Viral: influenza				1
					Subtotal	1
					No diagnosis indicated	0
					Total	1

Table A14: The number of medical conditions or disease states where theophylline and furosemide were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Groblersdal	Heart failure					1
	Low back pain	Cough				1
Parow	Viral: Influenza					1
	Heart failure: mild	Infection: bronchitis: acute				1
	Pleural effusion					1
Rosslyn	Hypertension	Heart failure: moderate	Viral: Influenza			1
	Heart failure: moderate	Upper respiratory tract	Anaemia: iron deficiency			1
Verulam	Heart failure: pulmonary					2
	Pleural effusion					1
					Subtotal	10
					No diagnoses indicated	4
					Total	14

Table A15: The number of medical conditions or disease states where theophylline and quinolone antibiotics were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Cough	Headache	Pelvic inflammatory disease			1
Groblersdal	Infection: bronchitis: acute	Pelvic inflammatory disease				1
Parow	Pelvic inflammatory disease	Cough				1

Table A15 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	Pelvic inflammatory disease	Cough	Fungal infection: tinea			1
	Pelvic inflammatory disease	Infection: bronchitis: acute				1
	Vulvovaginitis: bacterial	Rhinitis: allergic				1
	Infection: bronchitis: acute	Vulvovaginitis: bacterial				1
Pietersburg	Pelvic inflammatory disease					1
	Candida: balanitis	Acute pharangitis	STD: bacterial urethritis			1
Rosslyn	Infection: vulvovaginitis: gardnerella					1
	Pelvic inflammatory disease	Upper respiratory disease				1
Verulam	Infection: vulvovaginitis					1
					Subtotal	**12**
					No diagnoses indicated	**1**
					Total	**13**

Table A16: The number of medical conditions or disease states where theophylline and macrolide antibiotics were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Groblersdal	Infection: bronchopneumonia					2
	Infection: bronchitis: acute					6
	Viral: Influenza					1
	Acute laryngitis					1
	Infection: bronchiolitis					1
Kwanobuhle	Viral: infective mononucleosis					1

Table A16 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Kwanobuhle	Infection: bronchitis: acute					3
	Vaginal: discharge: children	Upper respiratory tract				1
	Impetigo	Viral: Influenza				1
	Infection: primary atypical pneumonia					1
	Infection: bronchitis: acute	Otitis media				1
Parow	Infection: bronchitis: acute					12
	Viral: Influenza					10
	Bacterial: pertussis					1
	Deep burns	Acute pharyngitis				1
	Infection: primary atypical pneumonia					1
	Follicular tonsillitis					1
	Infection: bronchitis: acute	Otitis media				1
	Otitis media					1
	Viral: Influenza	Toe: ingrown toenail				1
	Bronchial asthma					1
	Cough	Atopic dermatitis	Toe: ingrown toenail			1
	Viral: Influenza	Fungal infection: tinea				1
	Cough	Impetigo				1
Pietersburg	Conjunctiva: allergic					1
	Infection: bronchitis: acute					3
	Uricaria: acute	Cough				1
	Cough	Atopic dermatitis				2
	Brochial asthma	Upper respiratory tract				1
	Viral: Influenza					1

Table A16 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Pietersburg	Cough	Lower abdominal pain				1
	Cough	Cutaneous abscess				1
	Cough	Lower abdominal pain	Bites:dog			1
	Upper respiratory tract	Urinary tract infections				1
	Infection: bronchopneumonia					1
	Lower respiratory infection					2
	Upper respiratory tract	Otitis media				1
	Infection: primary atypical pneumonia					1
	Severe tooth cavity	Backache: general	Urticaria: chronic persistent	Upper respiratory tract		1
	Larynx: stridor					1
	Infection: bronchitis: acute	Chronic sinusitis				1
	Upper respiratory tract	Atenatal booking visit				1
	Upper respiratory tract					1
	Cough	Dermatitis herpitiformis				1
	Upper respiratory tract	Otitis media				1
	Cough	Follicular tonsillitis				1
	Cough	Genital ulcers				1
	Deep hands and feet burns	Headache: migraine	Upper respiratory tract	Genital ulcers		1
	Upper respiratory tract	Viral: measles				1
	Impetigo	Cough				1
Rosslyn	Bronchial asthma	Acute sinusitis				1
	Bronchial asthma					1
	Viral: Influenza					10
	Episodic weakness	Cough	Rhinitis: acute			1
	Respiration infection: bacterial	Conjuntiva: conjunctivitis				1

Table A16 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Rosslyn	Infection: bronchitis: acute	Hypertension				1
	Infection: bronchitis: acute					8
	Infection: bronchopneumonia					2
	Viral: Influenza	Family planning: depo provera	Stress disorders: ptsd			1
	Weakness	Upper respiratory tract	Urinary tract infections			1
	Viral: Influenza	Breasts: lumps				1
	Depression	Bronchial asthma	Infection: bronchitis: acute			1
	Infection: bronchitis: acute	Stress disorder: acute				1
	Otitis media: acute					1
	Acute pharyngitis					1
	Viral: Influenza	Osteoporosis	Hypertension	Hypothyroidism		2
	Viral: Influenza	Gastritis: uncomplicated	Muscle pains			1
	Viral: Influenza	Boils and carbuncles				1
	Nausea: non-specific	Infection: bronchopneumonia				1
	Infection: bronchitis: acute	Penis: impotence: erectile				1
	Viral: Influenza	Nappy rash				2
	Viral: Influenza	Hypertension	Anaemia: iron deficiency			1
	Muscle pains	Upper respiratory tract				1
	Viral: Influenza	Conjuntiva: conjunctivitis	Urticaria: acute			1
	Upper respiratory tract	Bacterial: erysipelas				1
	Episodic weakness	Bacterial: erysipelas	Fungal infection: tinea cruris	Cough		1
	Hypertension	Infection: bronchopneumonia				1

Table A16 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Verulam	Infection: bronchitis: acute					2
	Tonsils: tonsillitis					2
	Bronchial asthma	Chronic sinusitis				1
	Upper respiratory tract					3
	Viral: Influenza					1
	Acute tonsillitis					1
	Infection: bronchiolitis					2
					Subtotal	**140**
					No diagnoses indicated	**9**
					Total	**149**

Table A17: The number of medical conditions or disease states where theophylline and beta-blockers were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Hypertension	Infection: bronchiolitis				1
Pietersburg	Bites:dog	Cough	Lower abdominal pain			2
	Weakness	Hypertension	Viral: Influenza			1
					Subtotal	**4**
					No diagnoses indicated	**0**
					Total	**4**

