UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Prescription patterns and drug duplication in specialist outpatient clinics at a tertiary hospital in the greater Tshwane metropolitan area

Musawenkosi Genius Ncube

A dissertation submitted in fulfilment of the requirements for the degree

Magister Scientiae

in

Pharmacology

In the Faculty of Health Sciences

University of Pretoria

February 2020

Supervisor: Dr A Marais (Department of Pharmacology, UP)

Co-supervisor: Dr GP Grobler (Department of Psychiatry, SBAH)

Declaration of Originality

University of Pretoria
Faculty of Health Sciences
Department of Pharmacology

I, Musawenkosi G Ncube,

Student number: 16301375
Subject of the work: Prescription patterns and drug duplication in specialist outpatient clinics at a tertiary hospital in the greater Tshwane metropolitan area

Declaration

1. I understand what plagiarism entails am aware of the University's policy in this regard.
2. I declare that this project (dissertation) is my own, original work. Where someone else's work was used (whether from printed source, the internet or any other source) due acknowledgement was given and reference was made according to departmental requirements.
3. I did not make use of another student's previous work and submitted it as my own.
4. I did not allow will not allow anyone to copy my work with the intention of presenting it as his or her own work.

Signature:

Acknowledgements and Funding

The University of Pretoria for funding my studies is hereby acknowledged.

I would like to thank Prof. Steenkamp and the Department of Pharmacology for affording me the opportunity to pursue my Master's degree and further my knowledge of pharmacology with the hope to continue contributing in the growth of the field.

To my supervisor Dr. Andre Marais, thank you for believing in me yet again and continuing to guide me through my postgraduate studies. Your expertise has been of great help in advancing my research skills and this study would not have been possible without your guidance and patience.

To my co-supervisor Dr. Gerhard Grobler, thank you for your expert analysis and providing a different set of knowledge beyond pharmacological skills.

To Prof. Piet Becker, thank you for your assistance with statistical analysis.
To Dr. Mangwane, thank you for the permission to carry out the study at Steve Biko Academic Hospital.
To Mr. Somo at the Steve Biko Academic Hospital registrar office, thank you for your help in ensuring all hospital records were made readily available.

In the list of people to thank, the greatest gratitude goes to the strong women in my life; mama (Sheila), sister (Samu) and partner (Sandie), none of this would be possible without your love, patience, sacrifices and prayers. This degree is a dedication to my role models my father and brother (NN Ncube and Thabani), never forgotten. To the rest of the family, Bryan, Cedric, Keith, Mmeli, Mkhululi, Nyarai, Themba and Trevor, thank you for the support.

"For everything comes from Him and exists by His power and is intended for His glory. All glory to Him forever! Amen."

Ethics

Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria for the collection of medical information from SBAH patients (Approval number: 508/2018, appendix 1). Approval to carry out the study was also obtained from the Faculty of Health Sciences Masters Committee. Permission to collect data from the prescriptions at the hospital pharmacy, including perusal of the appointment logbooks from the different outpatient departments, was obtained from the Steve Biko Academic Hospital chief executive officer (CEO) (appendix 2). The study was conducted in accordance to the 2013 revised version of the declaration of Helsinki, 1975 (appendix 3). Patient confidentiality was ensured through the exclusion of any identifying personal information on the data-capturing sheet.

Abstract

Keywords: Chronic diseases, comorbidity, hospital information system, irrational drug prescribing, multiple visits and tertiary hospitals.

Background: Tertiary hospitals have multiple specialist outpatient clinics attended by patients suffering from various comorbid diseases. This results in individuals attending more than one clinic per month, since dedicated clinic days are seldom on the same day. As patients attend discrete clinics, they have separate encounters with various prescribers, increasing the potential for irrational drug use. In addition, multiple clinic visits have a negative socio-economic impact on health care users from poorer communities where financial resources are limited due to transport expenses and days of work missed. The aim of this study was to determine the prescribing pattern of drugs to chronic disease outpatients, and find possible solutions to provide a system that would reduce overprescribing of chronic medication at Steve Biko Academic Hospital (SBAH) in one measure namely drug duplication.

Methods: A retrospective descriptive cross-sectional study with the use of convenience sampling was employed to determine the medication prescribing practises to comorbid chronic disease patients attending multiple specialist clinics at SBAH from February 1, 2018-May 31, 2018. Participants were selected according to their appearance in the hospital records, with sample saturation reached when each participant had visited all the different clinics. Chronic disease outpatients attending the SBAH clinics had reviews every three months. The reviews were controlled by issuing patients with medication for a three-month period, where after a follow up visit was mandatory in order to ensure prescription and medication renewal. Therefore, each patient visited all the clinics rendering a service relating to a specific chronic condition within a four-month period that determined the study period chosen. Hospital records of patients attending the most frequently visited clinics as reported by the SBAH Pharmacy and Therapeutics committee (PTC) were evaluated. These clinics included outpatient departments of diabetes, haematology, internal medicine, neurology, oncology and psychiatry. Each drug prescription observed was evaluated using guidelines of World Health Organization

(WHO) titled, "*How to investigate drug use in health facilities: selected drug use indicators."* Prescribing indicators relevant to this study were used from the WHO guidelines.

Results: One hundred and six patients were multiple clinic-attendees during the study period. Of the 106 patients retained, 103 (97.17%) patients attended two clinics and three (2.83%) patients attended three clinics. Regarding the WHO prescribing indicators, the average number of visits to SBAH by the comorbid chronic disease outpatients observed was 3.03 visits during the four-month study period. Prescription analysis included 80 (75.47%) patients out of 106 patients attending multiple clinics at the same time. The average number of drugs prescribed per encounter was 4.97. The results also showed that 45.45% of the 187 prescriptions observed contained five or more drugs. Most frequently prescribed drugs were tramadol 51 (5.49%), followed by simvastatin 48 (5.17%) and enalapril 45 (4.84%). Drug duplication occurred in 68 individual cases in the 80 patients observed. In total, drug duplication affected 39 patients (48.75%) [95% CI = 37.80%: 59.70%]. The most duplicated drug classes were analgesics 18 (26.47%), followed by anti-depressants 14 (20.59%) cases recorded.

Conclusion: The results from this study support findings from similar studies at different institutions. The study confirmed multiple clinic visits are prevalent in the medical disciplines, often prescribing drugs from the same class. Clinical implications from these frequent and separate encounters may result in irrational prescribing, adverse drug events, drug-drug interactions and polypharmacy. The establishment of polypharmacy to comorbid chronic disease patients indicates the high risk of drug-drug interactions and adverse drug events. A prospective study would have provided more data for analysis to determine the level of polypharmacy and drug duplication. Thus, supplementation of this study with further studies could provide conclusions on whether the patients suffered from problematic or had appropriate polypharmacy. Physicians treating multiple clinic-attendees should be equipped to monitor rationality of prescribing encounters. Installation of an advanced electronic Hospital Information System (HIS) could aid in improving drug prescribing in tertiary hospitals. Use of electronic prescribing tools as shown in previous

studies is a requirement to improve tertiary hospitals in developing countries such as SBAH. The incidence of drug duplication at SBAH builds on existing evidence of unnecessary healthcare costs because of medication errors.

Table of contents

List of Figures

List of Tables

Abbreviation List

%	Percent
US$	United States of American Dollar
ADE	Adverse drug effect
ADR	Adverse drug reaction
AGS	American Geriatrics Society
AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
CEO	Chief executive officer
Ci	Confidence interval
COPD	Chronic obstructive pulmonary disease
CSIR	Council for Scientific and Industrial Research
CYP450	Cytochrome P450
DDI	Drug-drug interactions
e-Health	electronic Health
FDA	Food and Drug Administration
GORD	Gastro-oesophageal reflux disease
HIS	Hospital information system
HIV	Human immunodeficiency virus
HNSF	National Health Normative Standards Framework for Interoperability in e-Health in South Africa
HPRN	Health Patient Registry Number
HRQOL	Health-related quality of life
ICT	Information communication technology
IT	Information technology
Max cost	Maximum cost
MIMS	Monthly index of medical specialities
Min cost	Minimum cost
MOPD	Internal medicine outpatient department
MSO	Medication safety officer
NDoH	National department of health

NHI	National Health Insurance
NSAIDs	Non-steroidal anti-inflammatory drugs
OTC	Over-the-counter
PI	Principal Investigator
PIMS	Pakistan Institute of Medical Sciences
PPI	Proton pump inhibitor
PRIMA-eDS	Polypharmacy in chronic diseases- Reduction of Inappropriate Medication and Adverse drug events in older populations by electronic Decision Support
PTC	Pharmacy and Therapeutics Committee
SAMF	South African Medicine Formulary
SAMRC	South African Medical Research Council
SEP	Single exit price
SBAH	Steve Biko Academic Hospital
SD	Standard deviation
SSRI	Selective serotonin reuptake inhibitor
Stata	Statistical software package Stata Release 15.1
Stats SA	South African department of statistics
TB	Tuberculosis
THIS	Total Hospital Information System
USA	United States of America
VAT	Value Added Tax
WHO	World Health Organization

Chapter 1: Introduction and literature review

1.1. Global burden of disease

A World Health Organization (WHO) report published in June 2017 states that, "*chronic diseases tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioural factors.*"[4] The most common chronic diseases include hypertension, chronic obstructive pulmonary disease (COPD), stroke, hyperlipidaemia, diabetes mellitus, asthma, arthritis, cancer, hepatitis C and human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS).[5] These chronic conditions are among the leading causes of mortality according to the WHO. Approximately 40 million deaths worldwide are attributed to non-communicable diseases (cardiovascular disease, cancer, chronic respiratory disease and diabetes) annually.[5] Non-communicable diseases account for 70% of all deaths globally per year, with 80% (32 million people) residing in low and middle income countries, dying between the ages of 30 and 69 years.[4]

1.2. Disease burden in South Africa

South Africa is classified as an upper middle-income country according to the World Bank, with 55.50% of the population living under the poverty line.[6] Poverty of a majority of the population translates into an increased burden on the public health sector. South Africa is one of the most unequal countries in the world with wage gaps created by differences between the skill groups. Further differences are caused by the high unemployment rate reported at 29.1% in the third quarter labour force survey of 2019.[7] Poverty of a majority of the population in Africa is a factor in disease treatment. The average amount of money spent on healthcare per person in the Sub-Saharan Africa region has been estimated at US$100.00 and below per annum.[8] The amount of money used per person in Sub-Saharan Africa highlights the quality of services provided to the population. High-income countries spend a greater amount of money per person to help combat disease with higher quality resources. On average high-income countries spend over US$2,000.00 per person on health care expenditure per annum.[8] The estimate values on healthcare expenditure indicate the discrepancy in treatment quality between low income and high-income countries. High-income countries have abundant healthcare services and supplies allowing for efficient cover of communities. In remote areas, there are challenges in low-income countries in the provision of quality services.

Increasing levels of the HIV/AIDS pandemic in South Africa has contributed to an expansion in the chronic disease burden.[9] As of 2019, 7.97 million (13.50%) people in South Africa are estimated to be living with HIV.[10] Increase in HIV is demonstrated by the increase in incidence by 3.33 million people between 2002 and 2019.[10] The HIV/AIDS pandemic is one of the leading causes of premature mortality with numerous young adults affected. The death of young adults maintains or worsens the poverty cycle as children are orphaned, leaving them with insufficient financial resources and access to quality education. In addition, the cost of these chronic debilitating diseases negatively affects the elderly population who are tasked with spending their limited resources on caring for sick young adults.[9]

1.3. Risk factors in South Africa

Contributing to the occurrence of chronic diseases, are the risk factors leading to the presence of the different disease effects. These risk factors include lifestyle choices such as smoking, physical inactivity, drug and alcohol abuse and an excess sodium intake. Other risk factors include obesity, hyperglycaemia and hyperlipidaemia.[4, 5]

A high body mass index has been identified as a risk factor in the cause of non-communicable diseases like hypertension and diabetes mellitus.[11] South Africa is facing an obesity challenge as statistics show that across different races, the incidence of obese women is estimated between 48.90% and 58.50%.[12] An additional risk factor for hypertension is high sodium intake, where the majority of the South African population consumes above the recommended daily intake of salty foods. These effects and consequences are evident in the large amount of people receiving anti-hypertensive treatment.[11]

High blood glucose levels are established as another one of the leading causes of mortality with its effects seen in diabetes and stroke related deaths.[12] In a study performed in 2000, it was approximated that 20,000 (4.30%) of all deaths in South Africa were attributed to diabetes mellitus. Diabetes mellitus is the 7th leading cause of death in South Africa.[11]

Tobacco use is a known risk factor associated with increased probability of developing chronic respiratory diseases such as chronic bronchitis and COPD.[5] Globally tobacco smoking is estimated to be associated with 6 million deaths annually, causing 71% of lung cancer deaths and 42% of chronic respiratory disease deaths.[13] It is estimated that the national prevalence of tobacco smoking in South Africa is 16.40%, with an average of 7.40 cigarettes per day.[13] The smoking population has been reduced from 32% in 1993 to 16.40% in 2012.[13] The decline in smokers can be attributed to the education of the public concerning the risks associated with tobacco smoking.[13]

1.4. Economic consequences of disease burden

A 2002 World Health survey done in 72 low and middle-income countries including Zimbabwe, Ghana, Malaysia and China, has shown that impoverished people in these countries smoke more compared to the wealthy.[14] This study has shown how poverty-stricken countries are often vulnerable to certain chronic disease risk factors. Vulnerability to risk factors explains the high mortality rate in low-income countries due to chronic diseases.[4, 14] A secondary effect of chronic diseases is the reduction of labour productivity that leads to reduced income. The amount of time patients have to spend getting treatment negatively affects patients as they demur work duties. Furthermore, these patients face the stigma that mentally and physically unhealthy people have reduced productivity output, with job loss a consequence.[14]

Chronic diseases affect the economic development of South Africa among other low and middle income countries.[15] Between 2006 and 2014, losses to the South African gross domestic product due to diabetes, stroke and cardiovascular disease was estimated to be US$1.88 billion.[15] Companies and employers are affected by the number of hours staff members are absent due to illness, and the loss of employees to death caused by chronic diseases.[15] Obese workers are believed to cost employers significantly higher paid off-time than employees with a normal body mass index.[16] Chronic diseases are also seen to be affecting the poor communities as the death of underinsured relatives places an additional financial burden on numerous families that have to pay for funeral expenses.[15]

Regulatory boards across the world have implemented systems to control the price of medication with the observed increase in global chronic disease morbidity. The right to

access to medical care and affordable medication is regulated by policies aimed at pharmaceutical companies and healthcare providers.[17] In 1996 the South African government took a step to regulate medicine prices by the introduction of the National Drug Policy.[18] The policy enforced the use of a system that maintains an affordable visible consistency in drug supply from manufacturers, wholesalers, distributors and dispensing services. One of the main objectives of the National Drug Policy, was to introduce the single exit price (SEP) which was proposed to the minister of health by the national pricing committee.[18, 19] The government published regulations that contained the definition of SEP. The SEP was defined as, *"the price set by the manufacturer or importer of a medicine or scheduled substance, combined with the logistics fee and Value Added Tax (VAT), and is the price of the lowest unit of the medicine or scheduled substance within a pack multiplied by the number of unites in the pack."*[20] Implementation of the SEP into the South African pharmaceuticals market aided in the regulation of the private sector, to maintain affordable drugs for the population. The private sector has limited flexibility to add dispensing fees on the SEP that regulates how much the population spends on healthcare services in the country. There is an exclusion of the SEP in the control of drugs sold in the public sector. The government operates the public sector and uses prices of local companies elected through the tender process. Use of generics and the introduction of SEP has been seen as a step to reduce the consequences of disease burden on the economy.[21] Since the implementation of SEP, there has been a decrease in the cost of the majority of drugs including both new chemical entities and generics.[21, 22] The population receives regulated and cheapest possible drugs in the market whilst receiving quality drugs proven to be safe and effective.[17] Some studies however, have shown limited to no improvement on the cost of drugs upon implementation of price capitation on the pharmaceutical industry.[23] Further studies are still required to show the impact of price control on the general cost and impact on healthcare expenditure globally.

1.5. WHO global action plan

Healthy living through nutritious diets and increased physical activity, there is potential reduction of health care expenditure. Healthy diet and physical activity reduces the chances of obesity which is a risk factor associated with numerous chronic diseases.[16] Treatment of advanced chronic disease is much more costly than using preventative measures and delaying the onset of the disease.[16] Implementation of programmes in the

society to promote healthy living is believed to be a step in the reduction of the burden of chronic diseases on the healthcare system.[15, 16]

The WHO has estimated a loss of productivity and cost of health care to be US$7 trillion over the next 20 years.[24] The 25 x 25 global action plan has been initiated to reduce premature deaths from chronic diseases by 25% by 2025.[15] Implementation of the global action plan is expected to cost US$11 billion per annum.[24] The objectives to be used by WHO are the reduction of modifiable risk factors, promotion of advanced health research and improvement of health systems in different countries by providing the latest knowledge on disease management.[25] Furthermore, the prevention of chronic diseases will be made a priority by providing advice on health policies, ensure improved training and quality of healthcare professionals and vigilant monitoring of disease trends.[24, 25] The global action plan will have nine targets to be reached by 2025 they are as follows: ensure 80% of people can access affordable treatment, limit the rise in obesity and diabetes, 50% of people will have to have received preventative therapy for strokes and heart attacks.[24] Tobacco use and salt intake is to be reduced by 30%.[24] Harmful use of alcohol and prevalence of physical inactivity is expected to be reduced by 10%.[24] Hypertension prevalence is to be reduced by 25%.[24] Premature death of people aged between 30 and 70 from non-communicable diseases will be reduced by 25%.[15]

1.6. Comorbidity in chronic disease patients

To understand the relation in treatment of chronic diseases there is a need to look into the different diseases individually. Chronic disease patients are often seen to have co-existent conditions during treatment with one condition often co-occurring with and resulting in another.[26] For example secondary hyperlipidaemias can co-occur with or be a result of other disease states such as diabetes mellitus, chronic renal failure and liver disease.[27] Other factors that are seen to cause hyperlipidaemias are drugs such as thiazides and beta-blockers.[27] A third of ischaemic heart disease and stroke is associated to increased levels of cholesterol.[27, 28] Comorbidities have resulted in the creation of combined departments globally to treat often co-occurring conditions such as the neuropsychology and neuropsychiatry departments.[29]

Furthermore, in Africa the prevalence of human immunodeficiency virus (HIV) warrants consideration. The WHO defines HIV as, "*a virus that targets the immune system and weakens people's defense systems against infections and some types of cancer, with infected individuals becoming immune-deficient.*"[30] The African continent accounts for two thirds of newly reported HIV infections, with 25.60 million people infected in 2016.[30] There is no cure for HIV and the disease is managed through provision of antiretroviral therapy (ART).[30] Combination of entry inhibitors, reverse transcriptase inhibitors, integrase inhibitors and protease inhibitors are used in ART.[31]

In HIV diagnosis and treatment, tests for tuberculosis (TB) are considered as tuberculosis accounts for a third of HIV related deaths.[30] In 2016, it was reported that TB led to the cause of 1.70 million deaths globally.[32]

1.7. Change in pharmacokinetics

Age-related changes in pharmacokinetics complicates the treatment of comorbid geriatric patients. Pharmacokinetics is defined by the WHO as, "*the action of an organism on a drug and how the body affects a drug after administration through the mechanisms involved in absorption, distribution, metabolism and excretion of the metabolites of the drug.*"[33] The progressive decline in functional properties of numerous organs in the body results in changes in pharmacokinetic mechanisms.[34, 35] A reduction in liver mass and blood flow has been associated with the reduction in first-pass metabolism in geriatric patients.[34, 36] As a result, drugs that undergo extensive first-pass metabolism have increased bioavailability, however pro-drug bioavailability is reduced.[34] Drug distribution is also altered in elderly patients depending on whether polar or nonpolar drugs are administered.[36] The volume of distribution is reduced for polar drugs in geriatric patients that results in reduced half-life.[36] Vice versa occurs when nonpolar drugs are administered, patients have an increased half-life and volume of distribution.[36] Changes in clearance may result in increased drug toxicity. Renal function reduction is associated with increased drug toxicity as glomerular filtrate rate is reduced in geriatric patients.[34, 35]

The changes in the pharmacokinetic mechanisms in geriatric patients creates a factor for consideration in the treatment regimens in comorbidity cases. Comorbid patients require numerous medications at the same time. Factors such as increased bioavailability and

prolonged half-life can lead to increased risk for drug interactions and drug adverse events.[35] Referral of geriatric patients to specialists for continued care often occurs. The need for continued care by specialists and reviews on multiple disease conditions leads to patient referral to tertiary hospitals.

1.8. South African health care delivery

The South African National Department of Health (NDoH), principled by the National Health Act of 2003, governs provision of health services.[37] The responsibility of the NDoH is the provision of health care for all South African citizens and a framework for a structured health system.[37, 38] The public sector is facing a greater influx of patients daily in comparison to the private sector, as shown by a survey done by Statistics South Africa (Stats SA) in 2017.[39] 71.20% of South African households were attending a public health facility as the first option in cases of disease or accidents.[38, 39]

1.8.1. Public health services

Public health services serve the majority of the population as first point of access. In contrast to the private sector, public health centres are underfunded and understaffed.[40] Expenditures in both private and public sectors are similar, although the public sector covers 84% of the population.[38, 41] The government has proposed reforms to improve the quality and efficiency of health services to all residents. The policies were published in August 2011 in the green paper on National Health Insurance (NHI).[42] The proposal of an increase in general tax revenue used in public sector funding to improve facilities in order to improve services provided. Improvement of facilities and systems used by hospitals and clinics could reduce medication misuse.[40]

Underfunding in the public sector contributes to various factors that eventually lead to poor patient care and adverse events.[38] An example of factors leading to poor patient care are employment of insufficient staff members and inadequately trained staff. These factors lead to staff members not performing their duties optimally because of the high workload and inadequate knowledge of techniques.[38, 40] A contributor to low motivation resulting in toxic work environments is the low compensation for public service staff. A toxic work environment in hospitals can lead to rule violation by staff members such as

inadequate monitoring and reporting of errors. The different factors mentioned above all lead to adverse events being observed at a higher rate in the public sector.[43]

The lack of developed electronic devices such as advanced computer systems is causing a negative impact on the provision of modern and quality care. Use of computerised systems in the developed world and private sector has provided improved services and patient monitoring to reduce medication misuse.[43] A closer look at public facilities is required to assess the work outputs by the staff to chronic disease patients who have to attend these facilities on a constant basis.

1.8.2. Patient care in a tertiary hospital in Gauteng

Steve Biko Academic Hospital (SBAH) is a tertiary hospital located in Pretoria and is one of the largest public hospitals in Gauteng. Provided at SBAH is specialised health care services, a platform for training of health workers and research and also serves as a specialist referral centre for hospitals in the Tshwane region. The hospital is divided into specialist clinics such as nephrology, oncology, pulmonology, rheumatology, cardiology, and the lipid and diabetic clinic as well as psychiatry.[2] Outpatient services are offered to patients who have referrals from medical practitioners and district clinics.[2] 480,000 patients are reported to be attending the specialist clinics, whilst admitting up to approximately 40,000 patients as inpatients per year.[44]

The race, gender and age demographics of Gauteng province are of importance in the analysis of patients attending tertiary hospitals in the region. Statistical values used to ascertain the provincial population in studies are provide by Stats SA. Tshwane district statistics are required to further ascertain the population demographics of patients attending SBAH. According to Stats SA, Gauteng houses the largest proportion of the country's population, with approximately 15.20 million residents (25.80%) as of July 2019.[10] Gauteng comprises of the highest percentage - 23.90% (1.27 million) - of elderly people (60 years and older) in South Africa.[10] There are more females (705,471 (55.56%) than males (564,437 (44.44%) in the geriatric population of Gauteng.[10] A point of interest concerning chronic disease comorbidity treatment is the life expectancy at birth in South Africa. Life expectancy at birth is estimated at 61.50 years for males and even higher for

females at 67.70 years, which relates to high numbers of people susceptible to chronic disease comorbidity.[10]

Medical students from the University of Pretoria receive their practical training from various departments and clinics at SBAH during their clinical rotations. The department of Internal Medicine has eight specialist clinics, excluding the cardiology clinic, each operating at different times and days of the week (table 1).[2]

Table 1: Internal medicine clinics at Steve Biko Academic Hospital.[2]

Clinic	Days of the week
Internal Medicine Medical Outpatient Clinic	Mondays – Thursdays
Diabetic Clinic	Mondays/Tuesdays and Fridays
Endocrinology	Thursdays
Gastroenterology Clinic	Wednesdays/Fridays
Anticoagulation service (Internationalised Normalised Ratio) Clinic	Mondays – Thursdays
Rheumatology Clinic	Mondays/Tuesdays/Wednesdays
Nephrology Clinic	Tuesdays
Infectious Diseases Clinic/ARV	Wednesdays/Fridays

Clinic visits and consultations naturally conclude with the prescription of certain medication to treat a particular disease. A written prescription is a form of communication between the prescriber and the dispenser to the patient. Medical practitioners use prescriptions as an order for medication dispensed to a patient by a qualified dispenser. Prescriptions contain patient-related details such as name, age, address, sex of the patient, and medication-related information including the date, name, doses, dosage form and duration of the medicine. To be included in prescriptions also are the details, stamp and signature of the prescriber.[2]

The treatment and choice of medication prescribed relies on specific national guidelines, institutional protocols and prescriber preference. These factors do not necessarily take into account the presence of comorbidity. Patients with comorbid conditions often attend multiple clinics for each different disease, whereby they receive treatment in accordance to the standard guidelines only for that distinct condition. A factor to consider when patients with multiple chronic diseases receive prescription medication is the risk of

polypharmacy and irrational drug prescribing. In 1985, the WHO defined rational drug use as, "*the requirement that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community.*"[45] Irrational drug prescription and use would result in the incidence of failure in practises required in patient treatment. Irrational drug use often results in increased incidences of adverse drug events, drug-drug interactions, non-compliance and a burden on pharmaceutical resources.[45]

1.9. Polypharmacy

Up to 50% of adverse drug reaction-related hospital admissions may be prevented if appropriate drug prescribing is maintained.[45] Chronic disease co-existence and comorbidity often compels medical practitioners to prescribe multiple numbers of medication lines, which leads to the occurrence of polypharmacy.[26] Polypharmacy is defined by the WHO as, "*the administration of many drugs at the same time or the administration of an excessive number of drugs.*"[46]

1.9.1. Treatment implications of polypharmacy

Polypharmacy is long-known to be common in the elderly. In a United States of America (USA) national survey conducted in 2006, it was reported that 41.40% of people (65 years and older) use five or more different medications per week.[46] The survey further indicated that polypharmacy increases the risk of adverse events and drug-drug interactions. Polypharmacy has been associated with irrational drug prescribing practices by medical practitioners.[47] Extensive monitoring of patients at risk of polypharmacy is required and the extent evaluated in tertiary hospitals. Polypharmacy has been associated with physician incompetence, unavailability of therapeutically efficient drugs and lack of continuous improvement of the drugs provided with the continued change in disease forms and states.[48]

Some studies have shown that polypharmacy is not always a result of irrational drug prescribing. Polypharmacy can be a result of multiple comorbidities in cases where medical practitioners have no other option as to prescribe numerous different drugs. The extent of polypharmacy should be scrutinised taking into consideration the amount of comorbid diseases present in each individual patient.[47] In contrast, polypharmacy is

largely harmless in many patients increasing their quality of life and life expectancy. The result of the effects can be divided into two types; appropriate and problematic polypharmacy.[47] Problematic polypharmacy is mostly a result of irrational drug prescribing causing harmful outcomes that outweigh the beneficial outcomes.[47]

Previous studies have shown that 10% of prescriptions in complex regimens contain an error amongst graduate physicians.[49] Each prescribing encounter requires knowledge in clinical pharmacology. Clinical pharmacological knowledge ensures rational prescribing in the reduction of harmful outcomes in multi-regimen comorbid patients.[49] Rational prescribing reduces problematic polypharmacy and ensures appropriate polypharmacy.[49] To ensure and maintain appropriate polypharmacy, clinical pharmacology courses are essential. Integration of workshops and simulation courses into routine sessions done by physicians to improve pharmacological knowledge is required. Karpa *et al,* concluded that medical graduates who participated in pharmacological workshops showed increased skills in providing safe medication regimens to patients.[50] The indicators described in Table 2 as used in previous simulation sessions have been found useful to eradicate irrational prescribing.[3]

Table 2: Irrational prescribing indicators.[3]

• Complaint is a result of drugs used
• Adverse effects expressed as a result of drug used
• Abnormal drug levels
• Drug therapy resulting in constant monitoring of lab values
• Adverse effects resulting from dosages/formulations
• Diagnosis complete but no appropriate drug to prescribe
• Prescribed drug is not associated with any diagnosis
• Therapeutic duplication
• Therapeutic omission
• Drug is contraindicated due to allergy or comorbidity
• Transcription error
• Medication administration time incorrect
• Clinically-significant drug-drug interactions
• Drug too expensive/inexpensive drug is available with same indication

Most tertiary hospitals approach patient treatment by the use of multiple specialist units to deal with different diseases.[51] An increase in specialists treating each patient leads to an increase in different departments a chronic disease patient attends. Attendance of

multiple specialist clinics by comorbidity patients means these patients get to have multiple drug prescribers.[51] Multiple prescribers is associated with increased numbers of drugs a patient has to take. Increased number of prescriptions is one of the leading causes of drug-drug interactions that cause adverse events.[51] The use of one prescriber in the elderly is a possible solution to reduce polypharmacy that in turn reduces the risk of increased adverse events.[51] If multiple specialist units are used there is a need for a system that connects prescriptions across all units in the tertiary hospital.[51]

1.9.1.1. Adverse drug effects

Adverse drug effects (ADE) are harmful outcomes or injury resulting from the use of a drug.[52] Edwards *et al*, define ADE as, *"an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention of specific treatment, or alteration of the dosage regimen, or withdrawal of the product."*[53] An adverse drug reaction (ADR) is an injury or harmful outcome from drug use at the usual or optimal dosage.[53] ADRs in chronic disease treatment can result from long term use and classed under the time-related type.[53] In cases of time-related ADRs, the discretion of the prescriber is essential in identifying the need for withdrawal of the drug. Polypharmacy is associated with increased chances of ADRs depending on the number of drugs prescribed at the same time as the risks are estimated in comparison with two, five or seven drugs consumed concomitantly.[54]

Drug classes often associated with preventable ADEs are analgesics, anti-diabetic agents, platelet-aggregating inhibiting agents, diuretics and anticoagulants.[55, 56] Irrational drug use has been the cause of majority of preventable ADEs resulting in hospitalisations and fatalities. In the USA, it was reported that four drug classes were the most involved in hospitalisations namely; anticoagulants (warfarin), anti-diabetic oral agents (glibenclamide, metformin), platelet aggregating inhibiting agents (clopidogrel) and insulin (actraphane, protaphane).[57] In current studies, extensive supervision of the prescribing patterns of the mentioned drugs is required as they are likely to cause ADEs.