Table A18: The number of medical conditions or disease states where theophylline and oral contraceptives were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	Viral: influenza					1
	Family planning: depo provera	Infection: bronchitis: acute				1
	Viral: influenza	Family planning: depo provera				2
					Subtotal	4
					No diagnoses indicated	0
					Total	4

Table A19: The number of medical conditions or disease states where theophylline and allopurinol were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	Cough					1
					Subtotal	1
					No diagnoses indicated	0
					Total	1

Table A20: The number of medical conditions or disease states where theophylline and thyroid hormones were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Rosslyn	Osteoporosis	Hypertension	Viral: Influenza	Hypothyroidism		2
	Hypertension	Hypothyroidism	Depression	Infection: bronchitis: acute		1
					Subtotal	3
					No diagnoses indicated	0
					Total	3

Table A21: The number of medical conditions or disease states where theophylline and calcium channel blockers were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Rosslyn	Hypertension	Upper respiratory tract				1
					Subtotal	**1**
					No diagnoses indicated	**0**
					Total	**1**

Table A22: The number of medical conditions or disease states where glibenclamide and aspirin were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Diabetes mellitus: type 2: follow-up	Infection: bronchopneumonia				1
Parow	Diabetes mellitus: type 2: follow-up	Unstable angina				1
Pietersburg	Diabetes mellitus: non-insulin dependant	Foot: diabetic foot	Urinary tract infections			1
Rosslyn	Diabetes mellitus: non-insulin dependant	Hypertension	Septic arthritis			1
	Hypertension	Diabetes mellitus: type 2: follow-up	Atopic dermatitis			1
	Diabetes mellitus: type 2: follow-up					1
					Subtotal	**6**
					No diagnoses indicated	**0**
					Total	**6**

Table A23: The number of medical conditions or disease states where glibenclamide and corticosteroids were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Groblersdal	Low back pain	Cough				1
Kwanobuhle	Diabetes mellitus: non-insulin dependant	Hand eczema	Hypertension			1
Pietersburg	Diabetes mellitus: type 2: follow-up	Muscle pains				1
Verulam	Arthralgia	Diabetes mellitus: non-insulin dependant				1
					Subtotal	**4**
					No diagnoses indicated	**2**
					Total	**6**

Table A24: The number of medical conditions or disease states where glibenclamide and hydrochlorothiazide were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Pietersburg	Diabetes mellitus: non-insulin dependant	Chronic prostatitis				1
	Diabetes mellitus: non-insulin dependant	Bites: dog	Cough			1
	Diabetes mellitus: non-insulin dependant	Hypertension	Upper respiratory tract	Urinary tract infections		1
	Diabetes mellitus: non-insulin dependant	Bites: dog				5
	Diabetes mellitus: type 2: follow-up					2
	Diabetes mellitus: type 2: follow-up	Cutaneous abscess	Sebaceous cysts	Scurvy		1
	Diabetes mellitus: non-insulin dependant	Hypertension	Viral: Influenza			1
	Hypertension	Diabetes mellitus: type 2: follow-up				2

Table A24 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Pietersburg	Diabetes mellitus: non-insulin dependant	Osteoarthritis				1
	Diabetes mellitus: non-insulin dependant					2
	Diabetes mellitus: type 2: follow-up	Headache				1
	Diabetes mellitus: non-insulin dependant	Osteoarthritis	Hypertension			1
	Diabetes mellitus: non-insulin dependant	Osteoarthritis	Bites: dog			1
	Hypertension	Diabetes mellitus: type 2: follow-up	Acute sinusitis			2
	Diabetes mellitus: type 2: follow-up	Weakness				2
	Diabetes mellitus: non-insulin dependant	Muscle pains	Otitis media			1
	Diabetes mellitus: non-insulin dependant	Foot: diabetic foot	Urinary tract infections			1
	Diabetes mellitus: type 2: follow-up	Low back pain	Viral: Influenza			1
	Diabetes mellitus: type 2: follow-up	Recto-anal conditions				1
	Diabetes mellitus: non-insulin dependant	Bites: dog	Mild: hand lacerations			1
Verulam	Diabetes mellitus: type 2: new					1
	Diabetes mellitus: non-insulin	Arthralgia				1
	Diabetes mellitus: type 2: follow-up	Osteoarthritis	Bronchial asthma			1
	Diabetes mellitus: non-insulin					5

Table A24 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Verulam	Diabetes mellitus: non-insulin	Tonsillitis				1
	Diabetes mellitus: non-insulin dependant	Cerebrovascular accident				1
	Arthralgia	Diabetes mellitus: non-insulin dependant	Bites: dog	Gastritis: uncomplicated		1
	Diabetes mellitus: non-insulin	Bites: dog				2
	Diabetes mellitus: non-insulin	Upper respiratory tract				2
	Abnormal vaginal bleeding: post menopause	Diabetes mellitus: non-insulin dependant				1
	Diabetes mellitus: non-insulin dependant					2
	Diabetes mellitus: non-insulin dependant	Arthralgia				1
	Diffuse myalgias					1
	Diabetes mellitus: non-insulin	Arthralgia	Gastritis: uncomplicated	Urinary tract infections		1
	Arthralgia					1
	Diabetes mellitus: non-insulin	Viral: Influenza				1
					Subtotal	**52**
					No diagnoses indicated	**17**
					Total	**69**

Table A25: The number of medical conditions or disease states where reserpine and sympathomimmetics were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Groblersdal	Hypertension					1
	Hypertension	Upper respiratory tract				1
	Hypertension	Viral: Influenza				3
	Upper respiratory tract					1
Verulam	Chronic gout					1
					Subtotal	**7**
					No diagnoses indicated	**1**
					Total	**8**

Table A26: The number of medical conditions or disease states where doxycycline and cimetidine were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Heartburn	Urethral discharge				1
	Urethral discharge	Peptic ulceration				1
Groblersdal	Pelvic inflammatory disease	Peptic ulceration				1
	Peptic ulceration	STD: urethritis in men				1
	Nausea: non-specific	Chronic prostatitis				1
	Peptic ulceration	Chronic prostatitis	Hypertension			1
Parow	Pelvic inflammatory disease					1
	Pelvic inflammatory disease	Gastritis: uncomplicated				1
	Gastritis: uncomplicated	Vulvovaginitis: bacterial	Diabetes mellitus: type 2: follow-up			2
	Esophageal reflux	Infection: salpingitis				1
	Pelvic inflammatory disease	Gastritis: uncomplicated	Infection: salpingitis			1
Pietersburg	Heartburn	Vaginal discharge				1
	Hypertension	Urinary tract infections				1
	Heartburn	Muscle pains	Lower abdominal pain			1

Table A26 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Rosslyn	Osteoarthritis	Esophageal reflux	Urinary tract infections			1
	Cervix: cervisitis	Muscle pains	Gastritis: uncomplicated			1
	Cervix: cervisitis	Gastritis: uncomplicated				1
	Gastritis: uncomplicated	Constipation	Pelvic inflammatory disease			1
	Cervix: cervisitis	Esophageal reflux				2
	Cervix: cervisitis	Esophageal reflux	Muscle pains			1
	Esophageal reflux	Pelvic inflammatory disease	Vulvovaginitis: candida			1
	Gastritis: uncomplicated	Lower abdominal pain				1
Verulam	Urinary tract infections					1
					Subtotal	**25**
					No diagnoses indicated	**0**
					Total	**25**

Table A27: The number of medical conditions or disease states where oxytetracycline and cimetidine were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Peptic ulceration					1
	Peptic ulceration	Infection: bronchopneumonia				1
	Peptic ulceration	Severe tooth cavity	Tension headache			1
	Peptic ulceration	Fungal infection: tinea pedis	Subacute sinusitis			1
Rosslyn	Gastritis: uncomplicated	Viral: Influenza				1
					Subtotal	**5**
					No diagnoses indicated	**0**
					Total	**5**

Table A28: The number of medical conditions or disease states where co-trimoxazole and digoxin were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Abnormal vaginal bleeding	Heart failure: cardiomyopathy				1
Groblersdal	Heart failure: refractory					1
	Heart failure: refractory	Colon: non-specific diarrhoea				1
	Heart failure: moderate: follow-up	Urinary tract infections				1
	Heart failure: refractory	Acute cystitis: female				1
	Acute cystitis: female	Hypertension				1
Parow	Acute cystitis: female	Hypertrophic cardio-myopathy				1
	Acute cystitis: female	Heart failure: mild: newly				1
Rosslyn	Diabetes mellitus: non-insulin dependant	Acute cystitis: female				1
	Acute cystitis: female	Diabetes mellitus: type 2: new	Heart failure: mild: newly			1
	Gastritis: uncomplicated	Kidney: acute pyelonephritis	Heart failure: cardio-myopathy			1
	Hypertension	Artrial fibrillation: heart failure	Cough	Urinary tract infections	Anaemia: general considerations	1
					Subtotal	**12**
					No diagnoses indicated	**0**
					Total	**12**

Table A29: The number of medical conditions or disease states where co-trimoxazole and oral contraceptives were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Family planning: depo provera	Diabetes mellitus: type 2: follow-up	Diabetes mellitus: type 2: good	Urinary tract infections		1
	Family planning: depo provera	Urinary tract infections				3

Table A29 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Groblersdal	Family planning: depo provera	Acute cystitis: female				4
	Family planning: depo provera	Acne vulgaris	Loose stools			1
	Tonsillitis					1
Kwanobuhle	Family planning: depo provera	Pain: dysmenorrhoea	Urinary tract infections			1
Parow	Family planning: depo provera	Infection: bronchitis: acute				1
	Family planning: depo provera	Viral: Influenza				1
	Family planning: depo provera	Acute cystitis: female				1
	Family planning: depo provera	Gastroenteritis				1
					Subtotal	**15**
					No diagnoses indicated	**0**
					Total	**15**

Table A30: The number of medical conditions or disease states where theophylline and anatcids were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Gastritis: uncomplicated					1
	Gastritis: uncomplicated	Tonsillitis: recurrent				1
Kwanobuhle	Esophageal reflux	Infection: bronchitis: acute	Scabies	Superficial hands and feet burns		1
Parow	Cough					1
	Viral: Influenza					1
	Conjuntiva: allergic	Heartburn	Lower respiratory infections			1
	Arthralgia	Subacute sinusitis				1

Table A30 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	Heartburn	Infection: bronchitis: acute	Rhinitis: allergic			1
	Viral: Influenza					2
	Gastritis: uncomplicated	Cough				2
	Infection: bronchitis: acute	Gastritis: uncomplicated				2
	Viral: Influenza	Recto-anal conditions				1
	Gastritis: uncomplicated					1
Rosslyn	Gastritis: uncomplicated	Upper respiratory tract				1
	Esophageal reflux	Viral: Influenza				2
	Gastritis: uncomplicated	Viral: Influenza				2
	Gastritis: uncomplicated	Cough	Otitis media			2
	Gastritis: uncomplicated					2
	Heartburn	Infection: bronchitis: acute				1
	Viral: Influenza	Reflex oesophagitis				1
	Upper respiratory tract	Colon: constipation	Urticaria: acute			1
	Esophageal reflux	Viral: Influenza	Atopic dermatitis			1
	Gastritis: uncomplicated	Viral: Influenza	Muscle pains			1
	Lower respiratory infections					1
	Gastritis: uncomplicated	Cough				1
	Gastritis: uncomplicated	Acute sinusitis				1
	Viral: Influenza	Heartburn				1
	Gastritis: uncomplicated	Infection: bronchitis: acute				1
	Gastritis: uncomplicated	Infection: bronchitis: acute	Aphthous ulcers			1
	Gastritis: uncomplicated	Infection: bronchopneumonia				1
	Trauma: fracture: ribs	Viral: Influenza				1

Table A30 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Verulam	Viral: Influenza					1
	Gastritis: uncomplicated	Upper respiratory tract				3
	Peptic ulceration	Cough				1
	Gastritis: uncomplicated	Tuberculosis	Infection: bronchitis: acute			1
	Upper respiratory tract					2
	Gastritis: uncomplicated	Infection: bronchitis: acute				1
	Gastritis: uncomplicated	Cough	Rheumatoid arthritis			1
	Cough	Severe tooth cavity	Reflex oesophagitis	Tension headache	Uricaria: papular	1
	Gastritis: uncomplicated	Tonsillitis				1
					Subtotal	**50**
					No diagnoses indicated	**2**
					Total	**52**

Table A31: The number of medical conditions or disease states where theophylline and bensodiasepines were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Backache: general	Infection: bronchitits: acute	Mild/moderate dental abscess			1
Groblersdal	Oral bacterial infection	Hypertension	Insomnia			3
	Oral bacterial infection	Hypertension	Insomnia	Low back pain		1
Kwanobuhle	Infection: bronchitis: acute	Insomnia	Oral bacterial infection			1
	Generalised anxiety disorder	Viral: Influenza				1
Rosslyn	Oral bacterial infection	Insomnia	Cough			1
	Stress disorder: acute	Viral: Influenza				1
	Viral: Influenza	Family planning: depo provera	Stress disorder: ptsd			1
	Cough	Amenorrhoea	Acute cystitis: female			1
	Cough	Severe tooth cavity	Tension headache	Weakness		1