1.9.1.2. Drug interactions

Polypharmacy increases the risk of drug-drug interactions. Drug-drug interaction (DDI) refers to, *"the pharmacological or clinical response to the administration of a drug combination that differs from the response expected from the known effects of each of these two agents when given alone."*[58] Drug inefficacy is a major result of DDIs and in combination with altered pharmacokinetic composition of elderly patients, there is increased risk of drug toxicity.[59] DDIs may cause toxicity through increased plasma concentration of drugs as a result of altered biotransformation and reduced renal clearance.[59] Increase drug plasma levels increases drug bioavailability to levels beyond the therapeutic range, resulting in treatment failure.[59, 60] DDIs cause increased observation of multiple ADEs. The most common being renal failure, neuropsychological effects and hypotension.[58]

1.9.1.3. Prescribing cascades

Multiple drug prescribing as stated before often leads to ADE. An increase in ADE as a result of polypharmacy is seen to cause increased chances of misdiagnosis of ADE as a new medical condition.[61] Prescribing cascades occur when ADE signs and symptoms are misdiagnosed as a new illness resulting in the prescribing of a new drug to combat the effects caused by a previously prescribed drug.[61, 62] Adverse drug events such as constipation, edema, dizziness and gastric bleeding can lead to new drugs being prescribed to treat these effects as new medical conditions.[63] Prescribing cascades can result in increased ADE and drug-drug interactions.[63] A common example is the long term use of NSAIDs which causes gastric bleeding.[64] Patients taking NSAIDs have antacids often prescribed eventually as a result of ADEs from prolonged use of NSAIDs.[64]

Knowledge of clinical outcomes of previously prescribed drugs is essential in the identification of ADE.[63] Negative clinical outcomes arising in a patient can be diagnosed only if the patient's medical history is fully analysed and constantly updated.[65] Hospital database systems (electronic or otherwise) need to be available at all times to prescribers re-prescribing to allow for checking of patient medical history. Patient education about the importance of alerting prescribers of any over-the-counter (OTC) drugs taken is advised.[66] Medication reconciliation plays a role in the reduction of prescribing cascades

in elderly patients. Limiting prescribing cascades is a step in reduction of polypharmacy and unnecessary prescribing to outpatients.[65]

1.9.1.4. Medication non-compliance

Polypharmacy results in complex treatment regimens that patients have to adhere to during the course of treatment. Hugtenburg *et al*, define compliance as, *"the extent to which medication intake behaviour corresponds with the recommendations of the healthcare provider."*[67] Chronic disease patients receive complex regimens for a prolonged duration of time. Increase in drugs prescribed leads to increased chances of non-compliance for numerous reasons.[68]

One of the reasons for non-compliance related to polypharmacy are fear of numerous ADEs resulting from the multiple drugs prescribed.[68] As ADEs increase from the numerous drugs prescribed, patients fear for the disruption of their daily social and functional routines. Fixed-dose combinations are proposed for consideration in drug development for chronic disease patients to improve treatment outcomes.[68] Research shows fixed-dose combinations decrease non-compliance, as ADEs are limited. Prescriber recommendations may also be altered unintentionally as a result of confusion when to take drugs and also forgetting some of the drugs.[69, 70]

Recognition of non-compliance as a result of use of numerous drugs has prompted the introduction of automated electronic mobile reminders to patients.[70] The efforts to reduce non-compliance are affecting the healthcare costs of medical facilities as they act with the intentions to ensure positive treatment outcomes.[71] Therefore, implementation of reduction tools for the root causes of non-compliance are essential for the reduction of treatment failures and costs to hospitals. Polypharmacy is one of the root causes of non-compliance. The need to investigate problematic polypharmacy and its reduction is paramount to the improvement of health services provided globally.

1.9.2. Medicine stock-outs

A secondary effect of both appropriate and problematic polypharmacy is medicine stock-outs in hospitals and clinics.[51] Chronic disease patients are dependent on an efficient healthcare provider that has a constant drug supply at all times. Essential medicine stock-

outs would have detrimental impact on the services provided to chronic disease patients. According to WHO, "*essential medicines are drugs that satisfy the priority health care needs of the population, selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness.*"[72] Essential drugs are expected to be always readily available at all times, as it is the right of the population to gain access to them through the public health system, in adequate amounts, dosages, and at an affordable price.[72] Despite the population having a right to continued access to essential medicines, however availability is a concern in developing countries.[73] A survey in 36 low and middle-income countries has shown that essential medicine stock-outs in public health facilities occurred in two thirds of the total time of the survey.[73] The aim for practitioners is to reduce problematic polypharmacy in order to minimise medication wastage. Medicine stock-outs result in drug supply requirements increase that costs hospitals a lot. Medicine stock-outs are responsible for large numbers of patients being turned away by hospitals without appropriate treatment.[51] The country's health care system loses credibility over time as patients lose their confidence in health care providers' reliability and commitment towards their well-being. Loss of belief in local hospitals could be a factor in the increase of self-medication among the community. Self-medication is another example of irrational drug use which is of concern to overall community health.[47]

1.10. Medication errors

Medication errors often occur in health care settings catering for chronic disease patients. Medication errors are defined as, "*any preventable events that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer.*"[74] Such events in comorbid patient treatment could be duplications, omissions and drug interactions. Duplications often seen in health care facilities are therapeutic and drug duplication.[75] Medication errors are probable during the prescribing stage.[76] Kohn *et al*, reported that in USA, 7,000 deaths annually occurred as a result of preventable adverse drug events.[77] It was found that 52% of adverse drug events are preventable in adult outpatient clinics, which highlighted the need for measures to improve drug prescribing and use.[78]

Some groups of the population are more susceptible to medication errors depending on the frequency of hospital visits resulting in prescriptions. Comorbid patients are a high-risk group due to multiple hospital visits for the different ailments faced. Studies have also shown that women are health conscious than men leading to greater chances of hospital visits and acquiring medical services.[79, 80] Women's behavioural patterns towards health information is more rigorous in the act of obtaining, evaluating and searching for health interventions in comparison to men.[80] Men are often unwilling to engage in health conscious activities including visiting the hospital for continued care.[79] These findings are reflected in women using hospital services at a higher rate than men and potentially being affected by medication errors more progressively.

Medication errors are often associated with the most frequently prescribed drugs in previous studies.[81] Drugs classes often prescribed include analgesics, antidepressants, anti-epileptics and hipolipidaemics.[81, 82] In the case of analgesics the most prescribed have been tramadol and paracetamol.[82] Pain management is a vital aspect of treatment in chronic disease patient treatment. Tramadol is vastly prescribed as it is a weak opioid with limited control by regulatory boards because of its low addiction and tolerance levels.[83] In countries with limited tramadol control by the regulatory boards like Germany, Malaysia and Australia, tramadol is the most prescribed analgesic along with paracetamol.[83, 84] Tramadol use has been limited in countries like USA and United Kingdom because of adverse events such as seizures and respiratory depression.[85] Tramadol overdose related adverse events such as serotonin syndrome have resulted in increased visits by patients to emergency hospital services.[86] Serotonin syndrome is life-threatening with symptoms such as mental state change, agitation, hyperthermia, disorientation, tachycardia and tremors.[87] Paracetamol is the most common cause for acute liver failure globally, with paracetamol-induced hepatotoxicity a high risk in pain management.[88] Unintended overdose of paracetamol leads to renal toxicity and hepatotoxicity.[89] Comorbid patients on cytochrome P450 enzyme inducers are more susceptible to toxic effects of paracetamol.[88] Emergency room visits, hospitalisations and fatalities occur globally because of paracetamol prolonged overdose.[88, 89]

NSAIDs have been identified in literature as one of the main drugs classes responsible for hospital admissions because of medication errors.[90] The hospital admissions have

been a result of unnecessary prescribing of NSAIDs which are reported to occur 42% of the time in elderly patients.[91] Outcomes of overprescribing of NSAIDs are mostly gastrointestinal bleeding, and increased risk of stroke and heart failure.[90]

Antidepressants have been identified as drugs highly prescribed with elderly and comorbid patients the most vulnerable groups.[92] Antidepressant overprescribing is the outcome of inappropriate or excessive antidepressant prescription. Overprescribing occurs mostly due to the inappropriate prescription of newer antidepressants in off-label use and for non-specific psychiatric indications including the treatment of insomnia.[93] Antidepressant overprescribing has been associated with different reasons with some suggesting it is a result of the increase in depression, stress and anxiety.[92] Some have however reported the increase in the marketing of antidepressants and awareness of psychiatric disorders has resulted in over-diagnosis of patients.[92] General practitioners with limited expertise in psychiatry have been found to prescribe antidepressants more often.[94] This is despite general practitioners getting limited time with patients to prescribe for the symptoms of the disease that brought the patient to the healthcare facility. General practitioners have gone on to prescribe antidepressants on top of other drugs they are more skilled to prescribe.[94] The outcomes potentially contribute to the rapid increase of antidepressant prescribing over the years that could also be a result of better disorder detection and closing of the treatment gap. An increase of antidepressant prescribing of 58% was reported in Australia between 2000 and 2011.[95] Findings in Australia were similar to those in 2009 England studies where antidepressant prescribing was found to have increased by 35% over a five-year period.[96] Selective serotonin reuptake inhibitors (SSRIs) for example fluoxetine and tricyclic antidepressants (amitriptyline) have been identified as the most prescribed and over prescribed antidepressants.[94, 97] Side effects associated with antidepressants include sedation, seizures, weight gain, dry mouth, constipation and insomnia.[97]

Hipolipidaemics are among the most prescribed drugs globally.[82] Hyperlipidaemia diagnosis has increased over the years with this attributed to increased awareness of hyperlipidaemia incidence and effects globally.[98] Statins are overly prescribed in an effort to prevent cardiovascular disease.[99] Along with statin use, antacids are associated with comorbid patients suffering from mostly diabetes and hypertension.[100] Proton pump

inhibitors (PPIs) have been largely prescribed especially esomeprazole, omeprazole and lansoprazole.[101] Esomeprazole is among the most prescribed PPIs along with omeprazole among gastroenterologists.[102] Adverse reactions have been noted in comorbid patients because of the PPIs being metabolised by similar cytochrome P450 (CYP450) enzymes as many drugs resulting in extended half-life and eventually toxicity.[101, 103]

Antihypertensive agents are identified amongst drugs largely prescribed to elderly patients.[82] Susceptibility to hypertension causing agents such as salt due to the sensitivity of elderly patients is linked to increased hypertension treatment in the elderly.[104] Elderly patient prescriptions are often found to contain diuretics and other antihypertensive agents such as angiotensin converting enzyme (ACE) inhibitors.[104]

Despite reports of 50% of hospital admissions due to preventable ADRs, some studies report that there is no available tool that can readily assess if an adverse drug event can be measured to be preventable or not.[78] Tools are still required to be able to state if hospital admission or death has occurred due to a preventable drug reaction. The challenges of preventable adverse drug events is compounded by the poverty lines in African countries where automated systems are unavailable to provide quality service to patients.[76, 105] Underdeveloped infrastructure and lack of resources in African countries has been attributed to severe health risks including medication errors.[76]

1.10.1. Therapeutic duplication

Therapeutic duplication is defined as, *"the practice of prescribing multiple medication for the same indication or purpose without a clear distinction of when one agent should be administered over another."*[74, 75]

Therapeutic duplication can occur in tertiary hospitals when comorbid patients attend multiple clinics. Often, similar medication prescribing occurs in the treatment of the same condition at the same time. Safety concerns occur as a patient becomes susceptible to unintended drug overdose and adverse drug events. The altered body composition in geriatric patients further increases the risk of drug toxicity and serious harm in cases of unintended doses.[106] For this study, diagnosis and indications for individual drug items

prescribed was not included. There was omission of data collection on therapeutic duplication. Therapeutic duplication was beyond the scope of this study. Acknowledgement of the possibility of therapeutic duplication in tertiary hospitals highlights the need for future studies to analyse this medication error at SBAH. The methodological choices for this study constrained the principal investigator to drug duplication analysis as the main objective.

1.10.2. Global drug duplication

Drug duplication occurs when a patient uses two or more drugs from the same medication class.[107] Psychological, physical incapacities, preventable hospitalisations and fatalities globally have resulted from drug duplication.[108] Unnecessary healthcare costs is another negative outcome of drug duplication.[108]

Comorbid chronic disease patients are at a higher risk of drug duplication in comparison to patients suffering from a single disorder.[109] Comorbid patients tend to visit the hospital more often than patients suffering from a singular disease condition often do. Numerous hospital visits could result in substantial amounts of prescriptions. Multiple prescriptions coupled with a poor drug management system, increases chances of drug duplication.[109] Lack of communication between different prescribers in assorted outpatient clinics is a factor for consideration. Polypharmacy or the use of five or more drugs at the same time is a factor leading to drug duplication. Polypharmacy patients have been reported to have up to 2.6 times more chances of duplications in comparison to patients taking less than five drugs at the same time.[109]

i) Antidepressants

Antidepressants are one of the most commonly duplicated drug classes.[92] Tricyclic antidepressants (amitriptyline) are often used in chronic disease patient treatment including migraine headache prophylaxis, neuropsychiatric disorder and chronic pain.[110] Tricyclic antidepressant overdose is mostly seen in chronic disease patients, more than SSRIs overdose.[110] Hospitalisations are associated with the narrow therapeutic range of tricyclic antidepressants. Antidepressant overdose causes the serotonin syndrome, which is increased by concurrent use of drugs such as NSAIDs, tramadol, carbamazepine and valproate.[87] Antidepressant duplication toxicity causes seizures, hypotension,

cardiac toxicity, however asymptomatic patients may require intensive care as it is life-threatening.[111] Dry mouth, blurred vision and dry mouth (anticholinergic effects) present in the case of low dose toxicity.[112] Non-fatal cases resulting from unintentional self-poisoning with antidepressants have been reported to have occurred due to prescribing errors.[111, 112]

ii) Antiepileptic agents

Antiepileptic toxicity is a risk among elderly patient treatment. Antiepileptic agents such as gabapentin, lamotrigine and carbamazepine are largely prescribed to elderly chronic disease patients.[113, 114] The common uses of antiepileptic agents is mood stabilization, chronic pain, neuropathic pain and seizure treatment.[113, 114] Patients with seizure disorders have been involved in 3% to 8% of suicide attempts during administration of antiepileptic agents.[115] Antiepileptic toxicity commonly occurs with chronic supratherapeutic doses due to prescribing errors such as drug duplication.[115]

Clinical outcomes of chronic antiepileptic drug duplication exposure differ due to the different pharmacokinetic properties of the drugs mainly metabolism and elimination. Carbamazepine is metabolised by CYP450 enzyme CYP3A4 with toxicity resulting from concurrent intake of CYP3A4 inhibitors.[116] CYP3A4 inhibitors include valproate, allopurinol and fluoxetine.[116] Carbamazepine toxicity presents with acute hypertension, seizures and sinus tachycardia.[116] Drug duplication of valproate and lamotrigine can cause toxicity as these agents are both metabolised through the glucuronidation pathway.[117] Inadequate monitoring of low dose combination of valproate and lamotrigine often used in bipolar disorder treatment can potentially cause reduced metabolism and elimination leading to toxic serum levels.[118] Drug duplication of valproate, lamotrigine and a majority of antiepileptic agents cause respiratory depression, ataxia, nystagmus, coma and death.[118] Treatment failure can also result from antiepileptic agent duplication. Carbamazepine and phenytoin are glucuronidation inducers and can increase metabolism of valproate and lamotrigine.[117, 118] Increased metabolism leads to low serum levels of valproate and lamotrigine resulting in treatment failure.[118]

iii) Antihypertensive agents

Previous studies have shown severe hypotension and potential death as outcomes of antihypertensive overdose.[119] Drug duplication can cause the occurrence of antihypertensive agents overdose. Severe hypotension has been reported after prolonged or short-term exposure to supratherapeutic doses of ACE inhibitors.[119] Prescribing of ACE inhibitors has increased with increase in accessibility, making ACE inhibitors one of the most commonly prescribed drugs.[104] Hyperkalaemia and renal failure risk is increased by duplication of antihypertensive agents.[120] Duplication effects have been observed during the use of ACE inhibitors concurrently with angiotensin II receptor blockers.[121] Severe hypotension can result in a hospital admission for emergency care.[120] Al Khaja *et al*, reported the prevalence of potentially inappropriate prescribing of antihypertensive agents to be 34.10% in Bahrain, with the most common error being drug duplication.[121]

Diuretics are commonly prescribed along with antihypertensive agents in elderly patient hypertension and renal treatment.[122] The increased use of diuretics opens the possibility for toxicity cases incidence due to self-harm by patients or inappropriate prescribing. Drug duplication clinical outcomes research of diuretics is limited. Diuretics duplication contributes to increased electronic disturbances that are side effects of diuretics use.[122] Acid-base changes in high dose use of thiazides and loop diuretics become a common feature inducing metabolic alkalosis.[123] Hypokalaemia and hyponatremia are outcomes of diuretics toxicity.[122, 124] Prolonged use of thiazide diuretics at supratherapeutic doses decreases insulin secretion causing hyperglycaemia.[123] Hyperglycaemia is a cause for concern in comorbid chronic diabetic patient treatment. Extensive use of diuretics in hypertension treatment increases the chances of diuretics overprescribing and toxicity leading to hospital admissions. Diuretics are among the top five drugs globally to cause hospital admissions as a result of ADEs.[124]

iv) Sedative hypnotics

Numerous studies have found sedative hypnotics among the most duplicated drugs worldwide. Sedative hypnotics are used to treat insomnia and agitation in elderly patients.[125] Inappropriate benzodiazepines use is mostly common in hospitalized elderly patients than in outpatient internal medicine healthcare centres.[125] Observational studies

on potentially inappropriate prescribing across Europe identify benzodiazepines as the most inappropriately prescribed drugs to elderly patients.[126] Studies in the United Kingdom and Lebanon found benzodiazepine overprescribing in the primary health care centres.[127, 128] Overprescribing and overdose of benzodiazepines causes delirium, cognitive dysfunction, acute respiratory failure and physical imbalance.[126, 129] Increased risk of dementia in the elderly patients is emerging in studies as an outcome of prolonged use of benzodiazepines.[129]

v) Antacids

Antacid use in chronic disease patients requires an efficient medication reconciliation process. Majority of the population get antacids OTC, hence prescribing of antacids requires efficient medication reconciliation processes in place to prevent overprescribing.[130] Calcium carbonate duplication among the elderly and infants increases the risk of abdominal pain, hypercalcemia, constipation and nausea.[131] Drug duplication often occurs in the inappropriate long term prescribing of PPIs.[130] Proton pump inhibitors are considered generally safe although long term use of PPIs is directly linked to depression and onset of dementia.[130]

1.10.2.1. Africa

The risk of drug duplication is associated to the number of drugs patients receive per prescribing encounter and the number of physicians a patient visits at various periods. Prescribing indicators such as the number of drugs per prescribing encounter are used to evaluate the risk of polypharmacy and the related drug duplication. A recent study of 43 various articles from hospitals in the African region including 23.40% of African countries highlighted the prescribing indicators. The countries included in the prescribing indicator study were Botswana, Burkina Faso, Ethiopia, Gambia, Ghana, Kenya, Nigeria, South Africa, Tanzania, Zambia and Zimbabwe. The average number of drugs per prescribing encounter among 138,671 patient encounters were found to be 3.10 (Interquartile range 2.30-4.80).[132] Some studies use the range of drugs per prescribing encounter based on the WHO range to determine the prescribing patterns in Africa and other developing countries. The standard range by WHO is 1.80-2.20 drugs per prescribing encounter that is compared with ranges from African countries.[133] The geographical location of a hospital (rural or urban) and if it is in the private or public sector

is also influencing the prescribing values in African hospitals as the availability of essential medicines plays a role. The average number of drugs prescribed in various tertiary hospital studies in Africa show differences in prescribing patterns such as Botswana (2.30), Burkina Faso (2.30), Ghana (4.80), Nigeria (5.20) and Zimbabwe (1.30).[48]

1.10.2.2. United Kingdom

Drug duplication is a cause for concern in the United Kingdom's primary care setting. A study done in 2008, to identify trends in overprescribing showed that overprescribing was a significant problem in patients 65 years old and above.[128] Data was collected from 201 facilities with 230,000 patients observed between 1996 and 2005.[128] The measures used included the annual amount of drugs prescribed per patient, and the percentage of patients affected by drug duplication. The study results showed that in 2005, 28.30% of patients were affected by overprescribing.[128] Overprescribing of antidepressants (amitriptyline), benzodiazepines (diazepam) and paracetamol were the most recorded outcomes.[128]

1.10.2.3. New Zealand

Studies in New Zealand show incidence of drug duplication prevalence. Drugs duplicated in the United Kingdom have a similar outcome in New Zealand. Large numbers of geriatric patients attend chronic disease specialist clinics and affected by overprescribing and inappropriate polypharmacy. In 2015, Narayan and Nishtala concluded that 40.90% of elderly patients experienced inappropriate polypharmacy by the use of the Beers 2012 criteria.[134] The Beers 2012 criteria is a tool developed by the American Geriatric Society to inform clinical decision making and identify inappropriate drug prescribing in elderly patients.[134] The most potentially inappropriate drugs prescribed were diclofenac (6.00%), ibuprofen (4.60%), amitriptyline (4.90%) and zopiclone (3.20%) shown by the percentage of patients prescribed these drugs.[134]

1.10.2.4. Lebanon

Prescribing pattern studies in Lebanon between 2012 and 2014 showed the occurrence of drug duplication. Prescriptions collected in 27 pharmacies showed inappropriate prescription of benzodiazepines to 18 (2.30%) patients out of 786 patients observed as these patients were taking more than one benzodiazepine concomitantly.[127] One of the

main causes of drug duplication is the concurrent use of multiple prescribers.[127] Lack of communication and awareness by new prescribers of the duration of use and quantity of benzodiazepines provided by a previous prescriber was a concern.[127] The authors found overprescribing of benzodiazepines increasing the risks of psychological and physical side effects.[127]

1.10.2.5. Austria

Drug duplication in Austrian studies has been included in double medication studies. Double medication is defined as, *"unintended overlapping prescription of two identical substances with the same route of administration by two different prescribers to the same patient."*[135] Drug duplication was in internal medicine specialist departments with repeats often found in outpatients. 7,971,323 patients were observed which covers 97% of the Austrian population.[135] A record of the percentage of patients affected by double prescribing assisted in the measurement of the most duplicated drugs. The percentage of patients affected by drug duplication were antihypertensive agents (15.00%), hipolipidaemics (13.10%) and anti-diabetic agents (13.00%).[135] The consequences of drug duplication were increased financial resource burden on the healthcare system and drug toxicity in the drug duplication affected patients.[135]

1.11. Medication reconciliation

Medication reconciliation according to The Joint Commission is defined as, "*the process of comparing a patient's medication orders to all of the medications that the patient has been taking.*"[136] The process of medication reconciliation serves to prevent medication errors. It is a possible solution for the reduction of overprescribing to multiple clinic attending chronic disease patients. Visits to different clinics requires the healthcare providers to write down a list of old drugs and new drugs prescribed to the patient.[136] To be included in the list are any OTC and traditional medicine. The list is to be included in the patients' medical history as a reference point for any new drug prescribers. The intention is to reduce the risk of drug interactions and duplications.[137]

A process of listing medication is to be followed when a patient is transitioning from one prescriber to another.[137] Before referral to another clinic, healthcare providers are required to write down all the drugs prescribed to a patient in the current clinic. Once a

patient is at another clinic, there is production of a record of the newly prescribed drugs. Before dispensing, a comparison of the previously prescribed drugs and newly prescribed drugs is required. Upon completion of the comparison, implementation of a clinical analysis programme to check for duplications is the next step. Errors are corrected by the prescribers and the error is communicated to the patient.[66, 137] This process is to ensure patient safety by the reduction of medication errors. The steps mentioned are also useful when a patient is admitted after attending different outpatient clinics.[138]

Medication reconciliation standards education of hospital staff members especially the registry and pharmacy staff is crucial in patient safety.[139] Hospital staff members well educated in reconciliation have been found to significantly increase completeness of medical records.[140] Global use of computerised systems to enter patient information connecting different specialist clinics is a potential solution to reduce prescribing errors. Additionally, computers can print the medical records of a patient. New prescribers to educate the patient on the prescription medication provided can use printed medical records. The print outs can be kept in the patient file carried by patients in cases where they have to attend a different specialist clinic.

Introduction of Hospital Information System (HIS) and Information Communication Technology (ICT) is a step in medication error reduction.[141] ICT is a subset of HIS where caregivers are in constant contact with outpatients. As stated by the American Institute of Medicine, "*Patients should receive care whenever they need it and in many forms, not just face-to-face visits. This rule implies that the health care system should be responsive at all times and that access to care should be provided over the internet, by telephone, and by other means in addition to face-to-face visits.*"[142] Constant communication between comorbid outpatients and caregivers can be done through emails to ensure constant knowledge of treatment undertaken.[142] Caregivers to identify any duplications can constantly review communication records of last prescribed medication. In combination with constantly updated HIS, ICT can ensure comorbid patients are kept updated on their prescription records. Customisation of HIS to regions and particular hospitals in Africa is required to implement a system that will cater for the African tertiary hospitals.[143] During the customisation process, creation of a system that alerts caregivers on drug duplications is a potential solution to drug duplication unawareness.

1.12. Global recommendations

Tertiary hospitals are at risk, as multiple prescribers are potentially responsible for enabling oversupply of medication to patients.