Table A31 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Rosslyn	Viral: Influenza	Stress disorder: acute				2
	Deep burns	Low back pain	Acute pharyngitis			1
					Subtotal	**15**
					No diagnoses indicated	**0**
					Total	**15**

Table A32: The number of medical conditions or disease states where theophylline and loperamide were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Verulam	Upper respiratory tract					1
	Gastroenteritis					2
	Colon: non-specific diarrhoea	Infection: bronchitis: acute				1
					Subtotal	**4**
					No diagnoses indicated	**0**
					Total	**4**

Table A33: The number of medical conditions or disease states where glibenclamide and antacids were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Groblersdal	Diabetes mellitus: non-insulin dependant	Gastritis: uncomplicated				1
Kwanobuhle	Diabetes mellitus: non-insulin dependant	Hypertension	Gastritis: uncomplicated	Fungal infection: tinea cruris	Urinary tract infections	2
	Fibrositis					1
Parow	Diabetes mellitus: non-insulin dependant	Urinary tract infections				1
	Diabetes mellitus: non-insulin dependant	Gastritis: uncomplicated				2
	Gastritis: uncomplicated	Diabetes mellitus: type 2: follow-up	Diffuse myalgias			1

Table A33 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	Gastritis: uncomplicated	Diabetes mellitus: type 2: new				1
	Diabetes mellitus: type 2: new					1
	Gastritis: uncomplicated	Diabetes mellitus: type 2: follow-up	Vulvovaginitis: bacterial			1
	Gastritis: uncomplicated	Diabetes mellitus: type 2: follow-up				1
Pietersburg	Constipation	Diabetes mellitus: type 2: follow-up	Peptic ulceration			1
Rosslyn	Diabetes mellitus: non-insulin dependant	Esophageal reflux	Infection: acute cystitis: male	Knee: pain		1
	Diabetes mellitus: type 2: follow-up	Hypertension	Gastritis: uncomplicated			1
	Diabetes mellitus: type 2: follow-up	Hypertension	Gastritis: uncomplicated	Urinary tract infections		1
	Diabetes mellitus: non-insulin dependant	Peptic ulceration	Acute cystitis: female			1
	Diabetes mellitus: non-insulin dependant	Peptic ulceration				1
	Diabetes mellitus: type 2: follow-up	Esophageal reflux	Viral: Influenza			1
	Diabetes mellitus: non-insulin dependant	Esophageal reflux	Hypertension	Osteoarhtritis: generalised		1
	Diabetes mellitus: non-insulin dependant	Gastritis: uncomplicated	Conjuntiva: conjunctivitis			1
	Diabetes mellitus: non-insulin dependant	Hypertension	Gastritis: uncomplicated	Upper respiratory tract		1

Table A33 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Verulam	Weakness					1
	Diabetes mellitus: non-insulin dependant	Impetigo	Gastritis: uncomplicated			1
	Gastritis: uncomplicated	Diabetes mellitus: non-insulin	Arthralgia	Urinary tract infections		1
					Subtotal	**25**
					No diagnoses indicated	**1**
					Total	**26**

Table A34: The number of medical conditions or disease states where glibenclamide and captopril were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Diabetes mellitus: type 2: follow-up	Hypertension	Prostate: hyperplasia			1
	Diabetes mellitus: type 2: follow-up	Hypertension	Subacute sinusitis			1
	Diabetes mellitus: type 2: follow-up					1
	Diabetes mellitus: type 2: follow-up	Viral: Influenza				1
	Diabetes mellitus: type 2: follow-up	General examination	Genital ulcers			1
Kwanobuhle	Atopic dermatitis					1
	Diabetes mellitus: non-insulin dependant	Hypertension				1
	Diabetes mellitus: non-insulin dependant	Hypertension	Hand eczema			1
	Diabetes mellitus: type 2: follow-up	Osteoarthritis	Heart failure: cardiomyopathy			1
	Diabetes mellitus: non-insulin dependant	Low back pain				1

Table A34 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Kwanobuhle	Hypertension	Diabetes mellitus: insulin	Gastritis: uncomplicated	Fungal infection: tinea cruris	Urinary tract infections	1
	Fibrositis					1
	Hypertension	Eczema: chronic linchenoid	Fungal infection: tinea			1
Parow	Diabetes mellitus: type 2: follow-up	Gastroenteritis				1
	Diabetes mellitus: non-insulin dependant	Ankle: sprain				1
	Diabetes mellitus: type 2: follow-up					1
Pietersburg	Diabetes mellitus: type 2: follow-up					1
	Diabetes mellitus: non-insulin dependant					1
	Diabetes mellitus: non-insulin dependant	Hypertension	Urinary tract infections			1
Rosslyn	Diabetes mellitus: type 2: new	Acute gouty arthritis				1
	Reflux oesophagitis	Diabetes mellitus: type 2: follow-up	Hypertension	Chronic gout		1
	Diabetes mellitus: type 2: follow-up	Upper respiratory tract				1
	Diabetes mellitus: type 2: follow-up	Hypertension	Boils and carbuncles			1
	Diabetes mellitus: type 2: follow-up	Hypertension	Kidney stones			1
	Hypertension	Diabetes mellitus: non-insulin dependant				1
	Diabetes mellitus: type 2: follow-up	Hypertension				2

Table A34 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Rosslyn	Diabetes mellitus: type 2: new	Viral: Influenza				1
Verulam	Fibrositis					1
	Diabetes mellitus: non-insulin					1
					Subtotal	**30**
					No diagnoses indicated	**9**
					Total	**39**

Table A35: The number of medical conditions or disease states where multivitamin and corticosteroids were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Fibrositis	Weakness				1
Parow	Infection: bronchitis: acute					2
	Infection: bronchitis: acute	Bronchial asthma				1
Pietersburg	Diagnosis not indicated					1
Rosslyn	Episodic weakness					1
					Subtotal	**6**
					No diagnoses indicated	**5**
					Total	**11**