1.12.1. Hospital information systems

In an effort to permit all prescribers to have readily available patient information and history, multiple hospitals have introduced paperless technological systems.[144] The Hospital Information System (HIS), which is an integrated information system designed to store clinical and administrative details in hospitals, has been used in countries such as Malaysia.[144]

The electronic health (e-health) strategy was included in the NHI policy mandate to improve the operations of tertiary hospitals in South Africa.[42] The NDoH identified use of HIS as a step in reduction of medication errors. For the implementation of electronic systems at local hospitals, collaborations with information technology (IT) specialists was required. A collaboration between NDoH, the Council for Scientific and Industrial Research (CSIR) and the South African Medical Research Council (SAMRC) was formed in 2014.[145] Thereafter an extension to the National Health Act was adopted which became the National Health Normative Standards Framework for Interoperability in e-Health in South Africa (HNSF).[145, 146] The collaboration was a result of a need to produce electronic systems specific to the South African primary health care system. The outcome is to pioneer the Health Patient Registry Number (HPRN) at all public health facilities in South Africa.[145-147] Through the proposed systems, all clinics and healthcare facilities in the country will share data. The aim of the HIS programme is to improve patient health care in the public sector through improved database sets for physicians and nursing staff.[147]

Forecast on linked data systems in tertiary hospitals with multiple clinics for chronic disease patients predicts a helpful outcome. Reduction of over prescribing and prescription duplication would be useful in reducing drug-drug interactions and drug adverse events. Trained implementation and maintenance personnel, user-friendliness of the system and maintaining information confidentiality are some of the challenges faced by hospitals using HIS.[144] The biggest challenge in implementing such a system is financial costs of the purchasing and upgrading of the system over time to avoid any

server downtime and loss of patient information.[144] Selayang Hospital in Malaysia was the first paperless hospital in the region when they implemented the Total Hospital Information System (THIS).[144] Use of THIS was also implemented in Pakistan, however, the challenges faced were lack of adequate information technology services and lack of suitable software to maintain data flow throughout the hospital departments.[144] The NDoH launched the National E-Health Strategy in 2012 that aims to initiate e-health systems, which will provide electronic health records and upgrade the current computer systems used in public hospitals.[148] The objectives of e-health are to deliver efficient healthcare services, enhance quality of communication between healthcare providers and patients through quality information systems, providing accessible medical records, enabling communication between healthcare facilities and transparency of medical data.[148] There are various challenges in the implementation of HIS in South Africa. High-level challenges include the purchase of expensive hardware products required to change from paper systems to paperless systems, incorporating electronic systems into daily routines for different staff members such as nurses and physicians, implementation of standardized systems in urban and rural areas, and the funds required to compensate IT personnel to operate and update the new systems.[149] Low-level challenges include usability of the system, lack of availability of some patients' medical history files and acquiring patient consent to have their information accessible to various parties such as IT personnel assisting with the operation of the system.[149, 150]

Challenges in implementation of HIS in developing countries are the lack of sustainable funding and low availability of IT companies to consult.[151] A locally developed system is often required to cater for a particular hospital taking into account different factors such as uninterrupted electrical supply, IT knowledge, backup systems and support.[151] At the Pakistan Institute of Medical Sciences (PIMS), the installation of HIS in 2007 resulted in IT technical staff having to enter confidential data themselves that should only be accessed by practitioners as the system was complex.[151] The use of HIS at PIMS often experienced database overload that caused the system to be non-operational and resulted in data loss.[151] Successful installation of HIS is however, still considered as a possible solution to avoid over prescribing as practitioners can readily search patient history including data recorded in other hospital departments. Computerised systems allow for linking data in the entire hospital. Linked data systems can readily review

prescriptions from multiple clinics by prescribers before ordering of new drugs. Additionally, pharmacists can use linked systems as a final step in checking appropriateness of the prescribed medication.[152]

1.12.2. Physician/ Prescriber

The Garfinkel algorithm was developed in an effort to reduce inappropriate drug use in elderly comorbid patients.[1] The Garfinkel algorithm is a systemic approach to discontinue drug use in polypharmacy patients. Garfinkel *et al,* used the Good Palliative-Geriatric Practice algorithm to recommend discontinuation of some drugs in outpatient elderly people.[1] In a cohort study using the flow diagram in figure 1, the algorithm was appropriate in reducing medication responsible for adverse drug events.[1]

Further studies in reduction of polypharmacy in chronic disease patients resulted in the development of additional new tools. One such tool was the, "PRIMA-eDS *(Polypharmacy in chronic diseases- Reduction of Inappropriate Medication and Adverse drug events in older populations by electronic Decision Support).*"[153] The PRIMA-eDS system is an electronic application based on systematic reviews and treatment guidelines. The tool also accesses information on a wide variety of databases such as the European list of inappropriate medications for older people, RENBASE for renal dosing and PHARAO-database for adverse events.[153] Physicians receive recommendations during drugs prescribing to avoid adverse events, drug-drug interactions and polypharmacy. The PRIMA-eDS study protocol was registered and published in 2016 for the two-year multicentre cluster-randomized controlled trial to test its efficiency.[153] Use of the tool is seen as a step further from the Garfinkel Good Palliative-Geriatric Practice algorithm in an effort to reduce inappropriate drug prescribing.[153]

The American Geriatrics Society (AGS) 2019 Beers criteria for potentially inappropriate medication use in older adults is a clinical tool used to assist prescribers.[154] The AGS 2019 Beers criteria is a tool that provides prescribers with information on drugs most likely to produce undesirable effects in different elderly groups suffering from different chronic conditions. There is a categorical indication of consideration of comorbidity and age-related pharmacokinetics changes in the recommendations by the AGS 2019 Beers criteria. The tool is amended on a three-year basis, with amendments made based on

clinical outcomes from studies with relevance to elderly patients.[155] The aim of the tool is to improve patient safety through ensuring drugs prescribed have beneficial outcomes that outweigh harm, and eliminate the potential risk of medication errors.[154, 155] A healthcare provider's discretion is important in the application efficiency of the AGS 2019 Beers criteria to complement non-pharmacological factors. Non-pharmacological factors taken into consideration during prescribing include financial factors and drug availability. Drugs prescribed have to be the cheapest and most affordable option to the patient. Medicine stock-outs are a factor for consideration in drug prescribing at public hospitals in developing countries.[72, 73] The limitation of the tool is that individualised care is still required despite its recommendations are beneficial to a majority of elderly patients. The medical state of a patient, depending on environmental, behavioural and genetic factors have an impact on the choice of drugs prescribed.[155]

Tools developed in the reduction of polypharmacy in elderly and comorbid patients are to assist in reduction of adverse events associated with long-term use of multiple drugs. The term de-prescribing has been introduced which addresses action that can be taken by physicians to reduce overprescribing.[156] There are numerous definitions in literature for the active removal of drugs prescribed to a patient. A basic de-prescribing definition that has been proposed is, *"the process of tapering or stopping drugs, aimed at minimising polypharmacy and improving patient outcomes."*[156]

There are observational studies to evaluate the outcomes of de-prescribing some drugs to reduce the number of drugs taken by comorbid patients. Numerous definitions have been introduced which best elaborate the procedure to be undertaken during the de-prescribing process. Reeve *et al*, have defined de-prescribing as, *"the process of withdrawal of inappropriate medication supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes."*[157] Scott *et al*, defined de-prescribing as, *"the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values and preferences."*[156] De-prescribing has been earmarked to potentially reduce ADEs, drug-drug interactions, hospital-admissions due to ADEs from chronic disease treatment and even fatalities due to toxic levels of drugs taken.[157, 158] Economic advantages have also

been outlined with reduction of drugs dispensed, the healthcare system would have reduction in costs on drug purchases.[158]

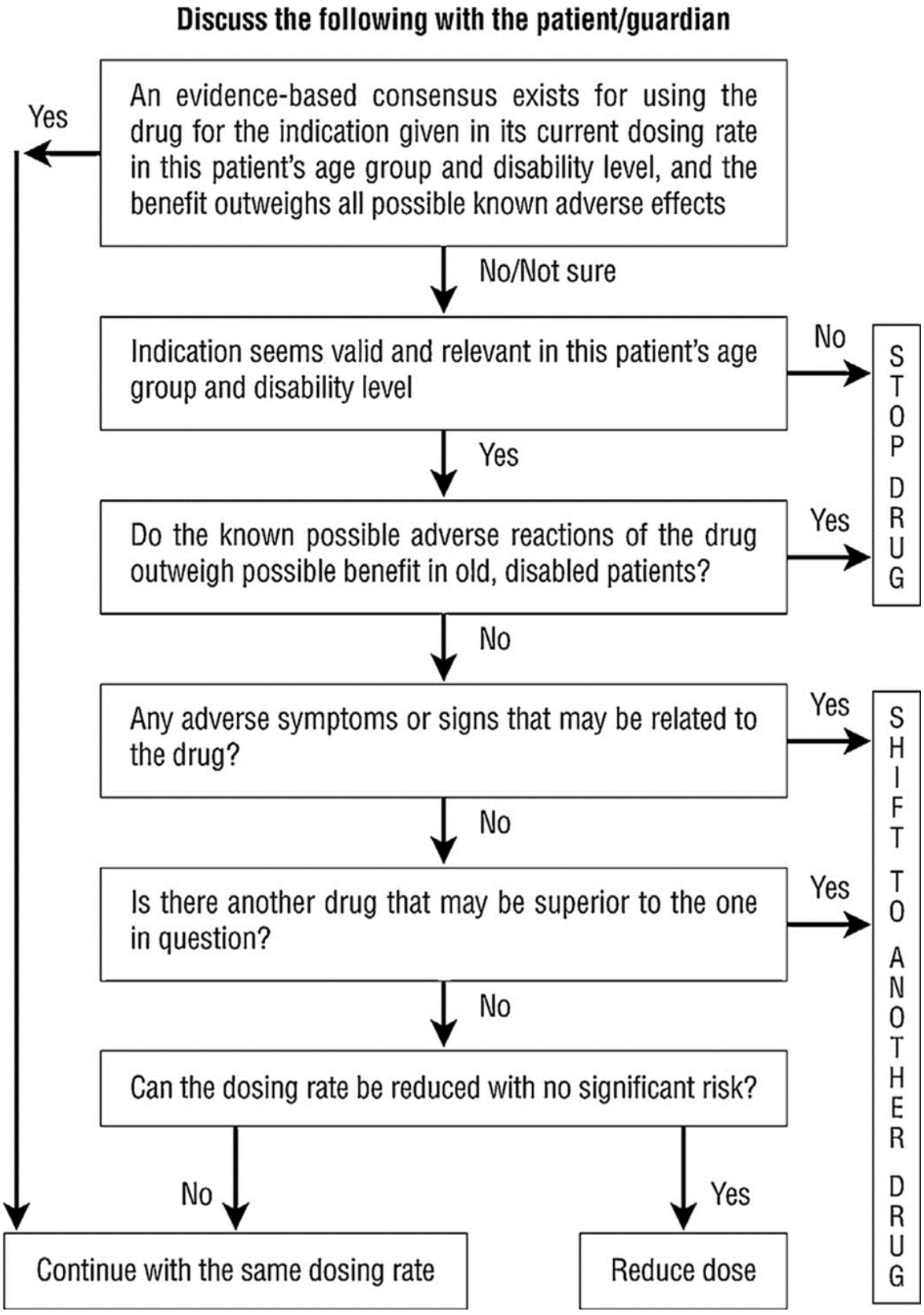

Figure 1: Garfinkel Good Palliative-Geriatric Practice algorithm.[1]

1.12.3. Pharmacist interventions

Collaboration between pharmacists and prescribers is essential in the eradication of drug duplication. The introduction of a medication safety officer (MSO) with extensive clinical pharmacological knowledge is a possible step to increase drug safety management in tertiary hospitals.[159] The MSO would be responsible for monitoring drugs prescribed to all patients in the transitional phases of treatment.[159, 160] The transitional phases includes changes from outpatient to inpatient, inpatient to outpatient and attendance of different clinics at the same time.[161] Such patients are often at high risk of medication errors. Hospital designed stickers can be used on patient files of multiple clinic attending patients. The patient file stickers could be a tool alerting pharmacists of the comorbidity status of the patient. Prescription orders of comorbid patients require extensive reviews of previous prescription prior to dispensing new drugs. Incomplete prescription data would automatically initiate an enquiry and the MSO alerted of possible duplications.[161]

Pharmacists are also required to monitor all prescriptions with reference to patient history.[162] Use of HIS is fundamental in readily providing pharmacists with previously prescribed and dispensed drugs.[152] Use of the HIS facilitates cross checking of patients' medical records which would include all medications taken by a patient including OTC drugs and traditional medicines. Cross Checking medical records enables pharmacists to identify possible therapeutic and drug duplication. Hauser *et al*, have reported significant error reduction through pharmacists' checking of prescriptions prior to dispensing.[162]

1.12.4. Patient/ Caregiver role

Definition of the role of the MSO is through the necessity of the communication process of healthcare providers with patients. Multiple clinic-attendees require specialised care in managing comorbidity and the complex treatment regimens experienced. Chronic disease patients attending tertiary hospitals have a right to care at all times.[142] The MSO's expertise in clinical outcomes can assist in the observation and diagnosis of comorbid patients for any unexpected drug effects. Visits to the hospital without any prescriptions are opportunities for counselling sessions to monitor patient compliance and treatment outcomes.[163] The MSO and his team can provide face-to-face sessions with patients to review prescriptions in patient files and cross check for any medication errors.

Furthermore, face-to-face sessions with comorbid patients can allow for evaluation of the mental health status of the patient.[163, 164] Comorbid patients are at an increased risk of acquiring mental disorders due to the various disorders and treatment regimens.[164]

1.13. Scope of the study

This study entails the prescription patterns at a tertiary hospital in the greater Tshwane metropolitan area.

1.13.1. Study motivation

Tertiary hospitals have multiple specialist clinics attended by chronic disease outpatients. Most of these patients have various comorbid diseases, resulting in them attending multiple clinics. As patients attend assorted clinics, they have separate encounters with more or less different prescribers whom may or may not know about each other and whose individual prescriptions that may result in drug duplication. Lack of prescriber continuity in tertiary hospitals around the world potentially increases drug duplication.[165] Duplication of drugs in tertiary hospitals results in adverse drug events, drug interactions, drug shortages and problematic polypharmacy.[45, 165]

Drug duplication is a major factor in the compromise of a patient's quality of life.[166] Negligence of drug safety and efficiency leads to ineffective and economically inefficient patient treatment.[167] Inefficient patient treatment leads to harmful outcomes that affect a patient's quality of life.[166] Overdosing of affected patients can lead to preventable hospital admissions. Emergency unit hospital visits due to drug duplication increases a patient's healthcare costs and eventually burden the healthcare system.[168] This is a wasteful cost driver. Constant monitoring of possible drug duplication and evaluation of hospital systems is required in an effort to avoid medication errors. Maintenance of the patient's safety and the improvement of a chronic disease patient's health-related quality of life (HRQOL) is imperative.

This study will aim to determine the prescribing patterns of drugs to chronic disease outpatients with focus on one aspect of overprescribing, drug duplication at Steve Biko Academic Hospital (SBAH). The study will determine the extent of drug duplication and polypharmacy related to drug duplication in the specialist chronic disease outpatient

clinics at SBAH, since studies regarding these incidents are limited in South African literature. The output of the study is the provision of recommendations to reduce drug duplication and polypharmacy at SBAH upon completion of data collection and analysis.

Use of prescribing indicators as a starting point to identify the quality of the healthcare system in South African tertiary hospitals is part of the outcome of this study. In the case of polypharmacy, this indicator is used to further evaluate both prescriber expertise and the quality of drugs available.[169] High incidences of polypharmacy can also be an indicator of the availability and quality of essential drugs available to prescribers. Poor availability of essential drugs can result in prescribers providing multiple drug combinations to achieve treatment efficiency.[170] In a good quality healthcare system, essential drugs availability would ensure treatment efficiency with low numbers of drugs prescribed.[171]

This study will provide an overview of the prescribing indicator outcomes to highlight if further studies are required to ensure, the healthcare system is sufficient for best treatment outcomes in the Tshwane metropolitan area. The WHO have highlighted treatment of comorbid and elderly patients as an area requiring increased involvement in studies.[170-172] This study focuses on the populations that are on the rise in recent years, with chronic diseases projected to be on the rise until 2030, and possibly beyond with the increase in the population and life expectancy.[173] Referral of geriatric patients to specialists for continued care often occurs and SBAH is facing the risk of being affected by the increase in chronic diseases hence requiring studies to ensure rational prescribing is provided to chronic disease patients. Chronic disease related deaths are expected to rise by 48% between 2005 and 2030, with disease burden also projected to increase.[174] Increase in chronic diseases relates to increased costs on the healthcare system, consequently reduction of costs is crucial at all levels of healthcare.[175] Interventions are required for the reduction of excessive drug use.[175]

New drug formulations are required to combine drugs and target multiple conditions at the same time, with limited side effects.[172] Evaluation of prescribing patterns to comorbid and elderly patients essentially highlights the need for development of drug formulations by the pharmaceutical industry to target these groups. Innovation in drug formulations

would essentially decrease excessive drug use in tertiary hospitals whilst reducing ADEs.[170, 172] This study acts as a means for the identification of irrational use of drugs at a tertiary hospital through the evaluation of prescribing patterns. Upon completion, development of interventions will assist future health economic studies to identify cost drivers in the excessive drug prescribing and use in the South African healthcare system.

1.13.2. Investigation of drug prescription patterns

Retrospective or prospective cross sectional studies are carried out in the investigation of drug prescription patterns in hospitals.[176, 177] The data collection method is influential on the validity of data reported and the limitations thereof. In the presence of historical medical records, retrospective studies use is preferred. Medical records referenced include namely; appointment logbooks, pharmacy records, patient files and prescription copies. When random selection is not used, all patients meeting the selection criteria are often included in previous studies.[178] As in this study, all patients attending the chosen clinics were included between February 1, 2018 and May 31, 2018. Use of data collected and stored before the commencement of the study in retrospective studies is cheaper and has reduced bias to prospective studies.[176] Avoidance of the Hawthorne effect is important, as the principal investigator and the drug prescriber cannot manipulate the data collected. The Hawthorne effect is when the investigator or the investigated subject changes their behaviour in order to produce a favourable outcome in the study.[179] Prescribers are highly likely to change their prescribing patterns in prospective studies altering the findings from daily practises.[180] Retrospective studies are chosen for prescribing patterns, provided data records are readily available in avoidance of the Hawthorne effect associated with prospective studies.[180]

The data collected is relevant if it includes different individuals from the population.[181] Diverse patients are treated post-referrals from different areas in the Tshwane region. The inclusion of diverse patients allows for the use of a sample that is a highly likely representative of the rest of the clinics contained at the hospital.[182] Inclusion of all patients attending the selected clinics allows for the reduction of selection bias, thereby increasing the study's validity.[181] The use of retrospective studies is however complicated when the data stored is misplaced or incorrectly recorded.

In 1993, WHO developed a manual for the investigation of prescribing patterns in health facilities.[133] The WHO manual is a standardised guideline to investigate prescribing indicators, patient care indicators and health facility indicators. Average number of drugs per prescription is a core indicator of the extent of polypharmacy in health facilities.[133, 183] However, to ascertain the kind of polypharmacy observed there is a need for further data analysis on the indication and choice of drugs prescribed.[47] When investigating individual departments the sample size is required to be a minimum of 30 cases, with a minimum of 100 cases required for the entire health facility.[133]

Basic knowledge in pharmaceuticals is a prerequisite for the investigation of prescribing indicators in health facilities. Data collection requires familiarity with drugs often prescribed. Computerised programmes during data extraction and data management processes produce statistically reliable information. Stata statistical software is used for data extraction of numerous prescribing encounters.[184] During data collection, codes for drug names simplify the data collection process. Coded data can be efficiently de-coded post-analysis with the chosen statistical software.[185] Use of codes reduces errors and the time spent entering specific drug names multiple times.[133, 185]

Upon completion of data analysis, findings are reported to the investigated health facility as per the WHO recommendations.[133, 186] Staff members such as involved prescribers gain access to the study outcomes upon completion. Reporting to the staff allows for in-depth analysis for the possible reasons for the observed outcomes. A point of importance is the inclusion of recommendations and solutions from the interaction with the hospital staff. Additionally, WHO recommends another meeting be organised to report findings to the management of the health facility.[133] Presentation of previous studies' outcomes in comparison with findings recorded to management is of importance. The aim is to provide possible solutions to improve prescribing at SBAH, thereafter reduce negative outcomes of irrational prescribing such as ADEs. Consideration of the limitations of the investigation of prescribing patterns using WHO prescribing indicators is essential to provide a reliable study. WHO prescribing indicators exclude the investigation of the clinical rationality of prescribing and outcomes of treatment. Thorough investigation of clinical outcomes are recommended beyond the use of prescribing indicators.[180]

1.14. Study aim

The aim of this study was to determine the prescribing pattern of drugs to chronic disease outpatients, and find possible solutions to provide a system that would reduce overprescribing of chronic medication at Steve Biko Academic Hospital (SBAH) in one measure namely drug duplication.

1.15. Study Objectives

The study attempted to achieve the following objectives:

- Determine how many different departments a single patient visits during the study period.
- Determine the extent of polypharmacy at the Steve Biko Academic Hospital outpatient clinics.
- Ascertain the most frequently prescribed medication and identify the cost drivers.
- Perform a prescription analysis in determining possible drug duplication.
- Formulate recommendations (if any) for reducing irrational drug prescription at Steve Biko Academic Hospital.

Chapter 2: Materials and methods

2.1. Study design and type

A retrospective descriptive cross-sectional study with the use of convenience sampling was carried out. Actual prescriptions from the hospital pharmacy were recorded focusing on the quantity of drugs prescribed, and the most frequent medication prescribed was considered. Each drug prescription observed was evaluated using guidelines of WHO titled, "*How to investigate drug use in health facilities: selected drug use indicators.*"[133]

2.2. Study population and setting

The study was conducted at SBAH. Outpatient services are offered to patients who have referrals from medical practitioners and district clinics. Four hundred and eighty thousand (480,000) patients are reported to be attending the specialist clinics.[44] Drugs prescribed to outpatients were dispensed in the hospital pharmacy, which is the second largest tertiary hospital pharmacy in Gauteng servicing residents from the Tshwane metropolitan area. All prescription records are stored at the SBAH archives department. Additionally, the pharmacy records were made readily available to the principal investigator (PI). Permission to access patient files was obtained from the SBAH CEO (appendix 2). Ethical approval was obtained from the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria for the collection of medical information from SBAH patient files (Approval number: 508/2018, appendix 1).

2.3. Patient/research object selection

Convenience sampling was implemented in the selection of chronic disease outpatients. Participants were selected according to their appearance in the hospital records, with sample saturation reached when each participant had visited all the different clinics. The objectives could be determined upon completion of collection of data from individual patients attending the various clinics once in the study period. Chronic disease outpatients attending the SBAH clinics had reviews every three months. The reviews were controlled by issuing patients with medication for a three month period, where after a follow up visit was mandatory in order to ensure prescription and medication renewal. Consequently, each patient visited all the clinics rendering a service relating to a specific chronic condition within a four-month period. The study period was thus determined

according to the expected dates in which a patient attended the hospital for any follow-up or review. Chronic disease outpatient prescriptions at SBAH clinics in a four-month period between February 1, 2018 and May 31, 2018 were used as the object of this study. The study period chosen was the latest time in which data collection would not interfere with daily hospital operations. Use of the four-month study period was advantageous in providing ethical number of participants that produce effectively required data. The study period also limited logistical challenges by the reduction of the time interfering with hospital staff operations and further plans to conduct the study using hospital equipment.

2.3.1. Inclusion criteria

Internal medicine was included with focus on diabetes and internal medicine outpatient department (MOPD). Other departments of focus were oncology, haematology, neurology and psychiatry. Only patients who attended the six chosen clinics identified by the SBAH Pharmacy and Therapeutics Committee (PTC) to be the most affected by drug duplication and polypharmacy were included in this study. Adult outpatients attending the six clinics were estimated from internal PTC reports to be between 50 and 100 patients per day. All male and female patients who attended the specified six clinics during the indicated four-month period were included in the first phase of the study. Patients with complete appointment details were retained. The detail requirements in the appointment book include the name, surname, date of birth, gender, appointment date and the patient number. Data collection in phase two only included patients who attended two or more clinics from the list of clinics observed. Complete patient files were used for analysis post-recording the number of patients attending more than a singular clinic. The patient files analysed for drug duplication had to have prescriptions from two or more different clinics. The prescriptions analysed had to have the patient name, surname, date, list of drugs, route of administration and the prescriber's name and signature.

2.3.2. Exclusion criteria

Patients younger than 18 years were excluded from this study as limited numbers of these patients suffer from chronic disease comorbidity. In addition, the chosen clinics were mainly adult outpatient clinics. Patients who had incomplete appointment details on the appointment register (at least hospital number and date of follow up) were excluded from phase one data collection to avoid collection of unreliable patient information. Patients

attending a singular clinic (even if more than once in the four month period), were excluded from phase two of the study as these patients had one prescriber and would not contribute to the objectives of this project. In addition, patients with illegible or incomplete prescription records were excluded from phase two of the study. The aim was not to evaluate the National Core Standards regarding compliance to prescription requirements, thus any prescription detailing the date of treatment, patient hospital number, type, dose, administration route and quantity of drug prescribed were acceptable. Clinical indication or diagnosis were not a requirement for inclusion, since only polypharmacy related to drug duplication were evaluated.

2.4. Data management

Efficient data collection using prescribing indicators was fundamental in the production of accurate and precise data from this study.

2.4.1. Prescribing indicators

Prescribing indicators relevant to this study were used from the WHO guidelines.

2.4.1.1. Average number of drugs per prescribing encounter

The core-prescribing indicator included was, the average number of drugs per prescribing encounter. Average number of drugs per encounter served to measure the extent of polypharmacy. Polypharmacy was measured by dividing the total number of different drugs prescribed, by the number of prescriptions surveyed. Global studies by WHO, show the average number of drugs prescribed per encounter are between 1.30 and 2.20 drugs.[133] The standard for current prescribing pattern studies is the range provided by WHO that was included as a reference point in this study. Recent studies have shown a higher upper limit on the range provided by WHO standards in developing countries. The range for developing countries including Afghanistan, Botswana, Ghana, Nigeria, Sri Lanka and Zimbabwe has been estimated between 1.30 and 3.00 drugs per encounter.[48]

The extent of polypharmacy was used to measure the risks to supratherapeutic effects that may be affecting the observed patients. Supratherapeutic effects include toxic drug effects and drug-drug interactions.[46] Polypharmacy increases the chances of non-compliance in chronic disease patients. Increased numbers of medication prescribed to

the elderly patients increase the chances of non-compliance due to complicated dosing regimens.[46] Polypharmacy has also been found to reduce the quality of life in chronic disease patients.[187] Reduced quality of life is due to the effects caused by the increased risk of side effects because of the multiple drugs administered at the same time.[47, 187] The effects could be a factor in the social and functional activities of a patient, affecting for example the operation of machinery.[187] Measurement of this prescribing indicator was essential in determining the safety of patients affected by comorbidity. Prescribing cascades are a potential reason for polypharmacy.

2.4.1.2. Percentage of patients treated without the prescription of any drugs

The second prescribing indicator included was, the percentage of patients treated without the prescription of any drugs. This indicator was used to evaluate if patients are constantly monitored and follow-ups done by prescribers to ensure efficiency of treatment. Follow-ups allow physicians to monitor patient compliance and to provide counselling. Patients often stop treatment regimens when there are not any immediately visible clinical improvements.[188] The percentage of patients treated without the prescription of any drugs indicator was used to ensure prescribers monitor treatment outcomes in the patients.

The WHO states that, "*compliance is the extent to which a person's behaviour in taking medication, following a diet and executing lifestyle changes corresponds with recommendations from a healthcare provider*."[189] Non-compliance is the most prevalent factor in reducing the effectiveness of drug use in chronic disease patients.[190] One in four people have been reported non-compliant to drugs provided by healthcare practitioners.[190] Non-compliance is mostly a result of no data or poor patient-prescriber communication, as patients fear adverse effects that may result from long-term drug use. Adverse event reporting is a big step to evaluate during patient treatment to avoid unforeseen adverse events. Monitoring of visits without prescriptions allows to measure the communication between patients and prescribers.[163] Follow-ups are particularly important in the treatment of comorbid chronic disease.

The face-to-face consultations between prescriber and patient also allows for the evaluation of the mental health state of the patient. Majority of chronic disease patients

end up suffering from mental disorders as a result of the disease and treatment burdens.[164, 191] This indicator was used to measure communication standards at SBAH.

2.4.1.3. Average drug cost per prescribing encounter

The final prescribing indicator used was, the average drug cost per encounter. The cost of drugs required by multiple clinic-attendees was calculated for the study period building on the average drug cost per encounter.[133] The average cost of drugs was used to identify how much is required per patient and how much the hospital contributes. The reporting of costs allows for the analysis of the burden of disease on the healthcare system. In the case of comorbid patients attending multiple clinics the costs were likely to be further inflated by the medication errors measured.[9]

2.4.2. Data collection methods

For the collection of data, the ethical approval letter for this study from the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria was produced at all departments visited by the PI. The hospital staff requested the provision of the CEO's approval letter and the ethical approval letter for the collection of medical information from SBAH patient files (Approval number: 508/2018, appendix 1). Each of the six clinics made use of a manual appointment register to enter a patient's name and unique hospital number when booking an appointment for a specific date. These hospital numbers remained unchanged and used by the hospital registry department. Nevertheless, each individual clinic had its own record system and patient files, these files were not provided among the different clinics. Prescriptions from individual clinics were dispensed at two clinics at SBAH. To obtain patients to be analysed as multiple clinic attending patients the data collection process was divided into two phases. The first phase was to register all patients attending the clinics without analysing the prescriptions given to them. Phase 2 contained the prescription analysis process.

2.4.2.1. Phase one data collection

In the first phase, information from the appointment logbooks was gathered on outpatients who attended the six clinics chosen for this study. The appointment logbooks were collected from the different clinics' registry desks. The data from the logbooks was recorded at the hospital without removal of the logbooks from the clinics. Fully completed

patient records were extracted from the appointment records. The PI recorded all the raw data to be uploaded into the statistical software including the folders containing the different clinics. The software folders included the name of the clinic. There was division of each clinic spreadsheet into four different sheets for each month of the study period. The different month sheets were named as follows; February, March, April and May.

The unique hospital number of each patient that attended every individual clinic during the study period was entered into the statistical software spreadsheets created by the PI. Before ascertaining the number of patients that attended the six clinics, the hospital numbers appearing more than once in the same clinic were identified. The identification of the hospital numbers that appeared more than once was done by using the “sorting” function of the statistical spreadsheet. When the repeat entries were identified, the repeat entries were removed to remain with one entry for each patient per clinic. The different spreadsheets for each month were combined into one list that would represent all the patients that attended the individual clinics. The number of patients that attended each clinic during the study period was recorded. The total number of patients that attended the six clinics was calculated by adding the total number of patients that were recorded for each clinic.

The statistician assisted in the provision of the statistical software Stata Release 15.1 (StataCorp, College Station, Texas, United States of America) which was used to enter the lists containing the different clinics and patient entries. Stata extracted the data from the different spreadsheets representing each clinic into a single spreadsheet in the software. The created spreadsheet tabulated the patient numbers into six columns representing the patients that attended each of the six clinics. Stata was commanded to highlight and extract the patient numbers appearing in more than one column. The patients that appeared in more than one column were recorded in a separate spreadsheet. The patient numbers that appeared in more than one column represented the patients that attended more than one clinic.

Stata identified and highlighted all patients that appeared in several clinic columns. This data was used to count how many clinics the individual patients visited in the study period. The patients were classified according to number of clinics they attended. The

spreadsheet containing patients attending more than one clinic was retained for use in the next phase of the study. These patients were to have their prescriptions analysed.

2.4.2.2. Phase two data collection

The total number of patients attending more than one clinic was recorded. In the second phase, the individual prescriptions for each of the identified multiple clinic-attendees were obtained from the patient files at the SBAH archives department. The archives packing staff gave assistance for the extraction of the patient files from the shelves.

Coding system for drug recording

The data collected from the prescriptions of identified multiple clinic-attendees was recorded without removal of the patient files from the archives department. To save time, the drug names were given code numbers entered onto the collection notepad before they were entered into the statistical spreadsheet. The code numbers had a key made which stated which drug each number represented. From the key, the number of different drug items that were prescribed was recorded.

Prescription analysis

The different prescriptions for each patient were analysed to check which clinics they were prescribed in. Statistical software data spreadsheet was used to transcribe each patient's de-coded prescription drugs. The prescription information was matched with the hospital number on the data collection sheet indicating prescriptions from each outpatient clinic. Each row on the spreadsheet was created to represent each patient. Thereafter for each patient, rows were added to represent the number of visits to the hospital. The visits that did not result in a prescription were marked and left empty to show that there was no prescription provided. The prescriptions were recorded according to the date and each row stating in which clinic the prescription was provided. The columns contained the drug name, quantity, route of administration and dose, as de-coded from the collection notepad used to record prescriptions. The WHO guidelines required collection of specific drug names and the route of administration for each drug in retrospective studies.[133] The prescriber notes were also analysed to ascertain which prescriptions were given during the study period. Some clinics had patient files that were not stored at the SBAH archives. Oncology and psychiatry had additional files stored at the clinics not accessed by the

SBAH medical records staff. The patient files from oncology and psychiatry were recorded upon completion of documentation of prescriptions at SBAH archives department.

Number of visits without a prescription

On the data collection spreadsheet, each row represented a patient and the number of visits to the hospital as recorded from the appointment logbooks. The number of visits by multiple outpatient clinic-attendees during the study period was recorded. The average number of visits to the outpatient clinics was calculated by dividing the total number of visits by the total number of patients that attended the clinics during the study period. The number of visits that resulted in a prescription were recorded. The average number of prescriptions to comorbid patients was obtained by, dividing the total number of prescriptions prescribed to comorbid patients, by the total number of comorbid patients retained for analysis. The empty rows from the data spreadsheet were also recorded as they represented the number of visits without a prescription.

Most frequently prescribed drugs

The PI collaborated with the statistician to extract and translate the data from the prescriptions spreadsheet. The spreadsheet data containing the prescriptions was uploaded onto Stata. Stata was commanded to calculate and tabulate the data for the number and percentages of times each drug was prescribed. The most frequently prescribed drugs were recorded from the data produced. Afterwards the total number of drugs prescribed during the study period was recorded.

Cost analysis

Drug costs were checked using the 2019 annual department of health SEP provided in the Monthly index of medical specialities (MIMS) book.[19] The definition of SEP used by MIMS is the definition according to the government. Single exit price is defined as, *"the price set by the manufacturer or importer of a medicine or scheduled substance, combined with the logistics fee and Value Added Tax (VAT), and is the price of the lowest unit of the medicine or scheduled substance within a pack multiplied by the number of unites in the pack."*[20] Monthly index of medical specialities reflects the SEP at the rate of 15% exclusive of VAT in line with pricing legislation (Government Notice, Gazette No

26304 of 30 April 2004).[20] The government controls SBAH operations and uses the tender system for the provision of drugs. The SEP system is designed for the private sector therefore the prices used in this study were estimations of the cost of drugs based on the private sector and pharmacy price estimates.[21] Accuracy and precision of the price differences between the SEP and the prices from the tender system used by SBAH were a limitation of the study.

Upon completion of extraction of the prescription details of all comorbid patients observed onto Stata, a new data spreadsheet was created. The new spreadsheet created contained only data of multiple clinic-attendees visits which resulted in prescribing encounters. The data contained had drugs prescribed to multiple clinic-attendees only. A cost analysis of these drug items was conducted. The drug name, quantities, route of administration and dose were used to check the drug costs. Each column represented different drug names, after which the PI entered the price of the drug on the heading of the column. When all the prices of the drugs were entered, the spreadsheet was uploaded onto Stata for data management and extraction. Each row on the spreadsheet represented a visit to the clinic that resulted in a prescribing encounter. Each row on the data collection sheet represented a single prescription. Addition of the drug item prices per row gave the total price of each prescription. This was recorded as the cost per prescribing encounter.

The cost of drugs was divided into the cost per prescribing encounter and the cost to each comorbid patient during the study period. The cost to each comorbid patient was calculated by adding the total price of all prescriptions received by a patient in all the clinics they attended during the study period. The average cost per prescribing encounter, was calculated using Stata.

Prescription cost versus dispensing fee

The average cost per prescribing encounter was compared with the price patients are required to pay to the hospital administration department per prescribing encounter (dispensing fee).

Average prescription cost versus average dispensing fee to comorbid patients

The average cost to each comorbid patient was also calculated through Stata using the prescription costs to all comorbid patients included in phase two. The average cost to each comorbid patient was extracted from Stata using the average number of prescriptions comorbid patients received during the study period. The average cost to each comorbid patient was obtained by, multiplying the average number of prescriptions per comorbid patient, by the average cost per prescribing encounter during the study period. The average cost to each comorbid patient was compared with the average dispensing fee for the study period. The average dispensing fee was calculated by, multiplying the average number of prescriptions received by comorbid patients, by the average cost per prescribing encounter.

Drug duplication cases

Drug duplication for each patient was identified as the use of two or more drugs from the same drug class, at the same time.[107] All drug items included in the study were classified according to which drug class they belonged to. To ascertain which drug class each drug was grouped in, relevant articles from peer reviewed journals and textbooks were used. The main reference book was MIMS with further cross referencing done using the South African medicine formulary (SAMF) book in identifying the pharmacological classifications of the drug items recorded in phase two of the study.[192] A spreadsheet containing the prescription lines for each patient, at each of the clinics attended was created. The drug names were grouped according to which drug class they belonged to and labelled on the column headings. A comparison for the prescription lines given at the different clinics was done. Drugs from the same drug class prescribed by different prescribers from different clinics were recorded. When different drug items from the same drug class were recorded from different clinics, these were recorded as one case of drug duplication. For example when the psychiatry clinic prescribed amitriptyline and the neurology clinic prescribed fluoxetine, this was recorded as drug duplication. The same drug item prescribed by different prescribers from different clinics was also recorded as drug duplication. An example was when the psychiatry clinic prescribed amitriptyline and the neurology clinic also prescribed amitriptyline, this was recorded as a case of drug duplication. The spreadsheet was uploaded onto Stata for data management and extraction. Stata was commanded to tabulate the drug duplication cases identified from the spreadsheet. The

drug duplication cases were tabulated into the number of times each drug class was duplicated, for example the number of times antidepressants were duplicated. In addition, the type and quantity of duplicate prescription items were assessed for the group in total to determine the drugs that were most frequently duplicated in comparison with the most frequently prescribed drugs. This was done to check if there was a link between the most prescribed drugs and the most duplicated drugs as reported in previous studies.[81, 82]

Demographics of drug duplication affected patients

When the drug duplication cases were recorded, Stata was commanded to produce a list of patients that were involved in the drug duplication cases. The list of patients affected by drug duplicated was used to determine the age and gender of the patients affected by drug duplication. Age and gender demographics were checked to analyse if they had any influence on comorbidity and the prescribing patterns to comorbid chronic disease outpatients at SBAH. Age and gender demographics were collected from the SBAH registry department. The hospital number of each patient was entered onto the registry computer system that provided the date of birth and gender of each patient. Thereafter, the demographics were recorded. The number of female patients was compared with the number of male patients affected. The comparison was used to check the gender demographics of patients affected by comorbidity in the Tshwane metropolitan area. The average age of the patients affected by drug duplication was calculated by, dividing the sum of ages of all patients affected by drug duplication by the number of patients affected by drug duplication. The definition of an elderly patient is different across different continents and countries. In Africa, the definition of an elderly person is alternated between 60 and 65 years or more by the United Nations depending on retirement ages of the population.[193] According to Stats SA, the elderly population was grouped from 60 years or more in the latest mid-year population estimates report.[10] The number of patients under the age of 60 years was compared with the number of patients over the age of 60 years. This was done to ascertain if the age groups of patients affected was mostly elderly patients or the younger adults were also affected the same level at SBAH. The ages of the youngest and the oldest patients affected by drug duplication were also recorded to ascertain the age range of patients affected.

Reproducibility of results

The principal investigator was responsible for all data collection. To ensure error limitation and an acceptable quality level, the PI collected the data from the second phase in duplicate, which was checked by the supervisors prior to statistical interpretation. The principal investigator in reporting that may have occurred during the study and how it affected the study findings described any relevant changes. A major change reported was the collection of data from both patient files at archives and use of dispensing receipts from the pharmacy. This was done to reduce the study limitation of differences between prescribed and dispensed drugs.[133]

Recommendations to SBAH

Study material from the library at the University of Pretoria situated in the Basic Medical Sciences building was used as well as internet searches. Data was collected from the Food and Drug Administration (FDA) website: www.fda.gov. Journals contained in electronic databases such as EBSCOHOST, Google scholar, Medline, PubMed and Scopus were included in the literature review process. Information from similar studies in hospitals across the globe, published in peer-reviewed journals, were used to make recommendations for a system to improve drug prescribing at tertiary hospitals. Study material focused on was the prescribing patterns at tertiary hospitals and prescribing patterns to comorbid elderly patients. Key words used for literature review were; chronic diseases, polypharmacy, hospital information technology, irrational drug prescribing, comorbidity and tertiary hospitals.

2.5. Statistical consideration

Of primary interest was to assess to what extent duplicate prescriptions were issued to patients attending more than one clinic.

2.5.1. Study sample and size determination

Determination of the sample size was discussed with the Faculty of Health Sciences biostatistician, Professor Piet Becker. The final sample size could only be determined once phase one of the study had been completed and patients attending multiple clinics had been identified. The biostatistician for analysis assessed the number of patients that met the study inclusion criteria during phase two.

The records of those patients attending two or more of the participating clinics were assessed in this study. By clinic, these patients were identified in phase one using the hospital numbers of previously booked patients in the four-month period February 1, 2018 to May 31, 2018. Within the clinic records, unique patients were identified after which the records for those patients who attended multiple clinics were retained for this study. In phase two, information following from the files of those patients attending multiple clinics fed into the database for further analysis. The WHO guidelines recommended at least 100 cases within each hospital to get a reliable estimate of prescribing patterns. The results were expected to be more reliable, the higher the number of cases greater than 100. With 50 to 100 patients attending the six clinics per day, the minimum recommended sample size was expected to be achieved.[133] In total 9,177 patients were used in phase one of the study, with 106 patients included in phase two of the study.

2.5.2. Statistical analysis

The proportion of patients who were multiple clinic-attendees was reported along with a 95% confidence interval (ci) using the overall dataset from which the phase two dataset was derived. The full phase two dataset also included the actual prescription lines. Prescription analysis for the multiple clinic-attendees was done overall and by the clinic mainly using proportion with 95% confidence intervals. This full phase two dataset also enabled a cost analysis. Frequency and percentages were extracted from total Microsoft excel database doing data management using statistical software package Stata Release 15.1 (StataCorp, College Station, Texas, United States of America).

Chapter 3: Results and discussion

3.1. Phase one

These were findings from the assorted clinics' logbooks that were used to gather outpatients attending two or more clinics to be carried forward into the prescription analysis phase.

3.1.1. Data collection process

Six outpatient clinics were observed in this study. Each clinic had a different filing system and department specific number. The files stored and used by one clinic were not taken to another clinic by the patient. Different prescribers in different clinics were not aware of what was prescribed at other clinics in cases where a patient suffered from comorbidity. Most notably, patient numbers used at the diabetes were different from other clinics as each patient registered was given a number starting with the clinic's initials for example D12 (Table 3).

Table 3: Patient filing system for each department at SBAH.

Outpatient clinic	Patient filing system (example)
Diabetes	Department specific number (D12)
Haematology	National hospital number (GP63235675)
MOPD	National hospital number (GP63235675)
Neurology	National hospital number (GP63235675)
Oncology	SBAH hospital number (PT45655667)
Psychiatry	Surname, Date of birth (Van rensburg, 1952)

All patients meeting the inclusion criteria for phase one were recorded from the appointment logbooks. Delays were encountered at the MOPD clinic, as the appointment logbook could not be allocated. Failure to allocate the logbook cause confusion at the clinic. Some staff members suggested the logbook was sent to the hospital archives, while some suggested the logbook was misplaced. The staff members carried out a search at the clinic with the hospital archives also searched. The MOPD logbook could not be traced which gave the PI a problem in data collection. Misplacement of data records was noted as a possible retrospective method limitation before commencement of the study.[176] Loss of logbooks was identified as a weakness of the system used by the hospital in storing check-up information. Patients attending the MOPD clinic during the study period were recorded using the logbooks from later months. If a patient had a

follow-up date set within three months from the study period, their first visit was traced back to the study period. The need for advanced computerised systems was again highlighted to reduce loss of patient information.[147]

The haematology clinic was using a different recording system to the other clinics observed. On top of logbook used to record patients attending the clinic, the administration department of the clinic recorded patient details at the reception desk computer with all details of the encounter. This was useful to the PI as the patient information was printed and patient visits recorded at a faster rate. The haematology system could be of great assistance if applied to the rest of the clinics for future internal records studies.

3.1.2. Patient breakdown

Nine thousand one hundred and seventy-seven (9,177) chronic disease outpatients were recorded for the study period from February 1, 2018 to May 31, 2018. Data breakdown of patients recorded per clinic was noted. The most attended clinics were oncology 3,712 (40.45%) and neurology 1,693 (18.45%). Haematology had the least number of patients 150 (1.63%) (Figure 2). The difference in clinic sizes is potentially a reflection of the amount of referrals each clinic received and the demand for continued specialised care for particular medical conditions such as cancer. These findings also reflect the occurrence of specific conditions in the Gauteng region and highlights haematological conditions incidence to be minimal.

Phase one patients were evaluated to obtain patients who attend two or more clinics. One hundred and six (106) patients were attending two or more clinics. Of the 106 patients retained, 103 (97.17%) patients attended two clinics and only three (2.83%) patients attended three clinics during the study period.

Data breakdown of patients attending one clinic and another was recorded. The percentage of each clinic involvement of the total number of different clinic visits by patients attending two or more clinics (215 visits) was identified. The percentage outcome was an indicator of the most involved clinic in having a patient likely to be visiting another clinic at the same time. The most involved clinics were neurology 60 (27.91%) and

internal medicine outpatient clinic 59 (27.44%). The clinics with least involvement were haematology seven (3.26%) and oncology 23 (11.63%) (Figure 3).

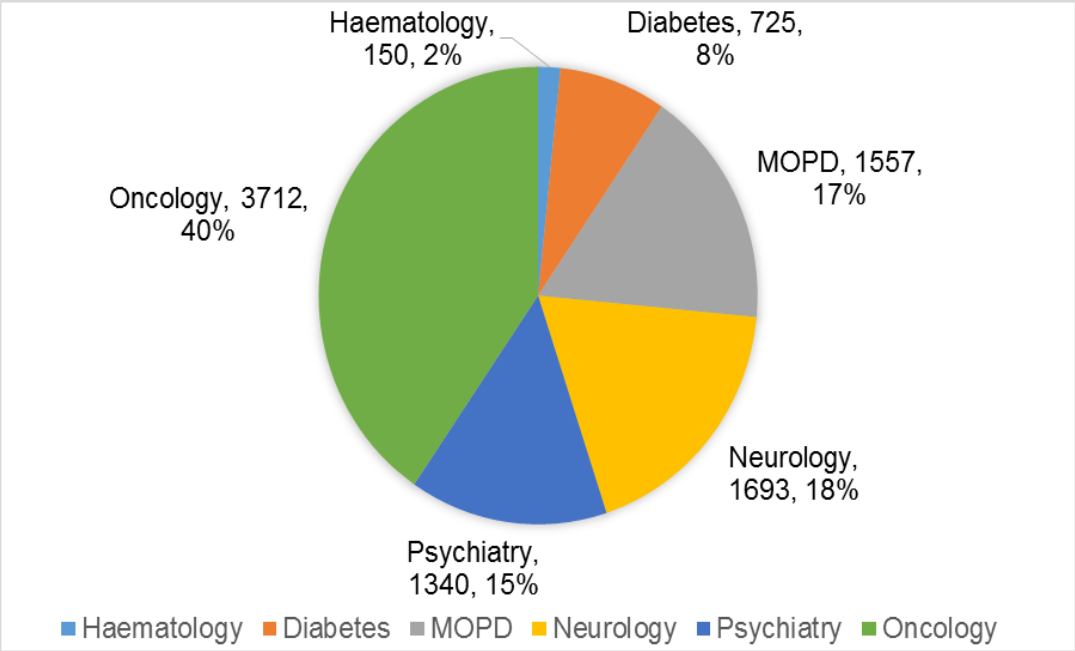

Figure 2: Patients attending all the six different chronic disease outpatient clinics from Feb 1, 2018-May 31, 2018 at SBAH.

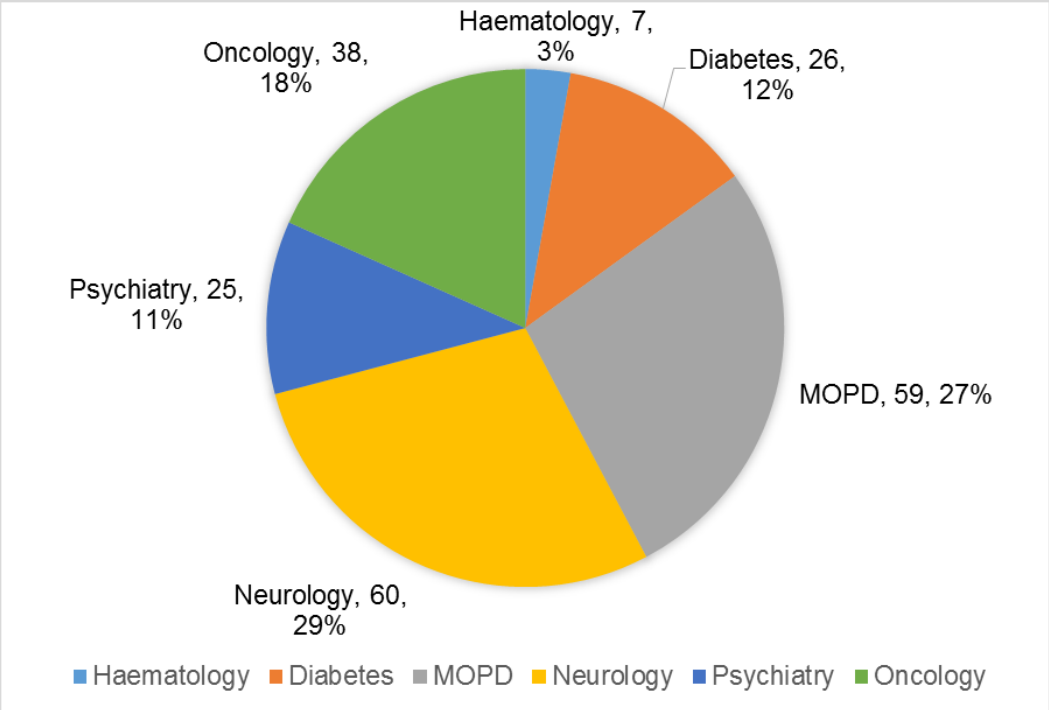

Figure 3: Patients attending two or more chronic disease outpatient clinics from Feb 1, 2018-May 31, 2018 at SBAH.

The combination of clinics was also recorded which reflected which clinics were attended by a patient at the same time. The most attended clinic combination at the same time by comorbid patients was MOPD and neurology with 26 (24.53%) patients involved (Table 4). Previous studies have reported on comorbidity resulting in patients attending MOPD and neurology as MOPD treats patients suffering from various conditions that cause neurological effects. Hypertension patients treated at MOPD are susceptible to ischemic stroke that leads to motor impairment requiring referral to the neurology clinic.[28] The findings highlighted the combined work of MOPD treatment of hypertension and ischemic stroke with neurology clinic in treating motor impairment and lacunar infarcts. Other clinic combinations of note were the 19 (17.92%) patients that attended neurology and psychiatry. This builds on the co-occurrence of psychological disorders during the treatment of neurological conditions. Neurological conditions such as Parkinson's disease often co-occur with or result in psychological effects such as mood, depression and anxiety disorders.[29] These findings compound on the high rate of comorbidities involving psychiatry and neurology as reported in previous studies leading to the creation of neuropsychiatry and neuropsychology departments in China.

Table 4: Frequency distribution of clinic combinations of patients attending multiple outpatient clinics from Feb 1, 2018-May 31, 2018 at SBAH.

Clinic combinations	Frequency	Percentage (%)	Cumulative percentage
Haematology + diabetes	1	0.94	0.94
Haematology + diabetes + MOPD	1	0.94	1.89
Haematology + MOPD	4	3.77	5.66
Haematology + neurology	1	0.94	6.60
Diabetes + MOPD	10	9.43	16.04
Diabetes + MOPD + neurology	1	0.94	16.98
Diabetes + neurology	7	6.60	23.58
Diabetes + oncology	2	1.89	25.47
Diabetes + psychiatry	4	3.77	29.25
MOPD + neurology	26	24.53	53.77
MOPD + neurology + oncology	1	0.94	54.72
MOPD + oncology	9	8.49	63.21
MOPD + psychiatry	7	6.60	69.81
Neurology + oncology	5	4.72	74.53
Neurology + psychiatry	19	17.92	92.45
Oncology + psychiatry	8	7.55	100.00
Total	106	100.00	

3.2. Phase two

These findings were from the analysed prescriptions of patients attending two or more outpatient clinics.

3.2.1. Evaluation of visits to SBAH by outpatients

Patients attending two or more clinics retained from phase one of the study were analysed in phase two. The information collected by the SBAH HIS department was of no use for the clinical analysis of data as it only contained limited data. On the computer systems used by the hospital, only identifying information of the patient was present, the date of hospital visit and follow-up dates without record of any prescribing or outcomes of the visits. Data from the patient file archives was used for prescription analysis and note if a prescription was provided.

One hundred and six (106) patients were analysed. Average age of patients analysed was 57 years. The average age of patients was calculated using information from the HIS that contained date of birth of all the patients. Patient visits were evaluated to identify the impact of attending two or more clinics to patients' quality of life. As reported in previous studies disease burden is seen in the amount of time a patient loses in their social and functional activities to obtain treatment.[9, 15] The overall number of visits by the 106 patients to the chronic disease outpatient clinic during the study period was 321 visits. The average number of visits to SBAH by the comorbid chronic disease outpatients observed was 3.03 visits during the four-month study period. Out of the 321 patient visits, there were 240 (74.77%) prescribing encounters to comorbid chronic disease patients. Average number of prescriptions to the 80 retained patients during the study period was three prescriptions.

Of the visits by patients attending the clinics as visitors for the first time or follow-up patients resulted in 74.77% prescribing encounters. The WHO prescribing indicator, on average number of visits without prescriptions was addressed at this point.[133] Eighty one (25.23%) of visits by comorbid patients to SBAH resulted in no prescriptions. The authors were able to identify the percentage of visits that resulted as check-ups. Visits without prescriptions were used to measure the availability of patient counselling by physicians. Physicians are required to constantly check the outcomes of treatment on patients for

drug safety and efficacy.[180] Interaction between prescriber and patient face to face, is an important tool in assessing patient mental health. Comorbid patients are highly susceptible to mental disorders.[164] Visits without prescriptions at SBAH highlighted existence of the opportunity for assessment of patient's mental health with face-to-face check-ups in 25.23% of the 321 patient visits.

The presence of different filing systems at the different clinics lead to patients attending two or more clinics having two or more separate files (Table 3). Patient files from the SBAH patient files records with misplaced prescriptions were excluded. Furthermore, files were excluded if they contained prescriptions from one clinic, with the second clinic prescriptions missing. Patients receiving prescriptions from one clinic were identified as drug receivers from one prescriber and for this reason did not meet the inclusion criteria. Among the total prescribing encounters, 53 (22.08%) prescriptions were excluded from the study (Table 5). The 53 prescriptions accounted for 26 patients. Eighty (75.47%) patients out of 106 patients were carried forward in the evaluation of polypharmacy, drug duplication and cost. Exclusion of some patients was a limitation of the method used in data collection. Retrospective studies often result in data loss as the PI has no control over the recordkeeping and filing system used by the hospital.[194]

Table 5: Summary patients attending multiple outpatient chronic disease clinics from Feb 1, 2018-May 31, 2018 at SBAH.

Study outcomes	Values observed
Clinics observed	6
Phase 1 patients	9 177
Phase 2 patients	106
Average age of patients	57 years
Number of visits by Phase 2 patients	321
Number of prescribing encounters	240
Number of retained prescriptions for analysis	187 (77.92%) of 240
Number of discarded prescriptions	53 (22.08%) of 240
Number of patients retained for analysis	80 (75.47%) of 106
Total number of drugs prescribed	929
Different drug types encountered	111

Patients attending multiple clinics increase the burden on the SBAH pharmacy as they have multiple prescribing encounters. The frequent visits by comorbid patients to the specialist outpatient clinics results in numerous prescribing encounters, often of

analgesics (appendix 4). The outcomes of comorbidity burden are observed in the frequent long queues at the SBAH pharmacy. Long queues are often observed in poverty stricken countries as patients have limited financial resources to attend pharmacies outside public hospitals.[14] Staff members at SBAH suggested that long queues were increased by the operating days of the outpatient clinics. The outpatient clinics were only operational during working days thus patients were forced to visit SBAH during the week. The combination of operating days and long queues resulted in patients spending a large amount of time getting treatment. Comorbid patients were the most affected by labour productivity loss as they spent more days visiting the hospital. The reduced productivity outputs leave comorbid patients the most susceptible to job loss.[14] Average visits of 3.03 by comorbid patients to SBAH during the study period compounded on the findings from previous studies that chronic diseases were a burden to the South African gross domestic product.[15]

Comorbid patients attending the SBAH specialist outpatient clinics from as far as other provinces such as Mpumalanga. Unconfirmed reports outline that patients travelling from far distances are obligated to arrive early at SBAH in order to register for drug collection at the SBAH pharmacy as early as possible.[195] In some cases, comorbid patients may have to attend another outpatient clinic in the same week, with patients having to travel early to the hospital again with more time taken out of working hours. Physicians may be compelled to prescribe chronic medication from another clinic in order to save the patient's time and financial resources. Unauthorised prescribing possibly resulted in drug duplication, as some physicians were not be aware of previous prescribing encounters.

3.2.2. Extent of polypharmacy

The extent of polypharmacy was measured for the study period per encounter. Five or more drugs were prescribed in 85 (45.45%) prescriptions (Table 6). The most frequently prescribed number of drugs per prescription were, three drugs (n=32, (17.11%) followed by two drugs (n=28, (14.97%). Two (1.07%) prescribing encounters resulted in prescriptions containing 19 drugs each. The average number of drugs per prescribing encounter during the study period was 4.97 (Table 7).

The extent of polypharmacy was measured by two methods. Average number of drugs prescribed per encounter was used in comparison to the WHO standard to ascertain rational drug prescribing. The global range for drugs prescribed per encounter provided by the WHO is 1.80- 2.20 drugs.[133] Average number of drugs per encounter to comorbid patients at SBAH of 4.97 was higher than the WHO standards. The average number of drugs prescribed per encounter at SBAH is higher than the average number observed in numerous African countries (3.10).[132] A higher value than that of the WHO might be a reflection of the study population, which consists of only chronic comorbid patients who often require assorted drugs concomitantly. Comorbid patients taking assorted drugs are susceptible to prescribing cascades that could be resulting in patients having drugs prescribed to treat side effects of previously prescribed drugs. Another reason that could be responsible for a higher average at SBAH than in other African countries is the abundance of drugs that allows prescribers to prescribe drugs without reservations for drug stock saving. Some African countries have drug shortages and high amounts of medicine stock outs that limits the amount of drugs per prescribing encounter for example Zimbabwe (1.3 drugs per encounter). In developing countries, some of the reasons responsible for higher values than WHO recommendations are the lack of institutional prescribing guidelines catering for the local population and medicine stock-outs.[48, 132]

High incidence of polypharmacy at SBAH should be taken into account as motivation for implementation of further studies to investigate if the prescribing encounters are rational in the absence of drug duplication. There was an incidence of polypharmacy however, this study does not confirm if it was appropriate or problematic polypharmacy in cases not related to drug duplication. Appropriate polypharmacy not related to drug duplication is common among comorbid and elderly patients. The benefits of appropriate polypharmacy outweigh the harmful outcomes allowing for its recommendation in some cases.[47]

There was potential of a relation between high incidence of polypharmacy and the lack of essential medicines dedicated to comorbid elderly patients. The exclusion of elderly and comorbid patients from clinical trials due to their different pharmacokinetic properties has been reported as a factor in inefficient treatment due to limited drugs dedicated to the elderly pharmacokinetic properties.[73, 106] Use of many drugs to treat multiple

conditions without fixed-dose combination drugs could be a factor in polypharmacy being reported at a much higher level for the observed group of patients.[171]

Table 6: List of prescribing encounters to patients attending more than one clinic from Feb 1, 2018- May 31, 2018 at SBAH outpatient chronic disease clinics.