Table A36: The number of medical conditions or disease states where multivitamin and salicylate were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Brits	Oral bacterial infection	Insomnia	Arthralgia			1
	Muscle: trauma	Heartburn				1
	Lymphadenopathy: generalised	Edema				1
	Arthralgia	Respiratory infection: bacterial pneumonia				1
	Severe tooth cavity	Backache: general	Infection: bronchitis: acute	Pellagra		1
	Muscle pains	Subacute sinusitis				1
	Muscle pains	Subacute sinusitis	General examination			1
	Arthralgia	General examination	Rhinitis: allergic			1
	Gallstones: chronic cholecystitis	Viral: Influenza				1
	Weakness	Fibrositis				1
	Hypertension	Arthralgia				1
	Shoulder pain					2
Groblersdal	Pelvic inflammatory disease					3
	Neck pain					1
	Hypertension	General: fibromyalgia				1
	Infection: salpingitis					1
	Feeding problems	Muscle pains				1
	Infertility					2
	Hypertension					2
	Hypertension	Insomnia	Oral bacterial infection			1
	Costochondritis: tietze's					1
	Viral : Influenza					2
	Osteoarthritis: hip	Acute cystitis: female				1
	Mononeuropathies: radial					1
	Chronic prostatitis					1
	Severe tooth cavity	Superficial hands and feet burns	Pain: dysmenorrhoea	Tension headache	Scabies	1

Table A36 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Groblersdal	Weakness					1
	Acute cystitis: female					1
	Cough: TB contact					1
	Weakness	Low back pain				1
	General examination					1
Kwanobuhle	Osteoarthritis	Hypertension				1
	Low back pain	STD: bacterial urethritis	Headache			1
	Upper respiratory tract					1
	Upper respiratory tract	Penis: impotence: erectile				1
	Arthralgia					1
	Low back pain	Penis: impotence: erectile	Acute sinusitis	Infection: bronchitis: acute		1
	General: fibromyalgia					1
Parow	Viral: Influenza					48
	Tonsillar membrane					4
	Acute sinusitis					12
	Viral: Influenza	Severe tooth cavity	Backache: general			1
	Muscle pains					6
	Viral: Influenza	Neck pain				2
	Anaemia: general consideration	Headache: general				1
	Diffuse myalgias	Acute cystitis: female				1
	Low back pain					1
	Viral: Influenza	Muscle pains				5
	Acute cystitis: female					1
	Infection: bronchitis: acute					6
	Bronchial asthma	Acute pharyngitis				1
	Atopic dermatitis	Tonsillar membrane				1
	Anaemia: general consideration	Arthralgia				4

Table A36 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	Infection: bronchitis: acute	Fibrositis				1
	Impetigo					1
	Infection: bronchitis: acute	Muscle pains				1
	Muscle: trauma	Rhinitis: allergic				1
	Pleura: Bornholme disease					1
	Acute pharyngitis					2
	Viral: Influenza	Otitis media				1
	Viral: Influenza	Arthralgia	Gastroenteritis			1
	Fibrositis	Upper respiratory tract				1
	Viral: Influenza	Low back pain				3
	Arthralgia	Upper respiratory tract				1
	Boils and carbuncles	Fungal infection: tinea pedis				1
	Stress disorder: acute					1
	Deep burns	Diffuse myalgias	Acute pharyngitis			1
	Diffuse myalgias					1
	Pelvic inflammatory disease	Anaemia: iron deficiency				1
	Headache: general					2
	Severe tooth cavity	Tension headache	Urinary tract infections			1
	Diabetes mellitus: non-insulin dependant	Arthralgia				1
	Infection: bronchitis: acute	Low back pain				1
	Muscle pains	General examination				1
	Viral: Influenza	Arthralgia				1
	Urinary tract infections					4
	Urinary tract infections	Family planning: depo provera				1
	Tonsillitis					3

Table A36 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	STD: bacterial urethritis					1
	Low back pain	Tuberculosis				1
	Otitis media					2
	Muscle pains	Tonsillitis	Infection: bronchitis: acute			1
	Diffuse myalgias	General examination				1
	Arthralgia					3
	Vulvovaginitis: bacterial					1
	Fungal infection: tinea	Knee: pain				1
	Superficial hands and feet burns					1
	Viral: Influenza	Boils and carbuncles				1
	Tonsillitis: recurrent					1
	Atopic dermatitis	Diffuse myalgias				1
	Deep burns	Acute pharyngitis				2
	Acute cystitis: female	Acute sinusitis				1
	Viral: Influenza	Otitis externa: acute				1
	Viral: Influenza	Family planning: depo provera				1
	Knee: pain					1
	Tonsils: acute					1
	Viral: Influenza	Foot: achilles tenditis				1
	Viral: Influenza	Colon: spastic colon				1
	Viral: Influenza	Muscle: cramps				1
	Viral: Influenza	Knee: pain				1
	Low back pain	Upper respiratory tract				2
	Infection: bronchitis: acute	Arthralgia				1
	Viral: Influenza	Backache: general				1
	Arthralgia	Upper respiratory tract				1
	Viral: Influenza	Conjuntiva: conjuctivitis				1
	Low back pain	Urinary tract infections				1

Table A36 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	Viral: Influenza	Gastroenteritis				1
	Viral: Influenza	Atopic dermatitis				1
	Infection: bronchitis: acute	Arthralgia				1
	Muscle pains	Cervical lymph nodes				1
	Viral: Herpes zoster	Viral: Influenza				1
	Ankle: sprain					1
	Viral: Influenza	Urinary tract infections				1
Pietersburg	Low back pain					9
	Diabetes mellitus: type 2: follow-up	Osteoarthritis				1
	Low back pain	Mild/moderate dental abscess	Backache: general			1
	Osteoarthritis	Diabetes mellitus: non-insulin dependant	Episodic weakness			2
	Osteoathritis	Diabetes mellitus: non-insulin dependant				1
	Diabetes mellitus: type 2: follow-up	Rheumatoid arthritis				1
	Menopause	Diffuse myalgias	Headache: migraine			1
	Menopause	Chronic sinusitis				1
	Muscle pains					6
	Fibrositis	Urinary tract infections				1
	STD: urethritis in men					1
	Episodic weakness	Muscle pains	Genital ulcers			1
	Low back pain	Diabetes mellitus: non-insulin dependant	Urinary tract infections			1
	Backache: general	Severe tooth cavity				4
	Low back pain	Lower abdomial pain				1
	Muscle pains	Otitis media	Protein energy malnutrition			1
	General examination					1