Number of drugs per prescription	Number of prescribing encounters	Percentage (%)	Cumulative Percentage
1	20	10.70	10.70
2	28	14.97	25.67
3	32	17.11	42.78
4	22	11.76	54.55
5	16	8.56	63.10
6	20	10.70	73.80
7	18	9.63	83.42
8	7	3.74	87.17
9	8	4.28	91.44
10	3	1.60	93.05
11	3	1.60	94.65
13	1	0.53	95.19
14	5	2.67	97.86
15	1	0.53	98.40
16	1	0.53	98.93
19	2	1.07	100.00
Total encounters	187	100.00	

These results build on existing evidence of the prevalence of polypharmacy among elderly and comorbid patients. The percentage of patients affected by polypharmacy at SBAH was as expected for clinics occupied by elderly patients. The percentage was relatively higher than in the majority of background studies as this study comprised of chronic comorbid patients compared with previous studies where patients suffering from single morbidities were also included. This study highlights the influence of comorbidity on the number of drugs a patient is prescribed as it shows a high percentage of patients receiving five or more drugs. A survey in the USA found a relatively similar outcome of 41.40% of elderly patients receiving five or more drugs per prescription.[46]

Table 7: Evaluation of WHO core prescribing indicators for patients attending multiple chronic disease clinics from Feb 1, 2018-May 31, 2018 at SBAH.

WHO core prescribing indicator	Observed values (SBAH)	WHO standard	Developing countries
Average number of drugs per encounter	4.97	1.30-2.20	1.30-3.00

3.2.2.1. Prescribing cascades

The two methods used in this study both confirm the existence of polypharmacy to comorbid outpatients attending SBAH. There is a need to ensure there is appropriate polypharmacy instead of problematic polypharmacy at tertiary hospitals. Problematic polypharmacy is a result of irrational drug prescribing.[47]

Recent studies have shown a higher upper limit in the range for prescribing encounters in developing countries than the WHO standards. The range for developing countries was reported to be between 1.30 and 3.00 drugs per encounter.[48] Average drugs per prescription to comorbid patients (4.97) at SBAH was higher than the upper limit mark of the range expected for other developing countries. The observed developing countries included Zimbabwe, Nigeria, Ghana, Thailand and Malaysia. The high number of drugs often prescribed to comorbid chronic disease patients could explain these findings. Identification of the extent of polypharmacy is essential when considering the treatment outcomes of comorbid patients attending multiple clinics at SBAH. Polypharmacy is associated with increased levels of ADEs, commonly misdiagnosed as new medical conditions by prescribers. The risk with misdiagnosis of ADEs is the continued increase of prescribing of more drugs to treat effects of previously prescribed drugs, creating a prescribing cascade.[63] Patients were consequently at risk of displaying poor clinical outcomes as ADEs from multiple drugs could be affecting their wellbeing and quality of life.

3.2.2.2. Adverse drug effects

The increased levels of ADEs due to polypharmacy could be a result of drug-drug interactions.[58] Risk of DDIs increases with the increase in number of drugs administered to a patient at the same time. Of the prescriptions analysed, 45.45% contained five or

more drugs. There were 8.56% prescriptions with extreme cases of ten or more drugs per prescription. The chances of adverse drug reactions (ADRs) as shown in literature when prescribed two drugs are 13%, that increases by 45% when prescribed five drugs and increases by a further 24% when prescribed seven drugs or more drugs.[54] The extreme cases were patients received up to 19 drugs in one prescription require further investigation to ascertain the rationality of the prescriptions. The findings contribute to a clearer understanding of the risk of drug-drug interactions in comorbid chronic disease patients at SBAH. Drug-drug interactions affect mostly the metabolism, distribution and elimination of drugs.[116]

The toxicity risks of the drug classes mentioned in this study potentially increase in the 45.45% prescriptions that contain polypharmacy. Multiple risks are associated with polypharmacy involving various drug classes. Toxicity clinical outcomes associated with numerous drugs could lead to hospitalisations and potentially death of the included patients. In consideration of the individual drug classes, their toxic outcomes are different, but negatively influence the safety, wellbeing and HRQOL of each patient. Drug toxicity can cause delirium, cognitive dysfunction, acute respiratory failure, renal toxicity, hepatotoxicity, seizures and cardiac toxicity.[118, 119]

3.2.2.3. Medication non-compliance

Numerous drugs administered at the same time causes unintentional non-compliance to the recommendations by the prescriber.[68] Polypharmacy levels at SBAH created the possibility of failure by patients to adhere to the recommendations provided to produce the best possible treatment outcomes. Failure to take each of the drugs at the recommended time and number of times a day could affect the effectiveness of the treatment. Numerous drugs also creates a risk in patient confusion on when each of the drugs are taken for example which drugs are taken before or after meals.[68] Chronic disease treatment is long term thus, how a patient corresponds to the prescriber's recommendations affects the long-term outcomes of prolonged treatment.

The numerous ADEs that may be resulting from each of the different drugs administered can also cause non-compliance in polypharmacy cases.[69] An average of 4.97 drugs per prescription at SBAH increases the chances of ADEs, which eventually could cause

intentional non-compliance. The patients affected by polypharmacy ADEs could intentionally withdraw some of the drugs because of the severe ADEs they could be experiencing. Severe ADEs could be affecting the patients' daily functional and social activities. Functional activities affected could be activities such as operation of machinery due to tremors from sedative hypnotic use that could result in job loss.[126] ADEs such as blurry vision affect social activities as they cause prohibition from operating motor vehicles. The 45.45% of prescriptions indicating polypharmacy were potentially at risk of intentional and unintentional non-compliance. These findings indicate the need to investigate to what extent there is an existence of non-compliance related to polypharmacy. Identification of affected patients by non-compliance could potentially allow steps to provide solutions to assist in compliance amongst elderly and polypharmacy patients. Automated electronic mobile reminders have been used globally to reduce non-compliance, through reminding patients when to take drugs and avoid treatment failure.[69] Such systems could be of consideration at SBAH, to limit the effects of polypharmacy.

3.2.2.4. Medication stock-outs

Availability of essential drugs is a key component of chronic disease treatment. Constant supply and accessibility of chronic disease drugs is a competency standard by which healthcare facilities operate. Factors such as problematic polypharmacy cause excessive and unnecessary use of essential drugs in healthcare facilities.[47] Polypharmacy incidence at SBAH causes prolonged excessive drug use by chronic disease patients. Prolonged excessive use can lead to the occurrence of medicine stock-outs.[51] Studies have shown the existence of medicine stock-outs in the public sector in a majority of low and middle-income countries.[73]

Chronic disease essential medicine stock-outs infringes on the rights of the patients. Patients have a right to chronic disease essential drugs at all times, right quantities, doses and packaging to provide adequate safety, quality and efficacy.[72] Medicine stock-outs could however affect the credibility of SBAH in providing quality service to chronic disease patients. Patients could be receiving prescriptions but no dispensed drugs from the pharmacy due to unavailability of some drugs. Medication stock-outs lead to patients purchasing expensive drugs from private pharmacies. Credibility loss could result in

patients preferring to self-medicate than attend SBAH that could lead to increased ADEs and fatalities in the Tshwane district. Medicine stock-outs are responsible for a large number of patients being turned away from public hospitals globally, according to previous studies.[51] These findings have resulted in healthcare system failure and overall poor health of the population.

Considering SBAH is a public hospital, through application of the outcome of previous studies in developing countries, the potential of medicine stock-outs is high. Medicine stock-outs have been reported to occur two thirds of the time in public hospitals of low and middle income countries.[73] When assessing the risk of medicine stock-outs at SBAH, it is one of the contributing factors for problematic polypharmacy. This study has confirmed the existence of polypharmacy due to multiple clinic attending by chronic disease patients, however it was beyond the scope of the study to determine if there was problematic or appropriate polypharmacy. Further studies are required to ensure if the polypharmacy at SBAH is problematic polypharmacy, which causes unnecessary drug prescribing and dispensing. It is of importance to highlight the polypharmacy observed could contain appropriate polypharmacy. Appropriate polypharmacy is beneficial to the patient as the benefits outweigh the harmful effects. The impact of the type of polypharmacy could be measured to see if it contributes to the use of drugs unnecessarily, creating a risk of medicine stock-outs.

3.2.3. Frequently prescribed drugs

One hundred and eleven (111) different drugs items were prescribed to the chronic disease outpatients evaluated during the study period. The outpatients observed received 929 drugs in the four-month study period. Most frequently prescribed drugs were tramadol (n=51, (5.49%), followed by simvastatin (n=48, (5.17%), enalapril (n=45, (4.84%), lansoprazole (n=43, (4.63%) paracetamol (n=40, (4.31%) and amitriptyline (n=38, (4.09%) (Appendix 4). The most prescribed drugs were analysed to ascertain which their drug classes. The most prevalent drug classes were, analgesics followed by hipolipidaemic agents, antihypertensive agents, antacids and anti-depressants (appendix 4).

Tramadol (n=51, (5.49%) and paracetamol (n=40, (4.31%) being the most prescribed analgesics confirm global findings of extensive analgesic prescribing for pain management.[83] Tramadol was the most prescribed drug to comorbid patients in this study. High levels of tramadol prescribing build on findings of existing evidence from Germany, Australia and Malaysia.[83] The findings could imply the limited control of tramadol use in South Africa in comparison with USA and the United Kingdom.[85] There was a prevalence of pain management leading to the combined use of NSAIDs adding up to 47 (5.04%) prescriptions. Use of multiple treatment agents including NSAIDs could be linked with the extensive use of antacids namely lansoprazole (n=43, (4.63%).[90] High levels of antacid prescribing has been a result of use of multiple agents in the treatment of concomitant conditions This study confirms the extensive use of pain management agents results in gastrointestinal disease, eventually leading to increased antacid prescribing.[90]

Simvastatin (n=48, (5.17%) was the second most prescribed drug. High levels of statin prescribing has been associated with the increased desire to prevent cardiovascular disease by physicians.[99] With the majority of patients included in the study being elderly patients, physicians at SBAH identified risk of cardiovascular disease. Cardiovascular conditions associated with elderly patients include hypertension. Findings in this study show significant encounters of antihypertensive agents prescribing. The most prescribed antihypertensive agent were enalapril (n=45, (4.84%). These findings were expected as it has been previous reported that elderly and comorbid patients are often susceptible to high levels of hypertension.[104] Diuretics prescribing was also of note with hydrochlorothiazide (n=36, (3.88%) found as the most prescribed in combating hypertension.

As patients suffer from numerous conditions resulting in assorted medication being taken, they are often affected by substantial amounts of adverse drug reactions.[163] Numerous adverse drug events often affect the social and functional activities of patients leading to mental conditions occurring.[164] Anxiety and depression were factors in the monitoring of comorbid patient outcomes. Antidepressants prescribing increase has been reported in previous studies.[96] This study builds on findings of previous studies that of the high levels of antidepressants prescription to elderly patients. Amitriptyline (n=38, (4.09%) which is

a tricyclic antidepressant (according to the pharmacological classification guidelines) was the most prescribed drug in this study. It has been reported that the increased levels of antidepressant prescribing could be as a result of increased awareness and diagnosis by physicians.[92] The use of amitriptyline for other indications is also a factor in the relatively high amitriptyline prescribing. Amitriptyline is used for a number of indications at low doses including muscle spasm, insomnia, pain and anxiety. Due to the lack of dosage data, the results cannot confirm the indication of amitriptyline as an antidepressant at high doses or its use for other indications at low doses.

There is commonly a relation between the results of the most frequently prescribed drugs and the most duplicated drugs to comorbid chronic disease patients attending the outpatient clinics at SBAH. In literature drug classes including, analgesics, antihypertensive agents, hipolipidaemic agents and antidepressants were associated with medication errors because of the high volumes at which they are prescribed.[81, 82] These drug classes are the most prescribed drugs globally which was also observed at SBAH. The specific reasons as to why these particular drug classes are the most prescribed drug classes at SBAH compared to reports of previous studies was beyond the scope of this study. More studies are required to determine the reason for the prescription and extent of certain drug classes at SBAH.

There are questions such as the reasons behind lansoprazole preference over omeprazole and esomeprazole. Similar studies have found omeprazole and esomeprazole as the most prescribed PPIs in the treatment of gastro-oesophageal reflux-disease (GORD) and peptic ulcers.[102] Factors such as cost of the different drugs determining their availability at SBAH or prescriber preference of one drug over the other can be analysed. Another factor to consider amongst low and middle income countries is the medicine stock-outs that may have an influence on the drugs prescribed at a certain period.[73] Medicine stock-outs have been identified in literature as a reason for increase in financial resource burden in hospitals.[51] Medicine stock-outs have been responsible for the change by hospitals to expensive drug use when the cheaper alternatives are depleted.[51, 73] During cost analysis with the use of MIMS omeprazole was cheaper than lansoprazole, however lansoprazole was the PPI of choice at SBAH.[19] As the prescriptions of focus were to chronic disease patients, long-term effects of lansoprazole

could be of preference over omeprazole. Prescriber preference and other factors other than cost of the drug are in need of more analysis. A possible factor affecting drug procurement at SBAH could be the change in drug prices due to the tender process allowing for the availability of cheaper lansoprazole than omeprazole to public health facilities. Further research is essential to establish the reason behind why particular drugs are available to prescribers over cheaper alternatives.

In future studies at SBAH, it would be of interest to monitor the trends of prescribing of these drug classes to see if there are any changes in the volumes prescribed over a long period. Prescribing trends studies would determine if there are similarities in South Africa with global studies. Global reports have identified an increase in prescription of drug classes such as antidepressants and hipolipidaemic agents.[98] Increase in prescription of many drug classes has been associated with probable increase in the disease conditions in the community or increased diagnosis by physicians due to better awareness of occurrence.[92] Further studies to determine what could be the cause of the decrease or increase in the prescribing volumes are vital. A foundation to highlight the disease burden in the Tshwane district and prescribing patterns over a number of years in epidemiology studies is a step to reduce overprescribing.

3.2.4. Cost drivers

Achievement of cost analysis with regard to the average cost of drugs to comorbid patients was obtained from the average cost per prescription. Drug costs were checked using the 2019 annual department of health SEP provided in MIMS.[19] Average cost per comorbid patient analysed was extracted using the average cost per prescription. Average cost of drugs per prescription was R899.77 during the study period (Table 8). According to the SBAH registry office, each patient was required to pay a minimum amount of R75.00 (dispensing fee) to obtain drugs from each prescription. A fixed drug-dispensing fee was used at SBAH per prescribing encounter at the hospital and for repeat prescriptions. Dispensing fee use prohibited the hospital from charging patients per drug item in the prescription, as in the operating system in private pharmacies. In the four-month study period, the mean cost of drugs prescribed to comorbid patients was R2 103.21 (Table 8). The cheapest prescription was R14.42 containing the diuretic hydrochlorothiazide. The most expensive prescription was at the oncology clinic and had

the sum of R21 983.60 for all drugs prescribed. The drugs prescribed were imatinib (R21 470.00), lansoprazole (R241.10), folate (R62.59), diclofenac (R61.80), tramadol (R119.58) and metoclopramide (R28.53).

Table 8: Cost data for comorbid patients attending multiple outpatient chronic disease clinics from Feb 1, 2018-May 31, 2018 at SBAH.

Variables	Frequency	Mean Cost (Rand)	Standard deviation (SD)	95% CI	Min cost (Rand)	Max cost (Rand)
Prescriptions	187	899.77	1 852.68	[632.49-1 167.04]	14.42	21 983.60
Comorbid patients	80	2 103.21	2 925.84	[1 452.09 - 2 754.32]	325.66	22 551.74

The use of a fixed dispensing fee over charging per drug prescribed to is control, limit prices to the public, and allow for continued access to chronic disease treatment. The NDoH introduced policies to cap prices of drug dispensing to ensure the whole population especially the patients below the poverty line can still access medical care.[18] The National Drug Policy is seen in effect at SBAH as one of its objectives was to ensure drug affordability and transparency to all patients.[18] As SBAH is a public hospital, it is among the public hospitals that are reported to cater for 84% of the population. The majority of patients attending SBAH are low-income patients.[38, 40] The use of a fixed dispensing of fee of R75.00 was deemed affordable to the majority of the population to gain access to treatment. In the use of the perceived affordable fixed dispensing fee, SBAH complies with the law that all patients have a right to medical care and treatment at all times.[142]

A financial cost gap was estimated between the dispensing fee and the cost of prescriptions for chronic disease patients. The cost gap was even bigger for comorbid chronic disease patients, as the number of visits to the hospital were greater. The hospital visits of comorbid chronic disease patients resulted in prescriptions in 74.77% of the visits (Table 5). The data showed that on average there was a difference of R824.77 between the dispensing fee (R75.00) and the average cost per prescription (R899.77) to chronic disease patients at SBAH (Table 8). The results indicated that SBAH had to cover R824.77 per patient per prescribing encounter. The cost burden of chronic diseases on SBAH was shown by the findings and it reflected the cost on the public healthcare system.

The cost of comorbid chronic disease patients attending multiple clinics was estimated. The average number of visits to SBAH for the chronic disease outpatients observed was 3.03 visits during the four-month study period. During the average 3.03 visits resulting in prescriptions, each patient was expected to pay a dispensing fee of R227.25 (3.03 multiplied by R75.00 dispensing fee). The results from cost analysis indicated that on average the drugs prescribed to each comorbid chronic disease patient during the study period, cost R2 103.21. The data showed that the difference between the estimated dispensing fee (R227.25) and the average cost of drugs prescribed to each comorbid patient during the study period (R2 103.21) was R1 875.96. These findings further indicate the extra drug costs SBAH had to cover to provide treatment to chronic disease patients.

These results build on existing evidence of the burden of chronic diseases on the health care system. The national health budget and its consequences on the country's economy reflect the amount of financial resources and quality of services required to operate the public health care system. Costs of chronic disease treatment have been associated with the underdevelopment of low and middle income countries.[15] In 2014 Hofman reported that diabetes, stroke and cardiovascular disease contributed to the loss of US$1.88 billion of the South African gross domestic product between 2006 and 2014.[15] A burden on the public healthcare system resources results in reduced quality of services to patients. Reported global increase in chronic diseases could lead to even greater costs incurred by the government in the provision of affordable drugs in the public sector. Increase in the population, life expectancy and chronic diseases has been projected globally.[173] The increase in disease burden is projected to result in increased healthcare costs affecting the economy of developing countries.[175] There is a need to provide a solution in the reduction of cost on the public healthcare system.

The burden of chronic disease treatment costs leads to a great amount of the health ministry's budget focusing on provision of funds for drug procurement. Increased loss of funds in drug procurement can lead to reduction of funds in hospital development. Underfunding causes underdevelopment such as the lack of introduction of computerised systems and advanced equipment in tertiary hospitals. The impact of underfunding and

underdevelopment is increased poor patient care and medication errors in hospitals which is often associated with the public health sector.[38, 43] Another effect of overuse of financial resources in drug procurement is the reduced funds directed to staff compensation. Low compensation staff at public hospitals contribute to the inadequate results in patient care. Staff with low motivation in hospitals often violate rules such as inadequately monitoring treatment outcomes and reporting of errors.[40, 43]

3.2.5. Drug duplication

Prescription analysis summed up the extent of drug duplication, represented in Table 9. Drug duplication occurred in 68 individual cases in the 80 patients observed. In total, 39 patients (48.75%) were affected by drug duplication [95% CI = 37.80%; 59.70%].

The results indicated a high incidence of drug duplication that is associated with high risk of toxic and inefficient drug use.[127] Chances of medication errors were shown by the authors in the use of assorted clinics resulting in multiple prescribers. The relationship between medication errors and multiple prescribers was compounded by findings in Lebanon that the lack of communication and awareness of what was previously prescribed at another clinic was a cause for drug duplication.[127]

The average age of patients affected by drug duplication was calculated from the hospital registry system. The average age of the 39 patients affected by drug duplication was 57 years. The youngest patient affected was 21 years old, and the oldest patient was 88 years old (appendix 5). Of the 39 patients affected, 20 (51.28%) patients were aged older than 60 years. These results indicate that drug duplication was not influenced by belonging to the elderly age group (60 years and older) but also affected the younger adults age group (59 years and younger). Drug duplication extent was similar for both young adults and elderly people (older than 60 years).

The majority of patients affected by drug duplication were female with 26 (66.67%) patients affected. In comparison, drug duplication was established in 13 (33.33%) male patients. These findings were reflective of the higher number of elderly female patients attending the SBAH outpatient clinics. The majority of patients referred to SBAH was a reflection of the elderly gender demographics in the Gauteng province consisting mostly

of female residents.[10] Additionally, more female patients being affected by drug duplication compounds on previous studies that female patients are more susceptible to medication errors such as drug duplication.[80] Females are health conscientious than males essentially being more prone to hospital visits and prescription encounters.[79] A greater number of female patients visit the outpatient chronic disease clinics at SBAH resulting in greater prescription encounters than for male patients. Increased prescription encounters increases the chances of drug duplication, which was reflected in the findings.

The most prevalent drug classes were analgesics with 18, (26.47%) cases, followed by antidepressants with 14, (20.59%) cases recorded. The most duplicated antidepressants were amitriptyline (tricyclic) and fluoxetine (SSRI). Analgesics duplicated the most were tramadol and paracetamol.

Table 9: Frequency distribution of drug classes duplicated in patients attending multiple outpatient clinics from Feb 1, 2018-May 31, 2018 at SBAH.

Drug class	Frequency	Percentage (%)	Cumulative percentage
Antidepressants	14	20.59	20.59
Anti-epileptics	7	10.29	30.88
Anti-vertigo	1	1.47	32.35
Analgesics	18	26.47	58.82
NSAIDS	2	2.94	61.76
Anti-hypertensive agents	7	10.29	72.05
Anti-angina agents	3	4.41	76.46
Hipolipidaemic agents	1	1.47	77.93
Haematinics	3	4.41	82.34
Antacids	4	5.88	88.22
Diuretics	4	5.88	94.10
Anti-diabetic agents	1	1.47	95.57
Thyroid	1	1.47	97.04
Vitamins	1	1.47	98.51
Minerals	1	1.47	100.00
Total	68	100.00	

Analgesics

The most prevalent drug class in drug duplication is analgesics with the most duplicated drugs being paracetamol and tramadol. Tramadol and paracetamol drug duplication may result in overdose of both drugs in a patient. The risk of treatment failure and toxicity is increased by the altered pharmacokinetic properties of elderly patients thus the number

of elderly patients was investigated.[34] Twenty (51.28%) of the patients affected by drug duplication in this study were 60 years or older. Drug duplication of analgesics is potentially one of the reasons for chronic disease patients treated at SBAH possibly attending emergency hospital units for treatment. Drug duplication of these analgesics could be contributing to the 50% of preventable hospital admissions that could be occurring at SBAH as reported globally due to ADEs.[45]

Antidepressants

To understand the outcomes of antidepressant duplication, the effects of antidepressants overdose and toxicity are analysed. Antidepressants were the second most duplicated drug class with 14 (20.59%) cases. The most commonly duplicated drugs were amitriptyline and fluoxetine. Common use of amitriptyline and fluoxetine is due to their use in elderly patients in treatment of neuropsychiatric disorders, chronic pain management and migraine headache prophylaxis.[110] Use of the three-monthly review system at SBAH is a great initiative that may assist in monitoring treatment outcomes in patients and potentially identifying ADEs. Reviews lead to medication reconciliation that enables to check patients' medical history and possibly identify duplications of antidepressants. Medication reconciliation can assist in identifying patients with asymptomatic amitriptyline toxicity amongst SBAH patients.[111]

Antiepileptic agents

Antiepileptic agents (n=seven, (10.29%) were among the most duplicated drugs at SBAH. Antiepileptic agents commonly prescribed to comorbid chronic disease patients at SBAH were lamotrigine, valproate and carbamazepine. Duplications involved these drugs amongst the observed clinics. Toxicity of antiepileptic drugs was a risk amongst the drug duplication affected patients especially if it results in prolonged supratherapeutic doses.[115] Patients at SBAH were mostly at risk when drug duplication involved prescription of carbamazepine in one clinic and valproate in another clinic. Affected SBAH patients were at risk of toxicity effects including acute hypertension, seizures and sinus tachycardia.[117] Monitoring of the use of valproate and carbamazepine is required at SBAH outpatient clinics.

Toxicity because of drug interactions is prevalent in previous studies especially amongst antiepileptic drugs. Valproate and lamotrigine are both metabolised through the glucuronidation pathway.[118] Duplication of these drugs as found at SBAH put the patients at risk of toxicity. The competition between valproate and lamotrigine during metabolism results in both the drugs being eliminated at a slower rate than would be observed in singular use of the two drugs.[118] Patients attending SBAH were at risk of having elevated serum levels of valproate and lamotrigine. The results show the need to address the concerns with the prescribing of antiepileptic agents at SBAH. There is a need to address life-threatening effects of drug duplication in order to ensure and maintain patient safety and good HRQOL during treatment.

Treatment failure was a risk of antiepileptic agent duplication at SBAH. Metabolism plays a key role in the clinical outcomes of antiepileptic agent interactions. Glucuronidation pathway is the metabolism pathway of some of the most commonly prescribed antiepileptic drugs at SBAH namely; valproate and lamotrigine.[114] The other two most prescribed antiepileptic agents at SBAH were carbamazepine and phenytoin, which are glucuronidation inducers.[117] These agents prescribed at the same time affects the elimination rate. Increased elimination rate leads to low serum levels that is in relation to treatment failure. Further studies are required at SBAH to ensure the drug interactions reported in literature do not affect the patients affected by antiepileptic agent duplication. The drug duplication risks faced by SBAH patients further highlights the results of drug inefficiency that can occur with drug-drug interactions.

As the patients affected by drug duplication had an average age of 57 years, drug interactions of antiepileptic agents could result in more detrimental clinical outcomes. The detrimental outcomes are higher due to the altered pharmacokinetic composition of the 20 (51.28%) elderly patients affected by drug duplication.[59] In the case of increased serum levels due to the metabolism competition between valproate and lamotrigine, the age of the comorbid chronic disease patients is a cause for concern. Combining factors of the outcomes of this study such as polypharmacy (45.45% prescriptions affected) and 20 (51.28%) elderly patients affected by drug duplication, raises concerns. High levels of polypharmacy, drug duplication and old age of patients increases the risk of toxic levels of antiepileptic drugs in the chronic disease outpatients.

Antihypertensive agents

Seven (10.29%) cases of antihypertensive agent drug duplications occurred during the study period. Among the most duplicated drugs were carvedilol, amlodipine and enalapril. Inappropriate prescribing was found in 34.10% of prescriptions in Bahrain, thus it was essential to evaluate potential duplication at SBAH.[121] Severe hypotension is a risk amongst comorbid patients especially those affected by polypharmacy as diuretics duplication potentially occurs. Carvedilol (n=28, (3.01%), amlodipine (n=34, (3.66%), enalapril (n=45, (4.84%), hydrochlorothiazide (n=36, (3.88%) were among the most prescribed drugs to comorbid chronic disease patients at SBAH. Drug duplication was likely to occur with the system used at SBAH, where prescribers at different clinics are not aware of drugs prescribed at the other clinics. Furthermore, there was no clinic dedicated to the treatment of hypertension making the prescribing of antihypertensive agents a possibility amongst all the clinics. The high levels of antihypertensive treatment at SBAH indicate a potential risk of overprescribing and severe hypotension.[119]

Antihypertensive agents prescribed to comorbid chronic disease patients at SBAH from the drug group combinations associated with increased risk of severe hypotension were enalapril (ACE inhibitor) and losartan (angiotensin II receptor blocker). Evaluation of angiotensin II receptor blockers was required when considering enalapril (n=45, (4.84%) was one of most commonly prescribed drugs during the study period. The results indicated minimal use of losartan with two (0.22%) prescribed. Elevated risk of hypotension through concurrent enalapril and losartan prescribing was minimal at SBAH.

Diuretics

Diuretics were involved in four (5.88%) cases of drug duplication during the study period. The most commonly prescribed diuretics were hydrochlorothiazide (n=36, (3.88%) and furosemide (n=14, (1.51%). These drugs are mostly prescribed to elderly patients along with antihypertensive agents for the hypertension and renal treatment.[122] The four cases of diuretics duplication at SBAH could result in supratherapeutic doses in the observed patients. Hypokalaemia and hyponatremia could present in affected patients at SBAH and have to be monitored.[122] The increased global accessibility of diuretics has resulted in increased evaluation of possible outcome of toxic use. Further studies can potentially

reflect the risks of extensive diuretics prescribing, as there is still limited literature on the topic.

Supratherapeutic doses of hydrochlorothiazide causes decreased insulin secretion that increases the risk of both diabetic and non-diabetic patients presenting with hyperglycaemia at SBAH. Twenty-six (12%) diabetes patients were included in phase two of this study. A considerable proportion of patients was at risk of increased diabetes effects due to prolonged hydrochlorothiazide duplication. Combination use of diuretics with antihypertensive agents could also result in severe hypotension. Overall, SBAH prescribers have to check for hyperglycaemia, severe hypotension, hyponatremia and hypokalaemia amongst the diuretic receiving chronic disease patients.[124] Clinical outcome monitoring of chronic disease patients would assist in the identification of the misuse or overprescribing of diuretics.

Sedative hypnotics

Sedative hypnotic use was minimal to outpatients at SBAH, (n=seven, (0.76%) out of the 929 drug items prescribed. The limited use of benzodiazepines contributes little to the drug duplication findings. Benzodiazepine duplication was not present in the observed patients during the study period. These results build on existing evidence of limited drug duplication of benzodiazepines in outpatient clinics when compared with inpatients.[125] Minimal use of sedative hypnotics at SBAH outpatient clinics ensures minimal to no risk of acquiring late on dementia due to prolonged use. There is a necessity to implement studies to evaluate the prescribing of sedative hypnotics amongst inpatients at SBAH instead of outpatients.

Antacids

Antacids were involved in four (5.88%) cases of drug duplication during the study period. The most prescribed antacids during the study period were lansoprazole (n=43, (4.63%), calcium carbonate (n=nine, (0.97%) and sucralfate (n=five, (0.54%). There was limited use of omeprazole (n=one, (0.11%), as lansoprazole was the PPI of choice amongst all prescribers. Limited variety in PPI prescribing at SBAH significantly reduced the risk of duplications and supratherapeutic doses of PPIs which cause onset of depression and dementia associated with prolonged use.[130] Efficient medication reconciliation process

was required to evaluate the extent of drug duplication of antacids. Since this study was to measure drug duplication through prescriptions, due to this there is lack of information on OTC drugs taken by outpatients. The lack of information on self-medication affects the results of antacid drug duplication by the patient, and only measures the drug duplication within the scope of the study. These findings highlight the requirement of an improved medication reconciliation system that would include OTC and herbal drug use in patients' medical history at SBAH in an effort to reduce drug interactions and drug duplication.[137] Prescribers could use data collected through medication reconciliation to reduce drug duplication of antacids.

Considerations at SBAH

In an effort to reduce drug duplication, SBAH pharmacy has implemented a system to monitor and cancel repeat orders for drugs. Each patient has a profile created that prints and stores information from every prescription. When a patient receives a repeat order of the same drugs, the pharmacist on duty can cancel the order. Nevertheless, if a patient is to collect medication from a pharmacy outside SBAH there is no means to prevent drug duplication. Furthermore, the scope of the SBAH pharmacy computer programme is limited to detecting repeat orders with exclusion of therapeutic drug duplication. The data collected showed numerous medications being provided at different clinics for the same indication such as paracetamol and tramadol.[75]

Another factor to consider in drug duplication prevention at SBAH pharmacy is the presence of two separate pharmacies within the hospital. Patients attending psychiatry and oncology outpatient clinics receive medication from a separate pharmacy from the other outpatient clinics. Patients attending multiple outpatient clinics that include the oncology clinic receive drugs from two separate pharmacies within the hospital. Drug duplication is a risk during attendance of different pharmacies as the system flags repeat orders only. Drug toxicity becomes a major concern that could be affecting the elderly patients attending the assorted pharmacies.

Costs of drug duplication

Each comorbid patient received an average amount of drugs worth R2 103.21 during the study period. Drug duplication has an effect on the cost of drugs to comorbid patients.

There were extra costs on duplicated drugs to the same patient. The drug duplication data contributes a clearer understanding of how medication errors can have an impact on the costs to the healthcare system. The incidence of medication errors at SBAH builds on existing evidence of unnecessary healthcare costs as a result of drug duplication, which occurred in 48.75% [95% CI = 37.80%; 59.70%] of comorbid patients.[108] Patients through the ADEs resulting from drug duplication can incur further costs during the course of treatment. An example of increased costs could be due to the prescribing cascade that can result from drug duplication.[61, 62] Prescribers respond through the addition of new drugs to treat the ADEs. Duplication of NSAIDs associated with gastric bleeding was in 2.94% of the duplication cases at SBAH.[63] The study provides an insight into the relationship between drug duplication, prescribing cascades, ADEs and polypharmacy. The combination of analysed factors in this study contributes to the increased cost burden of chronic disease treatment.

The patient and SBAH through the resultant hospitalisations from ADEs could incur further costs of drug duplication. Hospital admissions increase the costs to a patient in acquiring emergency transportation to the hospital and eventually receiving the required treatment. Hospitalisations contribute to the labour loss affecting local companies and the country's productivity. On a long-term basis, reduction of labour productivity has seen reduced income affecting chronic disease patients which could be occurring amongst SBAH outpatients.[14]

3.2.6. How SBAH can reduce irrational prescribing

The main findings by the authors were the incidence of polypharmacy, excessive costs encountered by the hospital and presence of drug duplication to multiple clinic-attendees. In providing recommendations, the problems encountered need to be clearly outlined. Findings from literature were analysed and summarised for presentation as recommendations to SBAH.

3.2.6.1. Polypharmacy reduction

i) Clinical pharmacological courses

Understanding of clinical pharmacological principles is essential in the provision of rational prescriptions. Knowledge of clinical pharmacology provides the adequate steps

to prescribers to prescribe and ensure patient safety. Graduate physicians provided with clinical pharmacological simulation sessions showed improved prescribing skills ensuring irrational prescribing was limited. Clinical pharmacological knowledge has been shown to ensure the reduction of irrational prescribing in multi-regimen comorbid patients.[49, 50] Clinical pharmacological programmes and simulation sessions used by Karpa *et al,* can be provided to physicians that treat comorbid patients.[50] The safety and efficacy of drugs can be improved by increased knowledge in clinical pharmacological practise in combination with, patient history and critical judgement.[49] Physicians at SBAH can be equipped to monitor rationality of prescribing encounters. The indicators described in Table 2 could be incorporated into the prescribing protocols at SBAH to eradicate irrational prescribing.[3]

ii) Prescribing cascade reduction

Determination of the type of polypharmacy is analysed by the introduction of tools including the Garfinkel Good Palliative-Geriatric Practice algorithm. Garfinkel *et al*, proposed the use of an algorithm that can reduce unnecessary drugs in elderly patients that cause preventable ADEs.[1] Implementation of the Garfinkel algorithm at SBAH can limit the number of drugs prescribed and possibly identify the drugs causing prescribing cascades. The prescribers at SBAH could take the steps to ensure the drug prescribed provides the best possible outcome if comorbidity is taken into consideration. The benefits have to always outweigh the harmful effects. In order to ascertain if change is required, analysing if any ADEs resulting from the drug prescribed cause the need for the prescription of another drug to treat these ADEs.[64] Possible elimination of prescribing cascades is through efficient analysis of ADEs. Reduction of prescribing cascades could possibly influence the prescriptions that contained up to nineteen drugs.

iii) De-prescribing

The role of de-prescribing has been highlighted in literature including reports by Reeve *et al*, and could be crucial in the reduction of polypharmacy related to drug duplication at SBAH.[157, 158] Drug prescribers have been given the task of analysing the prescriptions taken by their patients and working out best possible path to ensure withdrawal of inappropriate drugs is undertaken.[156, 158] Presence of an efficient diagnosis system for drug duplication outcomes would prompt physicians to reduce the ADEs associated with

the unnecessary drugs. Physicians would then be required to withdraw drugs prescribed as duplicates. Caution is key during the tapering off process as some patients may present withdrawal effects caused by prolonged use of duplicate drugs. Presentation of protocols from de-prescribing studies to SBAH prescribers can influence the future outcome of de-prescribing. However considering the lack of data available on de-prescribing and the long term consequences of de-prescribing protocols, studies can also be done at SBAH to contribute into the new field created to improve patient treatment outcomes in the elderly.[157]

iv) Advanced HIS implementation

Installation of an advanced electronic HIS can aid in improving drug prescribing in tertiary hospitals. Use of electronic prescribing tools as shown in previous studies is a requirement to improve tertiary hospitals in developing countries such as SBAH. One of the tools that may aid in polypharmacy reduction is the PRIMA-eDS tool.[153] PRIMA-eDS tool can assist physicians in recommending the best possible treatment regimens for comorbid patients. The tool would readily provide latest information from global studies to provide new protocols for treating patients attending multiple clinics. There is potential for new protocol proposals by PRIMA-eDS, as it has access to different databases. Databases used in rational prescribing protocols include the European list of inappropriate drugs to older people.[153] Another useful feature of PRIMA-eDS is the tool's access of the RENBASE data system that assists in renal dosing for polypharmacy patients.[153] The programme provides the platform to monitor the different responses to medication regimens experienced by elderly patients.

v) Non-compliance reduction

For this study compliance was defined as*, "the extent to which medication intake behaviour corresponds with the recommendations of the healthcare provider."*[67] Prescriber recommendations are paramount in the effort to ensure treatment success. Treatment success essentially ensures the maintenance of the number of drugs prescribed to chronic disease patients, without a need for increment. Increase of prescription drugs is often because of treatment failure. At SBAH, treatment failure amongst comorbid patients is potentially because of non-compliance due to polypharmacy. Polypharmacy causes unintentional non-compliance due to patients

having complex multiple regimens that may not be administered at the times recommended by the prescriber.[68] Automated electronic mobile reminders assist in compliance especially to chronic disease patients as they use drugs for long durations. Automated electronic mobile reminders have been used globally to ensure patients do not forget or skip treatment doses at the recommended time.[69] Short message service (SMS) use is a step in compliance maintenance, as large numbers of the population have caregivers with mobile phones or access to mobile phones. Use of this programme at SBAH post-HIS installation would ensure patients use drugs effectively, which increases the chances of treatment success. Achievement of the reduction of the need for new or additional drugs is through treatment success that essentially reduces the risk of ADEs. Elimination of non-compliance is vital in the ensuring of treatment success at SBAH and limiting the need for patients to receive more drugs and eventual overprescribing.

vi) Fixed-dose combination drugs

The drug procurement system of SBAH could have an impact on the number of drugs prescribed. An effort to consider comorbid patients in drug procurement, could be enabled by the purchase of fixed-dose combination drugs for comorbidity treatment.[68] In most cases, there are limited options in drug substitutes as there are limited fixed-dose combinations developed for comorbidities.[68] The collaboration of SBAH with pharmaceutical companies that cater for comorbid patients through the provision of fixed-dose combination drugs could possibly reduce polypharmacy. Fixed-dose combination drugs could be beneficial in producing positive treatment outcomes for patients. Treatment compliance has been associated with fixed-dose combination drugs as less ADEs, which cause non-compliance, affect patients.[69] Confusion on which drugs to take is also eliminated by fixed-dose combination drugs, making this a solution to more than one issue associated with polypharmacy.[69, 70] Compliance effectively limits treatment failure which often results in more drug prescriptions to produce the required treatment outcomes by the prescriber.

3.2.6.2. Drug duplication reduction

i) Clinical pharmacological syllabus

Tertiary hospitals including SBAH provide training to medical students during the clinical rotations stage.[2] The syllabus provided to medical students determines the level of

knowledge graduates possess upon completion of studies. Relevant to drug duplications and irrational prescribing is the basic knowledge graduates possess in diagnosis and prescribing. Graduates require adequate knowledge of the clinical presentations that chronic disease patients present with during diagnosis. Drug duplication contributes to misdiagnosis of ADEs that appear as new medical conditions. Misdiagnosis of ADEs often leads to prescribing cascades and polypharmacy. Graduates have to be aware of possible clinical outcomes that present due to toxicity of different drugs commonly prescribed to chronic disease patients. Drug duplication toxicity presents in the form of ADEs, commonly misinterpreted by physicians during consultations. Capability to diagnose patients by physicians determines the prescription provided as a new course of action. The course of treatment taken can lead to increased number of drugs prescribed which increases the risk of drug duplication.

Karpa *et al*, proposed the introduction of courses that educate medical students on the clinical pharmacological principles.[50] Clinical pharmacological principles provide students with the knowledge of pharmacodynamics and pharmacokinetic properties of different drug groups in different patient groups. The introduction of extensive clinical pharmacological courses to University of Pretoria medical students and improve the diagnosis of irrational prescribing outcomes. The ability of graduates to identify ADEs due to medication errors such as drug duplication can increase the level of awareness of their possibilities amongst chronic disease patients at SBAH. Simulation sessions where patients affected by drug duplication toxicity due to a particular drug class can educate medical students at the University of Pretoria. Improvement of the clinical pharmacology courses at University of Pretoria improves the quality standards of medical graduates that tend to comorbid chronic disease outpatients. Clinical pharmacological knowledge is key in the process of identifying drug duplication presence through clinical presentation of patients.

ii) Clinic specific prescribing restrictions

Drugs for certain chronic diseases were prescribed at clinics that were not set up to prescribe those particular drugs. Physicians stated helping patients to avoid visiting the hospital numerous times by prescribing all drugs required by a patient. Random prescribing caused physicians to prescribe drugs for conditions they are not qualified to

be specialists. Patients did not report random prescribing when they returned to other clinics. The problem with random prescribing was the provision of relatively similar prescriptions at two different clinics at the same time. Prescriber drug preference had the potential to cause repeat prescriptions with different drug choices from the same drug class provided. The SBAH pharmacy system did not flag different drug names from similar drug classes, resulting in drug duplication. One downside of clinic specific prescription is that it contributes to multiple visits to SBAH in order to attend different clinics. Another consideration is that clinics are not necessarily on the same day, requiring multiple visits. It is shown that SBAH already has more clinic visits especially for multiple clinic-attendees in comparison with international norms. It can be argued that a “one-stop service” where a single practitioner prescribed all the chronic medication required by a patient that would prevent drug duplication. Check-ups at specialist levels to de-prescribed or taper unnecessary medication would further prevent drug duplication.

There is a need to avoid drug duplication through random prescribing at SBAH. Medical oncology clinic staff have taken steps to ensure there is no random prescribing from their physicians. Prescriptions written by medical oncology staff were specific to the medical conditions related to cancer treatment only. Restrictions of prescribing drugs specific to an outpatient clinic specialty are required at SBAH to reduce drug duplication. Implementation of the system used at the medical oncology clinic would limit drug duplication of a majority of drugs.

For some drug classes prescribed in numerous clinics, the restriction system has constraints. All chronic disease outpatient clinics have a role in prescribing drugs for pain management, stress and insomnia. Antidepressants are a drug class raising concerns as physicians are increasingly prescribing them without particularly transferring a patient to psychiatry.[94] Insomnia treatment amongst elderly and comorbid patients has been responsible for considerable amounts of overprescribing, as they are not specialty specific.[127, 134] Contrary to findings from other countries, insomnia treatment to outpatients at SBAH was minimal with no drug duplicates recorded. There is a need for consideration of results from this study on the prescription of drugs for pain and stress management. Pain and stress management drugs were among the most prescribed drugs contributing significantly to the most duplicated drugs.

Drugs not specific to any particular clinic specialty are among the most duplicated drugs to multiple clinic attending chronic disease patents at SBAH. Analgesics 18 (26.47%) were the most duplicated followed by antidepressants (n=14, (20.59%). The study demonstrates a correlation between drug duplication and drugs that are not restricted to a specialty provided at SBAH. Further studies are required to produce a system that can reduce drug duplication of drugs that are not specific to a specialty provided by the SBAH outpatient clinics.

iii) Medication reconciliation

The research problem for this study was on the attendance of multiple clinics by chronic disease patients resulting in multiple prescribers. Lack of awareness of the prescription content by the previous prescriber at a different clinic is what the main problem was leading to drug duplication at SBAH. The problem arises because of the poor medication reconciliation procedures at SBAH. Poor medication reconciliation at public hospitals is associated to numerous medication errors including drug duplication.[136] One of the limitations of this study was the misplaced prescriptions in the medical files at SBAH medical records archives. Misplaced prescriptions led to the exclusion of twenty-six multiple clinic attending patients from the study that potentially affected by drug duplication (Table 5). The misplaced prescriptions indicate the standard of medication reconciliation at SBAH. Implementation of courses on medication reconciliation and the importance of medical records is required among the hospital staff in order to improve the completeness of medical records. Well-educated hospital staff on medication reconciliation have been seen to produce complete and efficient medical records.[140]

In order to reduce drug duplication, training of SBAH staff on the implementation of an efficient medication reconciliation protocol is a necessity. Well-trained staff and registry departments have been reported to increase the efficiency of the medication reconciliation process, and eventually patient safety.[139] Recording all drugs taken by a patient during the treatment period and before referral to SBAH is vital. The list of drugs taken by the patient have to be updated and entered into the patient's medical history file.[136] The patient in patient files can carry the list of drugs during the transition phase of movement from one clinic to the other.

Self-medication drugs also need to have a section where they are entered, as some of the most commonly prescribed drugs are all accessible through the OTC pathway.[137] The most commonly prescribed drugs that are available OTC include analgesics and antacids, which were among the drug duplicates (Table 9). It is detrimental that prescribers get an update from the patient of any unscheduled drugs that are taken with every consultation.[137] This procedure will enable the hospital staff to update the patient's medical record. Prescribers to cross-reference drugs taken by a patient in different settings, thereby avoiding drug duplication, can use the updated medical records. Upon identification of drug duplication, notification of the patient is important so that they are aware of the possible risks of drug duplication that can result thereof. Aware patients of drug duplication can practise caution when purchasing OTC drugs and using herbal medicines. The goal is to maintain patient safety and produce desirable outcomes from prescribed drugs.

Some of the analysed clinics had separate files from the files available at the SBAH medical records archives. Prescribers from other clinics could not gain access to a set of separate patients files used at medical oncology and psychiatry clinics. The problem with this system was that the prescribers at other clinics were not aware of the drugs prescribed in those two clinics (medical oncology and psychiatry). To ensure transparency between all the clinics, a consistent filing system is required throughout all the clinics. In the case of visits to another clinic, there is a need for the provision of prescribers with a list of drugs that a patient is currently taking before the prescription of new drugs. Upon completion of the consultation, there is to be the addition of a new list to the patient's file clearly stating any newly prescribed drugs.

iv) Advanced HIS implementation

Upgrading the HIS at SBAH can further the improvement of the medication reconciliation process. During the study period, the advanced HIS at SBAH was present at the SBAH pharmacy. The SBAH pharmacy could flag any repeat orders during the dispensing phase of drugs. The system at the SBAH pharmacy was however, not available during the prescribing phase. Prescribers were not aware of any repeat orders that may have occurred. Drug duplication also includes prescription of different drug items from the same drug class that has to be flagged at the discretion of the prescriber. The system at

SBAH pharmacy could not detect different drug items from the same drug class as it is programmed to flag repeat orders. The extra workload to identify drug duplication was given to pharmacists despite the long queues they provided service to during drug dispensing.

There was a clear need for an advanced HIS at SBAH which would be primarily used by drug prescribers at the different clinics. Physicians to update the medical records of patients can use advanced computerised systems. Computerised systems would allow prescribers to access online patient files used at other clinics and crosscheck the drugs administered to the patient. The installation of HIS could promote the reduction of drug duplication between different clinics. In other developing countries, there are challenges in the installation of such a system. Challenges include qualified implementation and maintenance staff, user-friendliness to physicians and the confidentiality of the systems.[144] The biggest challenge to developing countries has been the financial costs required to install and operate such a system effectively over a long period.[144] Implementation of HIS has to be specific to a particular hospital with factors taken into consideration including continuous electrical supply, ethical clearance for IT staff, backup and support systems.[151]

The government officials that initiated the e-Health strategy in the NHI policy noted the requirement of a specific system to South African hospitals.[42] For the implementation of electronic systems at local hospitals, collaborations with information technology (IT) specialists was required. A collaboration between NDoH, the Council for Scientific and Industrial Research (CSIR) and the South African Medical Research Council (SAMRC) was formed in 2014.[145] The NDoH hopes to pioneer the HPRN at tertiary hospitals to assist physicians and nurses in medication reconciliation.[146, 147] Tertiary hospitals such as SBAH involvement in the HPRN system could benefit in the reduction of drug duplication upon completion and implementation. The importance of the system is the linkage of information systems across all facilities and clinics within the nation. Implementation of HPRN would be ideal for the safety of multiple clinic attending chronic disease patients at SBAH.

v) Pharmacist interventions

Pharmacists have a role in maintaining patient safety. Pharmacists and prescribers collaboration is required at SBAH to eradicate drug duplication. Pharmacists at SBAH can assist in the cross checking of drug duplication beyond the current system that flags order repeats at SBAH. Alerting pharmacists on the existence of drug duplication to multiple clinic-attending patients at SBAH is a step in educating pharmacists about the present risks. Flagging of multiple clinic-attending patients on the pharmacy dispensing computer system to alert pharmacists of extra care in dispensing drugs to these patients is a potential solution. Another method that can be used to alert pharmacists of the extra care required for each multiple clinic-attending patients is, the use of different patient stickers used to collect drugs. To initiate such a programmes all patients attending more than a singular clinic, listing of these patients on a list provided to the prescribers, nurses, registry department and pharmacist is required. Crosschecking of medical records by pharmacists would enable the possibility to identify drug duplication. Hauser *et al,* reported that significant medication reduction has resulted from pharmacists cross-checking prescriptions prior to dispensing drugs.[162]

vi) Medical safety officer

Use of medical safety officers has been introduced in the developed countries to assist in ensuring patient safety and effective drug use in both public and private hospitals.[159] Introduction of a medical safety department with extensive clinical pharmacological knowledge could potentially improve the management of treatment regimens and outcomes at SBAH. The MSO could be responsible for monitoring drug regimens to elderly and comorbid chronic disease patients referred to SBAH. The MSO can be responsible for listing and attending to all the patients at risk of drug duplication with the most vulnerable group to drug duplication being the multiple clinic-attendees. Multiple clinic-attendees are among the transitional phases of treatment as there is constant transition from one clinic to another during the same period.[161] Medication errors including drug duplication commonly occur during transitional phases of treatment.[161] The MSO can also use their clinical pharmacological skills to monitor prescriptions for possible drug interactions and ADEs. Monitoring of prescription patterns in the future can assist in the eradication of prescribing cascades. MSO can collaborate with the prescribers at SBAH to perform a de-prescribing protocol upon confirmation of unnecessary drug prescribing.

According to WHO research, introduction of a MSO potentially reduces medication errors that could include the extent of polypharmacy.

vii) Visits without prescriptions

Beyond collaboration with the prescriber, the MSO can be involved in the face-to-face contact with multiple clinic attending comorbid patients. The MSO has been used in developed countries to monitor the mental status of chronic disease patients, as a majority are susceptible to mental health disorders during treatment.[163, 164] Eighty-one (25.23%) visits by multiple clinic attending comorbid patients resulted in no new prescriptions. Patients got the opportunity to have their health status monitored and repeat prescriptions confirmed to be effective. The consultations with no prescriptions confirm the use of global standards at SBAH by physicians to monitor treatment progress.[164] Incorporation of the MSO into the consultation protocols at SBAH non-prescribing encounters is a possibility in increasing face-to-face sessions with outpatients. Referral to the MSO department of multiple clinic-attendees with no prescriptions to undertake medication reconciliation procedures and face-to-face sessions is a possible approach. The sessions can be used to evaluate patient records are up-to-date through the review of previous prescriptions and drug currently administered by the patient.[163] Identification and limitation of drug duplication is possible during the sessions with the patient. Patients gain the opportunity to inform the MSO staff on the herbal medicines and OTC drugs administered concurrently with prescription drugs from SBAH. The MSO staff that contributes to the treatment outcomes can also evaluate the status of compliance to treatment regimens. Treatment failure often results in increased number of drugs prescribed, increasing the chances of drug duplication.[109] Ensuring and emphasising the effects of compliance to patients is essential in the reduction of drug duplication. Additionally, MSO clinical pharmacological expertise is useful in the evaluation of any ADEs associated with drug duplication in patients. The outcome of the evaluations can possibly notify prescribers of potential dangers in the future. Drug duplication causes toxic effects during drug use making clinical pharmacological knowledge is a necessity in evaluating presence in a patient and ensuring safety. Public hospitals have a role in the community to provide readily available quality care to referred chronic disease patients. The American Institute of Medicine stated that patients should receive care at all times required even beyond face-to-face

visits with physicians but care should be provided in any other means to ensure patient safety.[142] Consultations with the MSO enable the fulfilment of the role of the hospital to provide constant and quality care to patients at all times.

viii) Hospital admission studies

Preventable hospital admissions occur because of medication errors. Appropriate drug prescribing can prevent up to 50% of adverse drug reaction-related hospital admissions.[45] Of additional relevance to SBAH, studies have also shown that 10% of prescriptions in complex regimens contain an error amongst graduate physicians.[49] The University of Pretoria collaborates with SBAH. Medical students from the University of Pretoria receive their practical training from various departments and clinics at SBAH during their clinical rotations.[2] Presence of medical students potentially increases the risk of medication errors depending on their level of understanding of clinical pharmacology. Measures to mitigate prescription errors amongst students are essential. At SBAH, the students assess patients and write prescriptions under the supervision of qualified practitioners. Student supervision mitigates against prescription errors. Drug duplication incidence amongst multiple clinic attending chronic disease patients at SBAH shows the risk of hospital admissions related to this medication error. The lack of a hospital system that alerted new prescribers of previous prescriptions at other clinics and presence of polypharmacy created a risk for toxic effects at SBAH outpatient clinics.

Future studies into hospitalisations of multiple clinic attending comorbid chronic disease patients are required. In total, 39 patients (48.75%) were affected by drug duplication [95% CI = 37.80%: 59.70%] among the six clinics observed in this study. These results are significant when considering the hospitalisation of the patients attending the chronic disease outpatients. Hospitalisations could occur because of toxicity or treatment failure from drug interactions onset by drug duplication. Further studies are required at SBAH to monitor the effects of drug duplication that could be resulting in hospitalisations. Inspection of the causes of hospitalisations is potentially a factor to determine if the event is because of drug duplication effects that are potentially fatal. Regular inspections are required at SBAH inpatient wards to ensure hospitalisations are not medication error-related. Hospitalisation of multiple chronic disease clinic-attendees is of interest and requires extensive investigation into the patients' prescribed drug regimens.

ix) In-house referral to other specialist clinics

Reduction of irrational prescribing at SBAH requires the promotion and introduction of an advanced referral system within the hospital. One of the causes for drug duplication was found to be clinics providing treatment for conditions they do not specialise in. A referral system is required to ensure prescribers always have the appointed specialists by the hospital treating patients requiring services they specialise in providing. Often when prescribers provide treatment for comorbid patients they risk creating prescribing cascades that may not result if a specialist prescriber was having consultations with the particular patient and identifying clinical outcomes that may require special treatment.

3.2.6.3. Resource investment

The reduction of irrational prescribing of both polypharmacy and drug duplication requires financial investments. Financial investments are required in different aspects of providing healthcare to comorbid chronic disease outpatients at SBAH.

i) Advanced HIS installation

The poor quality of the HIS used at SBAH is responsible for a majority of drug duplication cases. The HIS used at SBAH was limited to information on the consultations of a patient and the follow-ups arranged. There is a need to invest into the installation of high quality HIS that will record patient medical records including all prescription information. HIS will improve the communication system between physicians in different clinics to avoid medication errors. The installation of HIS requires financial investment by the hospital to acquire modern computer systems that will allow the hospital to operate more efficiently. Further investments are required to set up an IT department with expertise for the installation and maintenance of an advanced HIS. Use of paperless services is the goal in upgrading of current HIS through to the eventual installation of THIS, currently used in developed countries. THIS has been introduced globally to provide paperless technological systems that contain patient information and history.[144]

ii) Automated electronic messages

Irrational prescribing can result from preventable treatment failure. An example of preventable treatment failure is the unintentional non-compliance to complex treatment regimens. Non-compliance occurs because of patients forgetting to administer drugs as

recommended by prescribers.[71] Investment by SBAH management into a system that would assist patients in taking drugs as and when recommended by the prescribers is required. Globally, the use of automated electronic systems has been used to encourage compliance.[69] Comorbid chronic disease patients at SBAH can receive reminders to take drugs for core conditions such as diabetes and hypertension through an automated SMS service. Financial resources are essential with the prospect of long-term benefits in treatment outcomes.

iii) SBAH medical archives

The medical archives require an upgrade into a more organised and modern standard. The staff members at the SBAH archives storage department misplaced one of the appointment logbooks used at the MOPD clinic. The misplaced appointment logbook contained all the information regarding the patients that visited the clinic during the study period. Misplacement of the appointment logbook complicated process of data collection. The appointment logbook was required to record and identify the patients attending the MOPD clinic during the study period. The reason given for the misplacement of the appointment logbook was poor organisation, limited staff members and lack of storage space. These findings highlighted the need for SBAH to invest into equipment required to upgrade the medical archives department.