Table A36 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Pietersburg	Pain: dysmenorrhoea	Colon: non-specific diarrhoea				1
	Muscle: trauma					3
	Muscle pains	Episodic weakness	Urticaria: chronic persistent			1
	Viral: Influenza					17
	Episodic weakness	Deep hands and feet burns	Cramps	Headache: migraine		1
	Viral: Influenza	Atopic dermatitis				1
	Esophagus: carcinoma					2
	Septic arthritis					1
	Viral: Influenza	Anaemia: iron deficiency				1
	Recto-anal conditions	Acute gouty arthritis	Lower abdominal pain			1
	Muscle pains	Lower respiratory disease				2
	Muscle pains	Cramps				1
	Muscle pains	Bites: dog				1
	Muscle pains	Peptic ulceration				1
	Conjunctiva: pterygium	Weakness	Cough			1
	Stress disorder: ptsd					1
	Sciatica	Penis: impotence: erectile				1
	Diffuse myalgias	STD: urethritis in men	Urethral discharge			1
	Episodic weakness	Nausea: non-specific				1
	Shoulder pain					1
	Muscle pains	Lower abdomial pain				2
	Arthralgia					1
	Weakness	Diffuse myalgias	Esophageal reflux			1
	Episodic weakness	Neck pain	Upper respiratory tract			1
	Viral: Influenza	Vulvovaginitis: candida	Urinary tract infections			1
	Ankle: sprain	Urinary tract infections				1
	Heartburn	Knee: dislocation				1
	Backache: general	Depression				1
	Acute gouty arthritis					2

Table A36 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Pietersburg	Lower abdominal pain					1
	Deep hands and feet burns	Muscle pains	Headache: migraine			4
	Oral bacterial infection	Pain: dysmenorrhoea	Insomnia			1
	Severe tooth cavity	Backache: general	Lower abdominal pain			1
	Deep hands and feet burns	Headache: migraine	Severe tooth cavity	Backache: general		1
	Severe tooth cavity	Tension headache	Shoulder pain	Episodic weakness		1
	Severe tooth cavity	Backache: general	Mild - other lacerations			1
	Severe tooth cavity	Low back pain	Tension headache	Episodic weakness		1
	Osteoarthritis	Hypertension				1
	Diffuse myalgias					4
	Lower abdominal pain	Pain: dysmenorrhoea				1
	Severe tooth cavity	Tension headache	Low back pain			1
	Low back pain	Weakness	Hypertension	Flatulence		1
	Fibrositis					1
	Weakness	Viral: Influenza				1
	Impetigo					1
	Acute tonsillitis					1
	Bruises and abrasions					3
	Rheumatoid arhtritis	Headache				1
	Ankle: sprain: severe					1
	Severe tooth cavity	Backache: general	Acute pharyngitis	Tonsillitis		1
	Knee: pain					2
	Muscle pains	Conjunctiva: allergic				1
	Low back pain	Hand, foot and mouth disease	Infection: epiglottitis			1
	Infection: bronchitis: acute	Infection: epiglottitis				1
	Osteoarthritis					2
	Deep hands and feet burns	Pain: dysmenorrhoea	Headache: migraine			1

Table A36 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Pietersburg	Severe tooth cavity	Backache: general	Engorged breast			1
	Deep hands and feet burns	Headache: migraine	Diffuse myalgias			1
	Muscle pains	General examination				1
	Mild- other lacerations					1
	Low back pain	Upper respiratory tract				1
	Low back pain	Episodic weakness				1
	Low back pain	Cough				1
	Deep hands and feet burns	Shoulder pain	Headache: migraine			3
	Urinary tract infections					4
	Atopic dermatitis	Diffuse myalgias				2
	Infection: cellulitis					1
	Oral bacterial infection	Insomnia	Muscle pains	Episodic weakness		1
	Knee: pain	Oral thrush				1
	Severe tooth cavity	Backache: general	Low back pain	Pruritis ani		1
	Viral: Influenza	Muscle pains	Episodic weakness			1
	Weakness					3
	Viral: Influenza	Weakness				2
	Headache					1
	Muscle pains	Weakness				1
	Viral: Influenza	Candida: Balanitis				1
	Weakness	Abnormal vaginal bleeding				1
	General: fibromyalgia					1
	Pain: dysmenorrhoea	Atopic dermatitis				1
	Peptic ulceration					1
	Vulvovaginitis: candida	Weakness	Viral: Influenza			1
	Neck spasm					1
	Follicular tonsillitis					1
	Otitis media: chronic					1
	Engorged breast					1

Table A36 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Pietersburg	Muscle pains	Epilepsy: treatment	Constipation			1
	Peritonsillar abscess					1
	Constipation	Lower abdominal pain				1
	Weakness	Osteoarthritis: spine				1
Rosslyn	Muscle pains	Episodic weakness	Stress disorder: acute			1
	Episodic weakness	Backache: general	Nausea: non-specific	Constipation		1
	Jaundice					1
	Diabetes mellitus: type 2: follow-up	Muscle pains	Fungal infection: tinea cruris			1
	Muscle pains	Weakness	Acute cystitis: female			1
	Upper respiratory tract					2
	Muscle: trauma	Hair loss: alopecia areata				1
	Muscle pains	Reflux oesophagitis	Episodic weakness			1
	Upper respiratory tract	Episodic weakness	Osteoarthritis: knee	Viral warts: plantar		1
	Colon: non-specific diarrhoea	Ankle: sprain				1
	Muscle pains	Episodic weakness	Diabetes mellitus: type 2: follow-up			1
	Episodic weakness	Colic	Pleura: pleurodynia			1
	Perianal abscess					1
	Episodic weakness	Osteoarthritis: generalised				1
	Muscle pains	Episodic weakness				1
	Muscle pains	Gastritis: uncomplicated	Urticaria: acute			1
	Weakness	Infection: cellulitis	Infection: acute cystitis: male			1
	Menopause	Osteoarthritis: generalised	Acute pancreatitis			1
	Menopause	Acute pancreatitis	Osteoarthritis			1
	Atopic dermatitis	Muscle pains	Episodic weakness	Cough		1
	Muscle pains	Colon: constipation	Upper respiratory tract			1
	Parasites: hook worm					1