A similar problem with shelves and space shortage occurred at the SBAH medical records department. The shelves were not sufficient for the increasing number of patient files stored at SBAH medical records. The poor quality of standards at SBAH medical records and medical archives affects the medication reconciliation process. Twenty-six (24.53%) multiple clinic attending chronic disease patients were excluded from the study due to misplaced prescriptions. The quality of standards of the SBAH medical archives and records contributes to the misplacement of patient records. Physicians have limited patient history records that results in irrational prescribing. Management have a role in setting up funds to upgrade the storage and archiving department at SBAH.

iv) MSO department

The role of the inclusion of staff members with clinical pharmacological knowledge has been highlighted in the reduction of irrational prescribing.[161] MSO staff provide extensive

clinical pharmacological knowledge, and have been implemented in numerous hospitals in developed countries.[159] Implementation of a MSO department to oversee patient safety at SBAH outpatient clinics is a step required to reduce irrational prescribing. Introduction of a new job objective to perform safety monitoring at tertiary institutes requires investment to set up. The number of staff members required to oversee the monitoring of all outpatients chronic disease clinics has to be determined. The number of patients attending the six clinics observed (9,177 patients) could be a guideline on the number of patients requiring special attention. Determination of the compensation packages for the each member of the team follows the determination of the number of required staff members. Availability of funds through government and eventually SBAH management is key to the introduction of a new framework in drug safety management. Funds would also be required to train and initiate the MSO department as recommended by WHO.[161] The MSO could further facilitate inter-department communication regarding the various treatment plans for the comorbid patient.

v) Research on comorbid/elderly patients

Introduction of clinical pharmacological simulation sessions of elderly and comorbid chronic disease patients has been proposed globally.[50] Simulation sessions include cases of commonly observed outcomes in comorbid patient treatment. Graduate physicians access to prescriptions to comorbid patients is essential. The prescriptions are analysed for any potentially inappropriate outcomes. Prescription observations are for possible drug interactions and medication errors. Simulation sessions train and constantly update physicians on global study outcomes. Studies included are on potentially irrational prescribing outcomes in hospitals globally.[155]

Initiation of workshops and courses is essential to inform physicians on the changes occurring on a three-year basis based on the frequency of updates to the AGS Beers criteria.[154] Funds are required to plan and carry out the simulation workshops at SBAH. Use of sponsors and collaboration with the University of Pretoria clinical pharmacological research departments is an important proposition. Seminars at University of Pretoria can ensure quality-prescribing criteria to elderly and comorbid patients. Forecast on chronic diseases by WHO showed an increase in chronic diseases and comorbidity until 2030, and potentially beyond that year.[173] Chronic disease related deaths have also been

projected to increase with the increase in life expectancy.[174] The forecast by WHO indicates the need for increased and more efficient treatment protocols to elderly and comorbid patients. Further investments into collaborations with the University of Pretoria are required to understand the population dynamics of patients attending SBAH.

One of the limitations of the AGS 2019 Beers criteria tool is the provision of recommendations that cater majority of patients globally however, individualisation is still required.[154] Beyond studying the outcomes of comorbid patients at SBAH, there is a need for a collaboration with the clinical research units in the Tshwane region. The University of Pretoria staff and SBAH physicians can undertake the introduction of studies directed at elderly patients. The focus of these studies is the observation of clinical outcomes of some preferred treatment regimens at SBAH. Knowledge on the pharmacokinetic properties of patients at different stages of illness and treatment could improve treatment protocols. The use of SBAH outpatients, SBAH physicians and University of Pretoria staff provides information specific to the population commonly treated at SBAH. Studies undertaken can contribute a clearer understanding of treatment regimens required by the African and developing countries globally. Consideration of risk factors and the type of disease burden are important when evaluating the treatment regimens required by a majority of developing countries chronic disease patients. Chronic disease risk factors specific to South Africa include, high levels of tobacco use, obesity, high salt intake and the HIV/AIDS pandemic.[11] The contribution of the HIV/AIDS pandemic to chronic disease increase has to be considered in the treatment of outpatients in South Africa.[9] The contribution of HIV is indicated by the statistic that as of 2019, 7.97 million (13.50%) people are estimated to be living with HIV in South Africa.[10] Collaboration with clinical research units requires extensive financial and time resources. The goal of SBAH participating in clinical research work on elderly and comorbid outpatients is to give physicians a better understanding of the Tshwane district population. Understanding of the population is useful in the improvement of the prescribing of drugs to chronic disease outpatients at SBAH.

vi) Pharmaceutical companies (Fixed-dose drug combination)

The results and literature review from this study have indicated the relation between treatment outcomes and increased irrational prescribing. Treatment failure is associated

with increase in drugs prescribing. Treatment failure can be in the form of drug ineffectiveness, severe ADEs, drug interactions and non-compliance.[67] Polypharmacy can result in severe ADEs due to increased chances of drug interactions.[48] The reduction of polypharmacy can be achieved using fixed-dose combination drugs.[68] Eradication of polypharmacy potentially decreases the chances of drug duplication in patients. Treatment failure can also occur due to intentional non-compliance by patients.[68] Self-withdrawal of drugs by chronic disease patients occurs in some cases because of fear and the desire to reduce the ADEs experienced. Unintentional non-compliance also occurs, with the cause being confusion on when and how to administer multiple drugs. Confusion is potentially brought on by the multiple drug regimens a patient has to comply to during treatment.[69] There is a need to provide services at SBAH that will minimise the chances of treatment failure occurring from severe ADEs, drug interactions and non-compliance.

Reduction of irrational prescribing and the effects associated with overprescribing can be achieved through collaborative work with pharmaceutical companies. The research done by SBAH and University of Pretoria in comorbid chronic disease patients can provide an insight on fixed-drug combinations. Despite the use of the tender system to acquire drugs in the public sector, collaborative work to provide pharmaceutical companies with research data on treatment outcomes can be initiated. Indication of the growing demand for chronic disease fixed-combination drugs is vital in influencing the involvement of pharmaceutical companies.[68] Findings by WHO, that population and life expectancy are expected to rise over the coming years can be used to highlight the demand for interventions to pharmaceutical companies.[173] Increase in population and life expectancy, are linked to the projected rise of chronic disease deaths by 48% between 2005 and 2030.[173, 174] The inevitable demand for fixed-dose combination drugs in comorbid chronic disease treatment could benefit SBAH. Pharmaceutical companies would get assurances from SBAH to provide sufficient research on elderly patient treatment. The aim would be to get fixed-dose drug combinations supply at SBAH. Fixed-dose drug combinations have been shown to potentially reduce irrational prescribing, treatment failure and ADEs in complex chronic disease regimens.[68]

vii) WHO global action plan

Poverty in Sub-Saharan Africa are a factor in chronic disease treatment and a social determinant of care. South Africa is rated as a middle-income country where 52% of households living under the poverty line.[196] The high percentage of poverty-stricken households places a burden on the public health system. A majority of the population uses the public health system, with numerous patients treated at public hospitals such as SBAH.[196] Poverty-stricken communities have limited education on chronic disease risk factors. Lack of knowledge of chronic disease risk factors complicates treatment and increases chronic disease incidence.[105] Further treatment complications occur with the rising levels of the HIV/AIDS pandemic and chronic diseases.[9] The rise in chronic diseases results in numerous patients suffering from comorbidity. Comorbid patients require numerous medications at the same time, increasing the risk of irrational prescribing.

There is a role for SBAH in the education of patients and the surrounding communities about chronic disease risk factors. Knowledge on risk factors can limit the rise of chronic diseases and healthcare expenditure.[16] One of the roles of tertiary hospitals outlined in the WHO global plan is the reduction of chronic diseases in communities that is the Tshwane district for SBAH. Education of patients and the community on chronic comorbidity prevention can reduce disease burden in Tshwane. Treatment of comorbidity is much more costly in comparison with implementation of preventative measures in the community.[16] Another step for SBAH is the investment in programmes to educate the local populations on lifestyle choices such as physical inactivity, excess sodium intake, drug and alcohol abuse and smoking. Physical inactivity in South Africa contributes to the incidence of obese women estimated between 48.90% and 58.50% of the population.[12] Obesity is a risk factor in the cause of non-communicable diseases such as hypertension and diabetes mellitus. Programmes to educate patients are required at SBAH on sodium intake reduction. The aim is to reduce the daily intake of sodium amongst South African communities. Sodium intake is higher than the recommended daily intake contributing to the incidence of hypertension and cardiovascular disease.[11] A number of patients receiving cardiovascular agents are due to the effects of obesity and high salty foods intake in the population. Simvastatin (n=48, (5.17%), enalapril (n=45, (4.84%), and

hydrochlorothiazide (n=36, (3.88%) were among the most prescribed drugs to comorbid chronic disease patients at SBAH.

Overall, reduction of comorbidity occurrence is the ultimate goal in the reduction of irrational prescribing to comorbid chronic disease patients.[75, 76, 78] Further studies into the reduction of the incidence of chronic disease comorbidity are required at SBAH. Communication of risk factors of chronic diseases is vital for preventative action in patients. Education of South African communities on chronic disease risk factors caused a decrease in the tobacco smoking population from 32.00% in 1993 to 16.40% in 2012.[13] The management at SBAH could increase investment on posters informing patients of dangers associated with the different risk factors. Further action through participation in drives to educate the community pre-hospital visits or symptomatic stages of illness could limit chronic disease burden. Annual programmes could include primary and high school visits by medical students from the University of Pretoria associated with SBAH. Compliance with the WHO global action plan is a step required at SBAH to reduce chronic disease. Vigilant monitoring of disease and prescribing trends could be utilised to improve specialised care to the community served by SBAH. Population demographics provided by Stats SA and risk factors are essential in chronic disease treatment at SBAH. Focus on the Gauteng population characteristics is a guide in specialised treatment. Characteristics of the community served by SBAH can be determined through evaluation of the risk factors often associated with the South African population. Preventative measures could be engaged to limit the rise in chronic diseases. Action plans are required to limit the rise in obesity, harmful use of alcohol and physical inactivity to reduce disease burden in Gauteng.[24]

Chapter 4: Conclusions and considerations

4.1. Conclusions

The outcome of this study builds on findings from similar studies at different institutions. Multiple clinic visits are more prevalent in the medical disciplines, often prescribing drugs from the same class. Clinical complications from these frequent and separate encounters may result in irrational prescribing, ADEs, drug interactions and problematic polypharmacy. The clinical complications are costly to patients and the public health sector. Inspection of prescribing patterns to comorbid chronic disease patients is of the utmost importance. Constant change in disease trends and development of new interventions prompts the need to provide new techniques and solutions to improve patient care and safety. The aim of this study was to determine the prescribing pattern of drugs to chronic disease outpatients, and find possible solutions to provide a system that would reduce overprescribing of chronic medication at SBAH in one measure namely drug duplication.

To achieve the aims of this study, a set of defined objectives were followed, the first being determining how many different departments a single patient visited during the study period. Patients included had to be attending more than a singular clinic among the six chosen chronic disease outpatient clinics at SBAH between February 1, 2018 and May 31, 2018. The six chosen clinics for the study were diabetes, haematology, medical oncology, MOPD, neurology and psychiatry. Based on the study period and clinics chosen, successful registration of participants occurred for the study. The sum of outpatients recorded in phase one was 9,177 outpatients. This was particularly important to confirm that a patient registered was suffering from comorbidity resulting in assorted clinic visits and was essentially at risk of drug duplication between different drug prescribers.

Following patient registration, the number of patients attending more than a singular clinic were counted. The results obtained from the list of patients appearing in more than a singular clinic showed that one hundred and six outpatients were suffering from chronic disease comorbidity. Of the 106 patients, 103 (97.17%) patients attended two clinics and three (2.83%) patients attended three clinics during the study period. This data indicated that the majority of multiple clinic attending comorbid patients at SBAH had two drug

prescribers (97.17%), while the minority had three drug prescribers (2.83%). Determination of how many different clinics were visited by a single patient during the study period was achieved. The overall number of visits by the 106 patients to the chronic disease outpatient clinic during the study period was three hundred and twenty-one visits. This was used to calculate the average number of visits per patient to the hospital during the study period, indicating potentially how often the outpatients received prescriptions. Average number of visits to SBAH for the comorbid chronic disease outpatients observed was 3.03 visits during the four-month study period.

Guidelines by WHO indicate the requirement to measure the average number of visits to the hospital that result in no drugs prescribed. This indicator was used to evaluate if patients are constantly monitored and follow-ups done by prescribers to ensure efficiency of treatment. Out of 321 hospital visits, there were 240 (74.77%) prescribing encounters to comorbid chronic disease patients. Eighty-one (25.23%) visits resulted in encounters without any drugs prescribed. This confirmed that outpatients at SBAH were receiving counselling sessions and treatment outcomes constantly monitored.

Second phase of the study involved the evaluation of prescriptions of the recorded patients attending more than a singular clinic. Some prescriptions were missing from the patient files at SBAH patient records department. Missing data was expected, as literature states that often in retrospective studies in public hospitals, data could be missing affecting the study outcomes. Record keeping was substandard at SBAH. Furthermore, there was exclusion of patient files that contained prescriptions from one clinic, with the second clinic prescriptions missing. Among the total prescribing encounters, there was exclusion of 53 (22.08%) prescriptions from the study. The 53 excluded prescriptions accounted for 26 patients. For polypharmacy, drug duplication and cost evaluation, 80 (75.47%) patients met inclusion criteria out of 106. The 80 patients analysed received 187 prescriptions during the study period. Consequently, it is imperative to consider the use of a prospective study in the future to ensure capturing of all data as the method used presented limitations that caused the exclusion of some patients.

The next objective was to determine the extent of polypharmacy at the SBAH outpatient clinics. The global standard for drugs prescribed per encounter provided by the WHO was

1.80- 2.20 drugs. Recent studies have shown a higher upper limit in the range for prescribing encounters in developing countries. The range for developing countries was reported to be 1.30- 3.00 drugs per encounter. The average number of drugs per encounter to SBAH comorbid patients of 4.97 was higher than that of both the WHO standards and developing countries range. The first method confirmed there was a substantial incidence of polypharmacy to comorbid chronic disease patients at SBAH. These findings were expected as a high number of drugs are often prescribed to comorbid chronic disease patients. The average number of drugs prescribed per encounter at SBAH is higher than the average number observed in numerous African countries (3.10). A higher value than that of the WHO might be a reflection of the study population, which consisted of only chronic comorbid patients who often require assorted drugs concomitantly. Comorbid patients taking assorted drugs are susceptible to prescribing cascades that could be resulting in patients having drugs prescribed to treat side effects of previously prescribed drugs.

The second method focused on polypharmacy incidence through the number of prescribing encounters resulting in five or more drugs during the study period. The results showed that 45.45% of the prescriptions to chronic disease outpatients contained five or more drugs per prescribing encounter. This confirmed the extent of polypharmacy occurrence at the SBAH outpatient clinics.

All the drugs contained in the 187 prescriptions were recorded, and in total 929 drugs were prescribed. Every new drug item encountered was recorded and the number of different drug items was 111 drugs. The most frequently prescribed drugs were tramadol (n=51, (5.49%), followed by simvastatin (n=48, (5.17%), enalapril (n=45, (4.84%), lansoprazole (n=43, (4.63%) paracetamol (n=40, (4.31%) and amitriptyline (n=38, (4.09%). This was in a bid to identify the drugs most likely to be causing irrational prescribing, ADEs, drug interactions and a burden on financial resources at SBAH. The most prevalent drug classes were, analgesics followed by hipolipidaemic agents, antihypertensive agents, antacids and anti-depressants. These results could potentially influence the most duplicated drugs to comorbid chronic disease patients attending the outpatient clinics at SBAH. In literature drug classes including, analgesics,

antihypertensive agents, hipolipidaemic agents and antidepressants were associated with medication errors because of the high global prescribing volumes.

With regard to the average cost of drugs to comorbid patients, cost analysis was achieved through obtaining the average cost per prescription. Average cost of drugs per prescription was R899.77 during the study period. According to the SBAH registry office, each patient was required to pay a minimum amount of R75.00 (dispensing fee) to obtain drugs from each prescription. The data showed that on average there was a difference of R824.77 between the dispensing fee (R75.00) and the average cost per prescription (R899.77) to chronic disease patients at SBAH (Table 8). The results indicated that SBAH had to cover R824.77 per patient per prescribing encounter. The results show the cost burden of chronic diseases on SBAH that essentially affects the public healthcare system. The average number of visits to SBAH for the chronic disease outpatients observed was 3.03 visits during the four-month study period. As 3.03 visits resulted in prescriptions, each patient was expected to pay a dispensing fee of R227.25 (3.03 multiplied by R75.00 dispensing fee). The results from cost analysis showed that on average the drugs prescribed to each comorbid chronic disease patient during the study period cost R2 103.21. The data showed that the difference between the estimated dispensing fee (R227.25) and the average cost of drugs prescribed to each comorbid patient during the study period (R2 103.21) was R1 875.96. These findings further indicate the extra drug costs SBAH had to cover to provide treatment to chronic disease patients.

The main objective was to perform prescription analysis in determining possible drug duplication and highlighting the research problem for this study. The definition used for drug duplication in this study was, the use two or more drugs from the same drug class at the same time. Drug duplication occurred in 68 individual cases in the 80 patients observed. In total, 39 patients (48.75%) were affected by drug duplication [95% CI = 37.80%: 59.70%]. The results indicated a high incidence of drug duplication that is associated with high risk of toxic and inefficient drug use. Toxic levels of drug use could lead to psychological and physical disabilities in numerous patients. The increase in the risk of medication errors rising from assorted clinic visits with multiple prescribers was shown by the findings of the authors.

The average age of the 39 patients affected by drug duplication was 57 years. The youngest patient affected was 21 years old and the oldest patient was 88 years old. Of the 39 patients affected, 20 patients (51.28%) were older than 60 years old. These results indicated that drug duplication was not influenced by belonging to the elderly age group (60 years and older) but also affected the younger adults age group (59 years and younger). The majority of patients affected by drug duplication were female patients 26 (66.67%). Drug duplication affected 13 (33.33%) male patients. These findings were potentially due to the higher number of elderly female patients attending the SBAH outpatient clinics. The majority of patients referred to SBAH was a reflection of the elderly gender demographics in the Gauteng province consisting mostly of female residents. Additionally, the higher number of female patients at SBAH could be a reflection of the reports from previous studies showing females to be health conscientious than male resulting in higher hospital visits. The most prevalent drug classes in drug duplication were analgesics 18 (26.47%) cases, followed by anti-depressants 14 (20.59%) cases recorded. The most duplicated anti-depressants were amitriptyline (tricyclic) and fluoxetine (SSRI). Analgesics duplicated the most were tramadol and paracetamol. The most duplicated drugs were as expected similar to the most frequently prescribed drugs. These findings show that a high frequency of drug class prescription is associated with the frequency at which the drug class is duplicated.

The last objective was to formulate recommendations for reducing irrational drug prescription at SBAH. Beyond the scope of this study, further studies are required to ascertain the outpatients affected by problematic polypharmacy at SBAH. Physicians treating multiple clinic-attending patients can be equipped to monitor rationality of prescribing encounters. Introduction of tools such as the Garfinkel Good Palliative-Geriatric Practice algorithm and AGS 2019 Beers criteria could determine the type of polypharmacy. Knowledge of clinical pharmacology causes rational prescribing and taking of adequate steps by prescribers to determine problematic polypharmacy existence. Implementation of the Garfinkel algorithm at SBAH can limit the number of drugs prescribed and possibly identify the drugs causing prescribing cascades. Reduction of prescribing cascades could possibly affect the prescriptions that contained up to 19 drugs. Installation of an advanced electronic HIS can aid in improving drug prescribing at SBAH. Use of electronic prescribing tools as shown in previous studies is

a requirement to improve tertiary hospitals in developing countries such as SBAH. One of the tools that may aid in polypharmacy reduction is the PRIMA-eDS tool. Use of the PRIMA-eDS tool can assist physicians in recommending the best possible treatment regimens for comorbid patients.

The authors highlighted a need for an advanced HIS at SBAH which would primarily be used by drug prescribers at the different clinics. Physicians to update the medical records of patients could use advanced computerised systems. Computerised systems would allow prescribers to access online patient files used at other clinics and crosscheck the drugs administered to the patient. The gradual use of paper-less data systems in developed countries is required in developing countries to ensure improved recordkeeping that would have allowed the collection of data for research in this study less time-consuming and labourious. There is expectation of challenges during the installation of such a system in developing countries. Challenges include qualified implementation and maintenance staff, user-friendliness to physicians and the confidentiality of the systems. Despite the challenges, advanced HIS is required for the safety of multiple clinic-attendees. Pharmacists also play a role in crosschecking prescriptions to ensure drugs dispensed do not contain any repeat medications. These solutions, in combination with an efficient medication reconciliation system, reduction of drug duplication is achievable at SBAH.

The findings by the authors build on existing evidence of elderly and comorbid patients attending multiple clinics, receiving a variety of medications, often results in drug duplication. There is a need to ensure appropriate monitoring, record keeping, and dispensing practices in large tertiary hospitals. Increased knowledge in clinical pharmacology practice in combination with critical judgement in the treatment of comorbid chronic disease patients could improve drug safety and efficacy. Further research, with the knowledge gained from this study could help to ascertain potential problematic or appropriate polypharmacy at SBAH. There is a need to implement programmes and systems to reduce irrational prescribing of drugs at SBAH outpatient clinics.

4.2. Limitations and considerations

Retrospective studies are prone to measurement and selection bias. The PI had no control over the quality standards of the data collection and recordkeeping at the hospital and had to rely on the hospital staff to produce suitable records. The hospital operating system is also largely responsible for the quality of data recorded in retrospective studies. This was a retrospective cross sectional study subsequently some of the data was lost as the patient files had missing prescriptions. Exclusion of some prescribing encounters occurred because of missing prescription records. The exclusion of 53 (22.08%) prescribing encounters resulted in the exclusion of 26 (24.53%) patients from the 106 patients initially recorded for phase two. The twenty-six excluded patients could potentially provide valid information to further the understanding of prescribing patterns at SBAH. Use of a prospective study could have allowed the PI to ensure all the prescriptions required for analysis were recorded immediately before loss in the files archives.[181] A prospective study would have provided more data for analysis to determine the level of polypharmacy and drug duplication. Inclusion of all patients in prospective studies produces a larger study than the method of choice for this study. There is consideration to use a prospective study in future research. There is a risk in the use of prospective studies. The Hawthorne effect potentially occurs when prescribers change their prescribing patterns to produce favourable results for the study. Consideration of the Hawthorne effect is essential in the use of prospective studies.[179] Furthermore, there is a risk of selection bias, as the chosen patients by the PI could bias the results towards showing outcomes that are more favoured. For this study, the inclusion of all patients during phase one was used to limit selection bias by the inclusion of all patients at risk of polypharmacy and drug duplication.[194]

Use of WHO prescribing indicators for specialist outpatient clinics provides a risk of over estimation of polypharmacy and often reflects a higher value for polypharmacy than recommended by WHO.[132] Therefore, use of the WHO core-prescribing indicator for average number of drugs prescribed potentially caused an overestimation of polypharmacy for comparison with other hospitals that provide primary care. A minimum period of one year is recommended by WHO to determine prescribing trends at healthcare centres.[133] The use of convenience sampling was employed, as the study objectives could be determined from identifying the different patients attending various

clinics at the same time within a short period than the recommended one year. The study period of four months (February 1, 2018 to May 31, 2018) used in this study was however seen as a limiting factor. Despite the study period allowing for the observation of all patients attending the chosen clinics as a mandatory three-month review process, a longer period is required to report prescribing trends In future studies, the approximation of prescribing trends requires a longer period than the four-month period used in this study. One-year study period would give more than one visit to each clinic for each patient and would represent a better approximation of the number of visits each patient undertakes to the hospital. The cost analysis over a longer period would also give a better approximation of trends of the amount of financial resources required by comorbid chronic disease patients.

The exclusion of the infectious disease clinic with focus on HIV/AIDS patients is potentially affecting the extent of comorbid patients recorded in the study. HIV/AIDS has been highlighted in literature as the leading cause for chronic disease comorbidity in Africa, however it is excluded from this study.[9] The increasing levels of the HIV/AIDS pandemic has been associated with the majority of comorbid cases in South Africa. Increase by 3.33 million people between 2002 and 2019 has been a contributing factor in increased scrutiny of HIV in South Africa.[10] As of 2019, 7.97 million (13.50%) people live with HIV in South Africa.[10] HIV is a critical factor in comorbid patient treatment in South Africa. Exclusion of the infectious disease outpatient clinic occurred as it also catered for acute conditions. Acute condition patients attending the infectious disease clinic would have affected the phase one data collection process from the appointment logbooks. The registration system in the appointment logbooks did not separate chronic disease patients from the acute disease condition patients and would have distorted the number of patients recorded in phase one as HIV/AIDS patients. The inclusion of HIV/AIDS patients is recommended in future studies to observe the effects of HIV/AIDS on the comorbid patients attending SBAH.

The use of the SEP for the cost analysis limits the study in accurately analysing the burden of chronic disease treatment per patient at SBAH. The SEP is for price control capping in drug purchases and dispensing in the private sector however, this study collected prescription data in a public facility. The results of the cost analysis process

from this study reflect the cost burden of chronic diseases according to the prices as observed from the private sector. There is a need to use the drug prices from the tender process suppliers to SBAH in future studies. Inclusion of specific drug prices from the pharmaceutical companies that provide SBAH with drugs is required to determine the cost burden of chronic disease patients at SBAH on the public healthcare system. The tender list with prices from local companies is fundamental to determine the cost of drug procurement at SBAH. Use of multiple public healthcare facilities would provide an even more accurate estimation of the cost of comorbidity in South Africa.

The use of a single facility is highlighted as a limitation, as the outcome of this study may not be generalised or be applicable to other similar tertiary hospitals in South Africa. Institutional policies regarding clinic visits and follow up consultations may differ from other tertiary hospitals. However, the data collected will be of value to the SBAH management personnel and may provide information not previously known. If these limitations are considered and improvements to avoid these limiting parameters implemented in future studies, more data can be collected that would provide prescription patterns that can be applicable to a larger population in South Africa.

Overall, this study identified the incidence of polypharmacy and drug duplication to comorbid patients attending assorted clinics at a single facility (SBAH) but also indicated with addition of other similar facilities, prescribing patterns could be analysed to identify possible causes of ADEs in elderly patients suffering from comorbidity on a larger scale. In future studies, the next step would be the provision of potential solutions for the prevention of adverse drug effects because of polypharmacy, prescribing cascades, drug duplication and drug-drug interactions nationally.

References

1. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults. Arch Intern Med. 2010;170(18):1648-55.
2. Steve Biko Academic Hospital. Out-patient services 2017 [cited 2018 January 17]. Available from: https://www.sbah.org.za/index.php/information/out-patients-services.
3. Karpa KD, Haidet P. Medication reconciliation clinical case - demonstration. MedEdPortal. 2012;8:9265.
4. World Health Organization. Non-communicable diseases: Fact sheet 2017 [cited 2017 December 12]. Available from: http://www.who.int/mediacentre/factsheets/fs355/en/.
5. Ward B, Black L. State and regional prevalence of diagnosed multiple chronic conditions among adults aged 18 or above - United states. MMWR. 2016;65(29):735-8.
6. World Bank. Overcoming poverty and inequality in South Africa: An assessment of drivers, constraints and opportunities. Washington DC: World Bank; 2018.
7. Department of Statistics South Africa. Quarterly labour force survey (QLFS) - Q3: 2019 [cited 2020 January 16]. Available from: http://www.statssa.gov.za/?p=12695.
8. World Health Organization. Public spending on health: A closer look at global trends 2018 [cited 2019 October 9]. Available from: https://www.who.int/health_financing/documents/health-expenditure-report-2018/en/.
9. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. Lancet. 2009;374(9693):934-47.
10. Department of Statistics South Africa. Mid-year population estimates: 2019 [cited 2019 September 20]. Available from: http://www.statsa.gov.za/?p=12362.
11. Goedecke J, Jennings C, Lambert E. Obesity in South Africa. In: Steyn K, Fourie J, Temple N, (eds) Chronic diseases of lifestyle in South Africa: 1995-2005. MRC. 2005:65-79.
12. World Health Organization. Diabetes fact sheet 2013 [cited 2017 December 21]. Available from: http://www.who.int/mediacentre/factsheets/fs312/en.
13. Shisana O, Labadarios D, Rehle T, Simbayi L, Zuma K, Dhansay A, et al. South African health and nutrition examination survey (SANHANES-1). Cape Town: HSRC Press, Council HSR; 2014.
14. Suhrcke M, Nugent R, Stuckler D, Rocco L. Chronic disease: An economic perspective. London: Oxford Health Alliance. 2006.
15. Hofman K. Non-communicable diseases in South Africa: A challenge to economic development. SAMJ. 2014;104(10):647.
16. Cecchini M, Sassi F, Lauer JA, Lee YY, Guarjardo-Barron V, Chisholm D. Tackling of unhealthy diets, physical inactivity, obesity: health effects and cost-effectiveness. Lancet. 2010;376(9754):1775-84.
17. Antonanzas F, Terkola R, Overton P, Shalet N, Postma M. Defining and measuring the affordability of new medicines: a systematic review. Pharmacoeconomics. 2017;35(8):777-91.
18. National Department of Health South Africa. National Drugs Policy 1996 [cited 2019 September 24]. Available from: https://www.gov.za/documents/national-drugs-policy.
19. Snyman J. Mims: Monthly index of medical specialities. Cape Town: Tiso Blackstar Group; 2019.