Table A36 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Verulam	Arthralgia					11
	Liver: cirrhosis: alcoholic	Liver: hepatitis: alcoholic				1
	Cough					1
	Chronic sinusitis					1
	Fibrositis					1
	Eczema: chronic linchenoid					1
	Diabetes mellitus: type 2: follow-up	Rheumatoid arthritis				1
	Upper respiratory tract					2
	Rheumatoid arhtritis					5
	Diffuse myalgias	Urticaria: acute				1
	Weakness					2
	Weakness	Arthralgia				1
	Infection: bronchitis: acute	Infection: bronchopneumonia				1
	Pain: dysmenorrhoea					1
	Backache: general					1
	Osteoarthritis	Eczema: linchen simplex				1
	Osteoarthritis					1
	Arthralgia	Infection: cellulitis				1
	Urinary tract infections					1
	Arthralgia	Ascaris: roundworm				1
	Aphthous ulcers	Anaemia: general consideration				1
	Weakness	Fibrositis	Cough			1
	Breast abscess					1
	Arthralgia	Eczema: linchen simplex				1
	Arthralgia	Eczema: chronic linchenoid	Infection: viral: warts			1
	Arthralgia	Anaemia: general consideration				2

Table A36 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Verulam	Episodic weakness					2
	Viral: Influenza					2
	Trauma: head injury					1
	Fungal infection: tinea	Acute sinusitis				1
	Weakness	Infection: cellulitis				1
	Muscle pains					1
					Subtotal	**450**
					No diagnoses indicated	**4**
					Total	**454**

Table A37: The number of medical conditions or disease states where reserpine and digoxin were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Groblersdal	Heart failure: moderate: follow-up	Urinary tract infections				1
					Subtotal	**1**
					No diagnoses indicated	**3**
					Total	**4**

Table A38: The number of medical conditions or disease states where reserpine and tricyclic antidepressants were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred					n
Parow	Infection: cellulitis	Depression	Fungal infection: tinea			1
					Subtotal	**1**
					No diagnoses indicated	**1**
					Total	**1**

Table A39: The number of medical conditions or disease states where diclofenac and thiazide diuretics were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred									n
Brits	Viral: Influenza									1
	Hypertension	Arthralgia	Subacute sinusitis							1
	Viral: Influenza	Hypertension	Osteoarthitis: knee	Vaginal candidiasis						1
	Viral: Influenza	Hypertension	Menopause	Foot: achilles tendinitis						1
	Severe tooth cavity	Backache: general	Stress disorders: acute							1
	Hypertension	Backache: general	Mild/moderate dental abscess							3
	Arthralgia	Hypertension								2
	Hypertension	Shoulder pain								1
	Hypertension	Backache: general	Mild/moderate dental abscess	Cough						1
	Hypertension	Muscle: trauma								1
	Severe tooth cavity	Bites: dog	Tension headache	Shoulder pain						1
	Hypertension	Knee: pain								1
	Hypertension	Diffuse myalgias								1
	Muscle pains									1
	Shoulder pain	Hypertension	Diabetes mellitus: type 2: follow-up	Urinary tract infections						1
	Mild/moderate dental abscess	Backache: general	Stress disorders: acute	Oedema						1
	Hypertension	Backache: general	Mild/moderate dental abscess	Peptic ulceration						1
	Hypertension	Backache: general	Mild/moderate dental abscess	Viral: Influenza						1
	Hypertension	Osteoarthritis: knee								1
	Hypertension	Viral: Influenza	Arthralgia	Otitis media						1

Table A39 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred									n
Brits	Hypertension	Arthralgia	Infection: bronchitis :acute							1
	Arthralgia	Bites: dog								1
	Oral bacterial infection	Menopause	Insomnia	Osteoporosis	Hypertension	Arthralgia	Muscle pains	Colic	Constipation	1
	Rheumatoid arthritis									1
	Trauma: fracture foot	Hypertension								1
	Diffuse myalgias	Oedema								1
	Hypertension	Infection: bronchopneumonia								1
Groblersdal	Hypertension	Urinary tract infections								1
	Hypertension	Osteoarthitis: erosive	Impetigo							1
	Hypertension	Severe tooth cavity	Backache: general							1
	Hypertension	Osteoarthitis: knee	Atopic dermatitis							1
	Hypertension	Osteoarthitis								7
	Neck spasm									1
	Hypertension									11
	Heart failure: refractory									5
	Heart failure: refractory	Osteoarthritis								1
	Severe tooth cavity	Backache: general	Heart failure: refractory							1
	Hypertension	Neck pain								1
	Hypertension	Depression								1

Table A39 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred									n
Groblersdal	Hypertension	Infection: bronchitis: acute								1
	Osteoarthritis									1
	Heart failure: coronary									1
	Hypertension	Osteoarthitis: knee								3
	Osteoarthritis: hip									1
	Hypertension	Shoulder pain								1
	Glaucoma									1
	Hypertension	Diffuse myalgias								1
	Hypertension	Muscle pains	Acute cystitis: female							1
	Mild/moderate dental abscess	Backache: general	Heart failure: moderate							1
	Hypertension	Fibrositis	Chronic prostatitis							1
	Hypertension	Low back pain								1
	Heart failure: moderate									1
	Hypertension	Mild/moderate dental abscess	Backache: general	Chronic prostatitis						1
Kwanobuhle	Osteoarthritis: generalised	Hypertension								1
	Arthralgia	Constipation	Dilated cardio-myopathy							1
	Hypertension	Severe tooth cavity	Seborrhoeic dermatitis	Backache: general						1
	Hypertension	Viral: Influenza	Diffuse myalgias							1

Table A39 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred									n
Kwanobuhle	Hypertension	Arthralgia	Diabetes mellitus: non-insulin dependant							1
	Diabetes mellitus: type 2: follow-up	Osteoarthritis	Heart failure: cardiomyophathy							1
	Severe tooth cavity	Backache: general	Heart failure: mild: new	Tonsillitis: acute						1
	Neck spasm	Heart failure: mild: follow-up								1
Parow	Muscle pains									1
	Infection: cellulitis									1
	Muscle pains	Urinary tract infections								1
Rosslyn	Muscle: trauma	Hypertension								6
	Hypertension	Osteoarthritis								2
	Hypertension	Arthralgia	Cough							1
	Hypertension	Severe tooth cavity	Backache: general							1
	Hypertension	Osteoarthritis: knee								2
	Hypertension	Septic socket	Osteochondritis	Fungal infection: tinea pedis						1
	Hypertension	Muscle pains								8
	Hypertension	Septic arthritis								5
	Hypertension	Acute cystitis: female								1
	Severe tooth cavity	Backache: general								1
	Hypertension	Septic arthritis	Oral bacterial infection	Diabetes mellitus: non-insulin dependant	Insomnia					1

Table A39 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred									n
Rosslyn	Hypertension	Neck pain	Infection: viral							1
	Hypertension	Sciatica								1
	Severe tooth cavity	Tension headache	Weakness	Osteoarthritis						1
	Hypertension	Acute gouty arthritis	Chronic gout							1
	Acute gouty arthritis	Chronic gout								1
	Weakness	Arthralgia	Herpes simplex							1
	Hypertension	Menopause	Low back pain							1
	Hypertension	Low back pain	Hypothyroidism							1
	Hypertension	Backache: general	Gastritis: uncomplicated							1
	Hypertension	Knee: pain	Acute cystitis: female							1
	Hypertension	Muscle pains	Urticaria: acute							1
	Hypertension	Acute cystitis: female	Septic arthritis							2
	Neck pain									1
	Hypertension	Cramps								1
	Hypertension	Osteoarthritis	Diabetes mellitus: non-insulin dependant							1
	Muscle pains									3
	Muscle pains	Infection: acute cystitis: male								1
	Hypertension	Osteoarthritis: generalised	Upper respiratory tract							1
	Hypertension	Weakness	Muscle pains							2
	Hypertension	Acute gouty arthritis	Acute cystitis: female							1
	Knee: pain									3

Table A39 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred									n
Rosslyn	Hypertension	Muscle pains	Severe tooth cavity	Diabetes mellitus: type 2: follow-up	Backache: general					1
	Gastritis: uncomplicated	Kidney: acute pyelonephritis	Heart failure: cardiomyopathy							1
	Backache: general	Mild/moderate dental abscess								2
	Knee: pain	Fungal infection: tinea cruris								1
	Hypertension	Muscle pains	Acute cystitis: female							1
	Osteoarthritis: knee									1
	Backache: general	Mild/moderate dental abscess	Nausea: non-specific							1
	Hypertension	Knee: pain								1
	Diabetes mellitus: type 2: follow-up	Heart failure: mild: new	Chronic sinusitis							1
	Osteoarthritis	Rhinitis: acute								1
	Osteoarthritis									1
	Weakness	Muscle pains								1
	Osteoarthritis: knee	Infection: acute cystitis: male	Urticaria: papular							1
	Fibrositis	Gastritis: uncomplicated								1
	Severe tooth cavity	Diabetes mellitus: non-insulin dependant	Esophageal reflux	Backache: general						1
	Diabetes mellitus: non-insulin dependant	Esophageal reflux	Hypertension	Osteoarthritis: generalised						1
	Severe tooth cavity	Backache: general	Hypertension	Diabetes mellitus: type 2: follow-up						1

Table A39 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred									n
Rosslyn	Hypertension	Tension headache								1
	Hypertension	General examination	Muscle pains	Urticaria: acute	Urinary tract infections					1
	Hypertension	Viral: Influenza								1
	Hypertension	General examination	Muscle cramps	Chronic diarrhoea						1
	Muscle: trauma									1
	Hypertension	Muscle pains	Weakness	Menopause						1
	Hypertension	Muscle pains	Diabetes mellitus: non-insulin dependant							1
Verulam	Varicose ulcers									1
	Arthralgia									12
	Arthralgia	Diabetes mellitus: non-insulin								1
	Diabetes mellitus: type 2: follow-up	Osteoarthritis	Bronchial asthma							1
	Fibrositis									1
	Varicose ulcers	Viral: Influenza								1
	Upper respiratory tract									8
	Arthralgia	Bites: dog								5
	Arthralgia	Bites: dog	Ascaris: roundworm							1
	Upper respiratory tract	Bites: dog								3
	Viral: Influenza									1
	Arthralgia	Upper respiratory tract	Bites: dog							2

Table A39 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred									n
Verulam	Arthralgia	Otitis externa: acute								1
	Otitis media									1
	Osteoporosis									1
	STD: bacterial urethritis									1
	Fungal infection: tinea									1
	Bites: dog									3
	Arthralgia	Upper respiratory tract	Fungal infection: tinea							1
	Tonsillitis									1
	Arthralgia	Upper respiratory tract								2
	Diabetes mellitus: non-insulin									2
	Rheumatoid arthritis									1
	Kidney: acute pyelonephritis									1
	Diabetes mellitus: non-insulin	Viral: Influenza								1
	Infection: cellulitis									2
	Arthralgia	Eczema: moist								1
	Upper respiratory tract	Abnormal vaginal bleeding								1
	STD: Herpes genitalia									1
	Arthralgia	Gastritis: uncomplicated								1
	Bites: dog	Varicose ulcers								1

Table A39 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred									n
Verulam	Diabetes mellitus: non-insulin dependant	Weakness	Arthralgia							1
	Pharyngitis: recurrent									1
	Arthralgia	Acute sinusitis								1
	Acute tonsillitis									1
									Subtotal	**236**
									No diagnoses	**15**
									Total	**251**

Table A40: The number of medical conditions or disease states where diclofenac and beta-blockers were prescribed together.

Medi centres	Medical conditions or disease states where drug-drug interactions occurred									n
Brits	Oral bacterial infection	Menopause	Insomnia	Osteoporosis	Hypertension	Arthralgia	Muscle pains	Colic	Constipation	1
	Shoulder pain	Hypertension								1
Groblersdal	Mild/moderate dental abscess	Hypertension	Backache: general							1
Kwanobuhle	Recto-anal conditions	Diabetes mellitus: insulin	Hypertension	Arthralgia						1
	Hypertension	Acute gouty arthritis								1
	Diabetes mellitus: non-insulin	Osteoarthritis								1
Parow	Arthralgia									1
	Knee: pain									1
	Acute gouty arthritis									3
	Muscle pains	Fungal infection: tinea								1

Table A40 (continued)

Medi centres	Medical conditions or disease states where drug-drug interactions occurred									n
Parow	Low back pain									2
	Gastroenteritis									1
	Bites: dog	Chronic gout								1
Pietersburg	Osteoarthritis	Hypertension								1
	Hypertension	Muscle pains	Viral: Influenza							1
Rosslyn	Deep burns	Diabetes mellitus: non-insulin dependant	Hypertension	Acute pharyngitis						1
	Hypertension	Severe tooth cavity	Backache: general	Gastritis: uncomplicated						1
	Hypertension	Acute cystitis: female	Knee: pain							1
	Hypertension	Weakness	Muscle pains							1
	Osteoarthritis	Rhinitis: acute								1
Rosslyn	Hypertension	Muscle pains	General examination	Urticaria: acute	Urinary tract infections					1
	Hypertension	Neck spasm	Menopause	Anaemia: iron deficiency						1
	Hypertension	Knee: pain	Menopause	Atopic dermatitis						1
Verulam	Upper respiratory tract									1
	Septic socket	Muscle: trauma								1
	Viral: Influenza									1
									Subtotal	**29**
									No diagnoses	**0**
									Total	**29**