20. National Department of Health South Africa. Regulations relating to a transparent pricing system for medicines and scheduled substances 2004 [cited 2019 September 23]. Available from: https://www.gov.za/sites/www.gov.za/files/26304.pdf.
21. Moodley R, Suleman F, Schneider H. The impact of the single exit price policy on a basket of generic medicines in South Africa, using a time series analysis from 1999 to 2014. PLoS One. 2019;14(7):e0219690.
22. Cameron A, Mantel-Teeuwisse A, Leufkens H, Laing R. Switching from originator brand medicines to generic equivalents in selected developing countries countires: How much could be saved? Value Heal. 2012;15(5):664-73.
23. Moreno-Torres I, Puig-Junoy J, Raya J. The impact of repeated cost containment policies on pharmaceutical expenditure: experience in Spain. Eur J Heal Econ. 2011;12(6):563-73.
24. Atun R. Decisive action to end apathy and achieve 25 x 25 NCD targets. Lancet. 2014;384(9941):384-5.
25. Briggs A, Persaud J, Deverell M, Bunzli S, Tampin B, Sumi Y, et al. Integrated prevention and management of non-communicable diseases, including musculoskeletal health: a systematic policy analysis among OECD countries. BMJ Glob Health. 2019;4(5):e001806.
26. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension and cardiovascular disease: An update. Hypertension. 2001;37:1053-9.
27. World Health Organization. Global health observatory (GHO) data: Raised cholesterol 2008 [cited 2018 January 14]. Available from: http://www.who.int/gho/ncd/risk_factors/cholesterol_text/en/.
28. Cipolla M, Liebeskind D, Chan S. The importance of comorbidities in ischemic stroke: Impact of hypertension on the cerebral circulation. J Cereb Blood Flow Metab. 2018;38(12):2129-49.
29. Zhu W, Pan W. Strengthening the ability of general hospital neurology department to treat neuropsychiatric diseases and mental disorders. Integr Med Int. 2017;4:208-14.
30. World Health Organization. HIV/AIDS: fact sheet 2017 [cited 2018 January 14]. Available from: http://www.who.int/mediacentre/factsheets/fs360/en/.
31. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV 2017 [cited 2018 January 15]. Available from: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL,pdf.
32. World Health Organization. Tuberculosis: fact sheet 2017 [cited 2018 January 15]. Available from: http://www.who.int/mediacentre/factsheets/fs104/en/.
33. World Health Organization. Clinical pharmacology in health care, teaching and research 2012 [cited 2019 August 26]. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/who_cioms2012/en/.
34. Shi S, Klotz U. Age-related changes in pharmacokinetics. Curr Drug Metab. 2011;12(7):601-10.
35. Vinks TH, de Koning F, de Lange TM, Egberts TC. Identification of potential drug-related problems in the elderly: the role of the community pharmacist. Pharm World Sci. 2006;28(1):33-8.
36. Mangoni A, Jackson S. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004;57(1):6-14.
37. National Department of Health South Africa. Revitalising public healthcare facilities [cited 2019 August 27]. Available from: https://www.gov.za/about-sa/health.

38. Naidoo S. The South African national health insurance: a revolution in health care delivery. J Public Health. 2012;34(1):149-50.
39. Department of Statistics South Africa. The latest household statistics and more: health 2017 [cited 2019 August 27]. Available from: http://www.statssa.gov.za/?p=11241.
40. Ataguba JE, McIntyre D. The incidence of health financing in South Africa: findings from a recent data set. Health Econ Policy Law. 2018;13(1):68-91.
41. Matsoso M, Fryatt R. National Health Insurance: The first 18 months. SAMJ, S Afr Med J. 2013;103(3):154-5.
42. National Department of Health South Africa. National Health Insurance in South Africa: Policy green paper 2011 [cited 2019 August 29]. Available from: http://www.health.gov.za/index.php/nhi.
43. Marcum Z, Handler S, Boyce R, Gellad W, Hanlon J. Medication misadventures in the elderly: a year in review. Am J Getriatr Pharmacother. 2010;8(1):77-83.
44. Medical Brief. Steve Biko Academic Hospital gets thumbs up from Zuma 2017 [cited 2018 January 17]. Available from: https://www.medicalbrief.co,za/archives/steve-biko-academic-hospital-gets-thumbs-zuma/.
45. World Health Organization. Rational use of medicines: fact sheet 2010 [cited 2018 January 17]. Available from: http://www.who.int/mediacentre/factsheets/fs338/en.
46. Hajjar E, Cafiero A, Hanlon J. Polypharmacy in elderly patients. Am J Getriatr Pharmacother. 2007;5(4):345-51.
47. Payne RA, Abel GA, Avery AJ, Mercer SW, Roland MO. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol. 2014;77(6):1073-82.
48. Atif M, Sarwar M, Azeem M, Naz M, Amir S, Nazir K. Assessment of core drug use indicators using WHO/INRUD methodology at primary healthcare centers in Bahawalpur, Pakistan. BMC Health Serv Res. 2016;16:684.
49. Maxwell S. How should teaching of undergraduates in clinical pharmacology and therapeutics be delivered and assessed. Brit J Clin Pharmacol. 2012;73:893-9.
50. Karpa KD, Hom LL, Huffman P, Lehman EB, Chinchilli VM, Haidet P, et al. Medication safety curriculum: enhancing skills and changing behaviors. BMC Medical Education. 2015;15:234.
51. Best Practice Advocacy Centre New Zealand. Polypharmacy in primary care: Managing a clinical conundrum 2014 [cited 2018 January 20]. Available from: http://www.bpac.org.nz/BPJ/2014/October/polypharmacy.aspx.
52. Machado-Duque M, Castano-Montoya J, Medina-Morales D, Castro-Rodriguez A, Gonzalez-Montoya A, Machado-Alba J. Drugs with anticholinergic potential and risk of falls with hip fracture in the elderly patients: a case-control study. J Geriatr Psychiatry Neurol. 2018;31(2):63-9.
53. Edwards I, Aronson J. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255-9.
54. Shah B, Hajjar E. Polypharmacy, adverse drug reactions, and geriatric syndromes. Clin Geriatr Med. 2012;28:173-86.
55. Hosseini S, Zabihi A, Amiri SJ, Bijani A. Polypharmacy among the elderly. J Midlife Health. 2018;9(2):97-103.
56. Howard R, Avery A, Slavenburg S, Royal S, Pipe G, Lucassen P, et al. Which drugs cause preventable admissions to hospital? A systematic review. Br J Clin Pharmacol. 2007;63(2):136-47.
57. Budnitz D, Lovegrove M, Shehab N, Richards C. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011;365(21):2002-12.

58. Palleria C, Paolo AD, Giofre C, Caglioti C, Leuzzi G, Siniscalchi A, et al. Phramacokinetic drug-drug interaction and their implication in clinical management. J Res Med Sci. 2013;18(7):601-10.
59. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: A study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. Drug SAF. 2007;30:911-8.
60. Gallelli L, Colosimo M, Tolotta G, Falcone D, Luberto L, Curto L, et al. Prospective randomized double-blind trial of racedotril compared with loperamide in elderly people with gastroenteritis living in nursing homes. Eur J Clin Pharmacol. 2010;66(2):137-44.
61. Nguyen P, Spinelli C. Prescribing cascade in an elderly woman. Can Pharm J (Ott). 2016;149(3):122-4.
62. Onder G, Bonassi S, Abbatecoia A, Folino-Gallo P, Lapi F, Marchionni N, et al. High prevalence of poor quality drug prescribing in older individuals: a nationwide report from the Italian Medicines Agency (AIFA). J Gerontol A Biol Sci Med Sci. 2014;69(4):430-7.
63. Anathhanam S, Powis R, Cracknell A, Robson J. Impact of prescribed medications on patient safety in older people. Ther Adv Drug Saf. 2012;3(4):165-74.
64. Fujita T, Kutsumi H, Sanuki T, Hayakumo T, Azuma T. Adherence to the preventive strategies for nonsteroidal anti-inflammatory drug- or low-dose aspirin-induced gastrointestinal injuries. J Gastroenterol. 2013;48(5):559-73.
65. DeRhodes K. The dangers of ignoring the Beers criteria - The prescribing cascade. JAMA Intern Med. 2019;179(7):863-4.
66. Barnsteiner J. Medication reconciliation: transfer of medication information across settings - keeping it free from error. Am J Nurs. 2005;105(Suppl 3):31-6.
67. Hugtenburg J, Timmers L, Elders P, Vervloet M, van Dijk L. Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. Patient Prefer Adherence. 2013;7:675-82.
68. Bangalore S, Kamalakkannan G, Parkar S, Messerli F. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007;120(8):713-9.
69. Vervloet M, van Dijk L, Santen-Reestman J, van Vlijmen B, van Wingerden P, Bouvy M, et al. SMS reminders improve adherence to oral medication in type 2 diabetes patients who are real time electronically monitored. Int J Med Inform. 2012;81(9):594-604.
70. Bogart K, Wong S, Lewis C, Akenzua A, Hayes D, Prountzos A, et al. Mobile phone text message reminders of antipsychotic medication: is it time and who should receive them? A cross-sectional trust-wide survey of psychiatric inpatients. BMC Psychiatry. 2014;14:15.
71. Kannisto K, Adams C, Koivunen M, Katajisto J, Valimaki M. Feedback on SMS reminders to encourage adherence among patients taking antipyschotic medication: a cross-sectional survey nested within a randomized trial. BMJ Open. 2015;5(11):e008574.
72. World Health Organization. Essential medicines and health products 2015 [cited 2019 September 18]. Available from: https://www.who.int/medicines/services/essmedicines_def/en/.
73. Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. Lancet. 2009;373(9659):240-9.
74. National Coordinating Council for Medication Error Reporting and Prevention. Definition and types of medication errors [cited 2019 August 27]. Available from: https://www.nccmerp.org/about-medication-errors.

75. Aronson JK. Medication errors: definitions and classification. Br J Clin Pharmacol. 2009;67(6):599-604.
76. Mekonnen A, Alhawassi T, McLachlan A, Brien J. Adverse drug events and medication errors in African hospitals: A systematic review. Drugs Real World Outcomes. 2018;5(1):1-24.
77. Kohn L, Corrigan J, Donaldson M. To err is human: building a safer health system. Washigton DC: National Academy Press; 2000.
78. Hakkarainen K, Andersson K, Petzold M, Hagg S. Methods for assessing the preventability of adverse drug events: a systematic review. Drug Saf. 2012;35(2):105-26.
79. Stefan E. Gender differences in health information behaviour: a Finnish population-based survey. Health Promot Int. 2015;30(3):736-45.
80. Lee I, Chang C, Du P. Do healthier lifestyles laed to less utilization of healthcare resources? BMC Health Serv Res. 2017;17:243.
81. Odhayani A, Tourkmani A, Alshehri M, Alqahtani H, Mishriky A. Potentially inappropriate medications prescribed for elderly patients through family physicians. Saudi J Biol Sci. 2017;24(1):200-7.
82. Fuentes A, Pineda M, Venkata KN. Comprehension of top 200 prescribed drugs in the US as a resource for pharmacy teaching, training and practice. Pharmacy (Basel). 2018;6(2):43.
83. Zin C, Nazar N, Rahman N, Alias N, Ahmad W, Rani N, et al. Trends and patterns of analgesic prescribing in Malaysian public hospitals from 2010 to 2016: tramadol predominatly used. J Pain Res. 2018;11:1959-66.
84. Tholen K, Hoffmann F. High use of tramadol in Germany: an analysis of statutory health insurance data. Pharmacoepidemiol Drug Saf. 2012;21(9):1013-21.
85. Miotto K, Cho A, Khalil M, Blanco K, Sasaki J, Rawson R. Trends in tramadol: pharmacology, metabolism, and misuse. Anesth Analg. 2017;124(1):44-51.
86. Tashakori A, Afshari R. Tramadol overdose as a cause of serotonin syndrome: a case series. Clin Toxicol. 2010;48(4):337-41.
87. Srivastava A, Singh P, Gupta H, Kaur H, Kanojia N, Guin D, et al. Systems approach to identify common genes and pathways associated with response to selective serotonin reuptake inhibitors and major depression risk. Int J Mol Sci. 2019;20(8):1993.
88. Lancaster E, Hiatt J, Zarrinpar A. Acetaminophen hepatotoxicity: an updated review. Arch Toxicol. 2015;89(2):193-9.
89. Chiew A, Gluud C, Brok J, Buckley N. Interventions for paracetamol (acetaminophen) overdose. Cochrane Database Syst Rev. 2018;2:CD003328.
90. Oscanoa T, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. Eur J Clin Pharmacol. 2017;73(6):759-70.
91. Durrance S. Older adults and NSAIDs: avoiding adverse reactions. Geriatr Nurs. 2003;24(6):348-52.
92. Alduhishy M. The overprescription of antidepressants and its impact on the elderly in Australia. Trends Psychiatry Psychother. 2018;40(3):241-3.
93. Bobo WV, Grossardt BR, Lapid MI, Leung JG, Stoppel C, Takahashi PY, et al. Frequency and predictors of the potential overprescribing of antidepressants in elderly residents of a geographically defined US population. Pharmacol Res Perspect. 2019;7(1):e00461.
94. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressants use and risk of adverse outcomes in older people: population based cohort study. BMJ. 2011;343:d4551.

95. Stephenson C, Karanges E, McGregor I. Trends in the utilization of psychotropic medications in Australia from 2000 to 2011. Aust N Z J Psychiatry. 2013;47:74-87.
96. Miani C, Martin A, Exley J, Doble B, Wilson E, Payne R, et al. Clinical effectiveness and cost-effectiveness of issuing longer versus shorter duration (3-month vs. 28-day) prescriptions in patients with chronic conditions: systematic review and economic modelling. Health Technol Assess. 2017;21(78):1-128.
97. Reid S, Barbui C. Long term treatment of depression with selective serotonin reuptake inhibitors and newer antidepressants. BMJ. 2010;340:c1468.
98. Smith M, Cox E, Bartell J. Overprescribing of lipid lowering agents. Qual Saf Health Care. 2006;15(4):251-7.
99. Torjesen I. Statins are overprescribed for primary prevention, study suggests. BMJ. 2018;363:k5110.
100. Machado-Alba J, Fernandez A, Castrillon J, Campo C, Echeverri L, Gaviria A, et al. Prescribing patterns and economic costs of proton pump inhibitors in Colombia. Colomb Med (Cali). 2013;44(1):13-8.
101. Ying J, Li L, Wu C, Yu Z, Kan L. The status of proton pump inhibitor use: a prescription survey of 45 hospitals in China. Rev Esp Enferm Dig. 2019;111(10):738-43.
102. Halfdanarson O, Pottegard A, Bjornsson E, Lund S, Ogmundsdottir M, Steingrimsson E, et al. Proton-pump inhibitors among adults: a nationwide drug-utilization study. Therap Adv Gastroenterol. 2018;11:1756284818777943.
103. Wilkinson G. Drug metabolism and variability among patients in drug response. N Engl J Med. 2005;352:2211-21.
104. Nguyen Q, Anderson S, Sanders L, Nguyen L. Managing hypertension in the elderly: A common chronic disease with increasing age. Am Health Drug Benefits. 2012;5(3):146-53.
105. World Bank. Health expenditure per capita 2014 [cited 2019 September 18]. Available from: http://data.worldbank.org/indicator/SH.XPD.PCAP.
106. Lavan A, Gallagher P. Predicting risk of adverse drug reactions in older adults. Ther Adv Drug Saf. 2016;7:11-22.
107. Witry M, Klein D, Alexander B, Franciscus C, Turvey C. Medication list discrepancies and therapeutic duplications among dual use veterans. Fed Pract. 2016;33(9):14-20.
108. Dilokthornsakul P, Chaiyakunapruk N, Nimpitakpong P, Jeanpeerapong N, Sruamsiri R. The effects of medication supply on hospitalizations and health-care costs in patients with chronic heart failure. Value Health. 2012;15(1 Suppl):s9-14.
109. Dilokthornsakul P, Chaiyakunapruk N, Nimpitakpong P, Jeanpeerapong N, Jampachaisri K, Lee T. Understanding medication oversupply and its predictors in the outpatient departments in Thailand. BMC Health Serv Res. 2014;14:408.
110. Khalid M, Waseem M. Tricyclic antidepressant toxicity. Treasure Island (Florida): StatPearls Publishing; 2019.
111. Bergen H, Murphy E, Cooper J, Kapur N, Stalker C, Waters K, et al. A comparative study of non-fatal self-poisoning with antidepressants relative to prescribing in three centres in England. J Affect Disord. 2010;123(1-3):95-101.
112. Guloglu C, Orak M, Ustundag M, Altunci Y. Analysis of amitriptyline overdose in emergency medicine. Emerg Med J. 2011;28(4):296-9.
113. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kalviainen R, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013;54(3):551-63.

114. Hanaya R, Arita K. The new antiepileptic drugs: Their neuropharmacology and clinical indications. Neurol Med Chir (Tokyo). 2016;56(5):205-20.
115. Wills B, Reynolds P, Chu E, Murphy C, Cumpston K, Stromberg P, et al. Clinical outcomes in newer anticonvulsant overdose: a poison center observational study. J Med Toxicol. 2014;10(3):254-60.
116. Yaylaci S, Demir M, Acar B, Sipahi S, Tamer A. Successful treatment of excessive dose of carbamazepine. Indian J Pharmacol. 2012;44(3):417-8.
117. Johannessen S, Landmark C. Antiepileptic drug interactions - principles and clinical implications. Curr Neuropharmacol. 2010;8(3):254-67.
118. Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. Epileptic Disord. 2014;16(4):409-31.
119. Lucas C, Christie G, Waring W. Rapid onset of heamodynamic effects after angiotensin converting enzyme-inhibitor overdose: implications for initial patient triage. Emerg Med J. 2006;23(11):854-7.
120. Carpenter J, Murray B, Saghafi R, Thomas B, Lee S, Kleiman R, et al. Successful treatment of antihypertensive overdose using intravenous angiotension II. J Emerg Med. 2019;57(3):339-44.
121. Khaja KA, Isa H, Veeramuthu S, Sequeira R. Potentially inappropriate prescribing in older adults with hypertension or diabetes mellitus
and hypertension in a primary care setting in Bahrain. Med Princ Pract. 2018;27(3):241-9.
122. Islam M. The art and science of using diuretics in the treatment of heart failure in diverse clinical settings. Adv Exp Med Biol. 2018;1067:47-65.
123. Kieboom B, Zietse R, Ikram M, Hoorn E, Stricker B. Thiazide but not loop diuretics is associated with hypomagnesaemia in the general population. Pharmcoepidemiol Drug Saf. 2018;27(11):1166-73.
124. Wehling M. Morbus diureticus in the elderly: epidemic overuse of a widely applied group of drugs. J Am Med Dir Assoc. 2013;14(6):437-42.
125. Pek E, Remfry A, Pendrith C, Fan-Lun C, Bhatia R, Soong C. High prevalance of inappropriate benzodiazepine and sedative hypnotic prescriptions among hospitalized older adults. J Hosp Med. 2017;12(5):310-6.
126. Dalleur O, Boland B, Groot AD, Vaes B, Boeckxstaens P, Azermai M, et al. Detection of potentially inappropriate prescribing in the very old: cross-sectional analysis of the data from the BELFRAIL observational cohort study. BMC Geriatr. 2015;15:156.
127. Ramadan WH, Khoury GME, Deeb ME, Sheikh-Taha M. Prescription patterns of benzodiazepines in the Lebanese adult popuplation: a cross-sectional study. Neuropsychiatr Sis Treat. 2016;12:2299-305.
128. Carey IM, Wilde SD, Harris T, Victor C, Richards N, Hilton SR, et al. What factors predict potentially inappropriate primary care prescribing in older people? Analysis of UK primary care patient record database. Drugs Aging. 2008;25(8):693-706.
129. Airagnes G, Pelissolo A, Lavallee M, Flament M, Limosin F. Benzodiazepine misuse in the elderly: risk factors, consequences, and management. Curr Psychiatry Rep. 2016;18(10):89.
130. Novotny M, Klimova B, Valis M. PPI long term use: risk of neurological adverse events? Front Neurol. 2018;9:1142.
131. Robinson R, Casavant M, Nahata M, Mahan J. Metabolic bone disease after chronic antacid administration in an infant. Ann Pharmacother. 2004;38(2):265-8.

132. Ofori-Asenso R, Brhlikova P, Pollock A. Prescribing indicators at primary health care centers within the WHO African region: a systematic analysis (1995-2015). BMC Public Health. 2016;16:724.
133. World Health Organization. How to investigate drug use in health facilities: selected drug use indicators 1993 [cited 2018 January 24]. Available from: http://apps.who.int/medicinedocs/en/d/Js2289e/
134. Narayan SW, Nishtala PS. Prevalence of potentially inappropriate medicine use in older New Zealanders: a population-level study using the updated 2012 Beers criteria. J Eval Clin Pract. 2015;21(4):633-41.
135. Heinze G, Jandeck L, Hronsky M, Reichardt B, Baumgartel C, Bucsics A, et al. Prevalence and determinants of unintended double medication of antihypertensive, lipid-lowering, and hypoglycemic drugs in Austria: a nationwide cohort study. Pharmacoepidemiol Drug Saf. 2016;25(1):90-9.
136. The Joint Commission. Medication reconciliation: Sentinel event alert 2006 [cited 2019 September 3]. Available from: http://www.jointcommission.org/SentinelEvents/SentinelEventAlert/sea_35.htm.
137. Barnsteiner J. Medication reconciliation. In Hughes RG, editor. Patient safety and quality: An evidence based-handbook for nurses. Rockville (MD): Agency for healthcare research (US);2008.
138. Jacobson J. Ensuring continuity of care and accuracy of patients' medication history on hospital admission. Am J Health Syst Pharm. 2002;59:1054-5.
139. Holloway K. Combating inappropriate use of medicines. Expert Rev Clin Pharmacol. 2011;4(3):335-48.
140. Whittington J, Cohen H. OSF healthcare's journey in patient safety. Qual Manag Health Care. 2004;13(1):53-9.
141. Chaudhry B, Wang J, Wu S, Maglione M, Mojica W, Roth E, et al. Systematic review: impact of health information technology on quality, efficiency and costs of medical care. Ann Intern Med. 2006;144(10):742-52.
142. Gentles S, Lokker C, McKibbon K. Health Information Technology to facilitate communication involving health care providers, caregivers, and pediatric patients: A scoping review. J Med Internet Res. 2010;12(2):e22.
143. Mozaffar H, Williams R, Cresswell K, Sheikh A. Anglicization o hospital information systems: Managing diversity alongside particularity. Int J Med Inform. 2018;119:88-93.
144. Ismail A, Jamil AT, Rahman AFA, Bakar JMA, Saad NM, Saadi H. The implementation of hospital information systsem (HIS) in tertiary hospitals in Malaysia: A qualitative study. MJPHM. 2010;10(2):16-24.
145. National Department of Health South Africa. National Health Insurance: white paper 2019 [cited 2019 August 20]. Available from: http://www.health.gov.za/index.php/national-health-insurance-right-menu.
146. Wolmarans M, Solomon W, Tanna G, Venter J, Parsons A, Chetty M, et al. eHealth Programme reference implementation in primary health care facilities. SAHR. 2014;1:35-43.
147. Paradath A, King J, Mackie EL. Overview of the 2016 South African health review. S Afr Med J. 2016;106(7):655-7.
148. National Department of Health South Africa. e-Health Strategy South Africa 2012-2016 2012 [cited 2020 January 15]. Available from: http://www.doh.gov.za/docs/stratdocs/2012/eHealth_Strategy_South_Africa_2012-2016.pdf.

149. Katurura M, Cilliers L. Electronic health record system in the public health care sector of South Africa: A systematic literature review. Afr J Prm Health Care Fam Med. 2018;10(1):1746.
150. Nuq P, Aubert B. Towards a better understanding of the intention to use eHealth services by medical professionals: The case of developing countries. Int J Healthc Manag. 2013;6(4):217-36.
151. Malik MA, Khan HR. Understanding the implementation of an electronic hospital information system in a developing country: A case study in Pakistan. CRPIT. 2009;97:1-6.
152. Quiett L. Clerical and data management for the pharmacy technician. New York: Cengage Learning; 2012.
153. Sönnichsen A, Trampisch U, Rieckert A, Piccoliori G, Vögele A, Flamm M. Polypharmacy in chronic diseases– Reduction of Inappropriate Medication and Adverse drug events in older populations by electronic Decision Support (PRIMA-eDS): study protocol for a randomized controlled trial. Trials. 2016;17(57):1-9.
154. American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67(4):674-94.
155. Corsonello A, Onder G, Abbatecola A, Guffanti E, Gareri P, Lattanzio F. Explicit criteria for potentially inappropriate medications to reduce the risk of adverse drug reactions in elderly people: from Beers to STOPP/START criteria. Drug Saf. 2012;35(Suppl 1):21-8.
156. Scott I, Hilmer S, Reeve E, Potter K, Couteur DL, Rigby D, et al. Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med. 2015;175(5):827-34.
157. Reeve E, Gnjidic D, Long J, Hilmer S. A systematic review of the emerging definition of 'deprescribing' with network analysis: implications for future research and clinical practice. Br J Clin Pharmacol. 2015;80(6):1254-68.
158. Machado-Alba J, Gaviria-Mendoza A, Machado-Duque M, Chica L. Deprescribing: a new goal focused on the patient. Expert Opin Drug Saf. 2017;16(2):111-2.
159. Cohen M, Kimmel N, Benage M, Cox M, Sanders N, Spence D, et al. Medication safety program reduces adverse drug events in a community hospital. Qual Saf Health Care. 2005;14:169-74.
160. Relihan E, Silke B, Ryder S. Design template for a medication safety programme in an acute teaching hospital. Eur J Hosp Pharm. 2012;19(3):340-4.
161. World Health Organization. WHO multi-professional patient safety curriculum guide 2011 [cited 2019 September 5]. Available from: https://www.who.int/patientsafety/education/mp_curriculum_guide/en/.
162. Hauser D, Young D, Braitman L. Adapting the bundles approach to reduce medication errors in pharmacy practice. J Clin Outcomes Manage. 2010;17(3):125-31.
163. Petersen I, Fairall L, Bhana A, Kathree T, Selohilwe O, Brooke-Summer C, et al. Integrating mental health into chronic care in South Africa: The development of a district mental healthcare plan. Br J Psychiatry. 2016;208(s56):s29-s39.
164. Petersen I, Rathod S, Kathree T, Selohilwe O, Bhana A. Risk correlates for physical-mental multimorbidities in South Africa: a cross sectional study. Epidemiol Psych Sci. 2017;28(4):418-26.
165. Cheng S, Chen C. Effects of continuity of care on medication duplication among the elderly. Med Care. 2014;52(2):149-56.

166. Karthikeyan M, Lalitha D. A prospective observational study of medication errors in general medicine department in a tertiary care hospital. Drug Metabol Drug Interact. 2013;28(1):13-21.
167. Pote S, Tiwari P, D'Cruz S. Medication prescribing errors in a public teaching hospital in India: a prospective study. Pharmacy Practice. 2007;5:17-20.
168. Poudel R, Piryani R, Shrestha S, Prajapati A, Adhikari B. Prescription errors and pharmacist intervention at outpatient pharmacy of Chitwan Medical College. JCMC. 2015;5(2):20-4.
169. Ball D, Maidza J, Rusike T, Sharief K, Taderera T, Tangawarima T. Drug use indicators at St Mary's clinic. Cent Afr J Med. 2000;46:54-5.
170. DiMasia J, Grabowski H. The cost of biopharmaceutical R&D: Is biotech different? MDE Manage Decis Econ. 2007;28:469-79.
171. World Health Organization. The world medicines situation 2011 [cited 2019 September 17]. Available from: https://www.who.int/medicines/areas/policy/world_medicines_situation/en/.
172. World Health Organization. Innovative care for chronic conditions: Building blocks for action 2004 [cited 2019 September 17]. Available from: http://www.who.int/diabetesactiononline/about/icccglobalreport.pdf.
173. Reinhart U. Does the aging of the population really drive the demand for healthcare? Health Aff (Millwood). 2003;22:27-39.
174. Abegunde D, Mathers C, Adam T, Ortegon M, Strong K. The burden and costs of chronic diseases in low-income and middle-income countries. Lancet. 2007;370(9603):1929-38.
175. Nugent R. Chronic diseases in developing countries: health and economic burdens. Ann N Y Acad Sci. 2008;1136:70-9.
176. Mann C. Observational research methods. Research design II: cohort, cross sectional, and case-control studies Emerg Med J. 2003;20(1):54-60.
177. Kumari R, Idris M, Bushan V, Khanna A, Agrawal M, Singh S. Assessment of prescription pattern at the public health facilities of Lucknow district. Indian J Pharmacol. 2008;40(6):243.
178. Stefan D, Stones D, Wainwright R, Kruger M, Davidson M, Poole J, et al. The South African paediatric tumour registry - 25 years of activity. SAMJ. 2012;102:605-6.
179. McCarney R, Warner J, Iliffe S, Haselen Rv, Griffin M, Fisher P. The Hawthorne effect: a randomised, controlled trial. BMC Med Res Methodol. 2007;7:30.
180. Ofori-Asenso R. A closer look at the World Health Organization's prescribing indicators. J Pharmacol Pharmacother. 2016;7(1):51-4.
181. Kooistra B, Dijkman B, Einhorn T, Bhandari M. How to design a good case series. J Bone Joint Surg Am. 2009;91(supp 3):21-6.
182. Hartz A, Marsh J. Methodologic issues in observtional studies. Clin Orthop Relat Res. 2003;413:33-42.
183. Alkot M, Shaheen H, Hathout H. Prescribing patterns and errors in family practice; a retrspective study of prescribing records. J Amer Sci. 2011;7(11):186-90.
184. Hamilton L. Statistics with Stata: Updated for version 12. Eighth ed. Boston Richard Stratton; 2012.
185. Saldana J. The coding manual for qualitative researchers. Third ed. Arizona: SAGE publications; 2015.
186. Gashaw T, Sisay M, Mengistu G, Amare F. Investigation of prescribing behaviour at outpatient settings of governmental hospitals in eastern Ethiopia: an overall evaluation

beyond World Health Organization core prescribing indicators. J Pharm Policy Pract. 2018;11:26.
187. Katon W, Cantrell C, Sokol M. Impact of antidepressant drug adherence on comorbid medication use and resource utilization. Arch Intern Med. 2005;165(21):2497-503.
188. Mailman R, Murthy V. Third generation antipyschotic drugs: partial agonism or receptor functional selectivity? Curr Pharm Des. 2010;16(5):488-501.
189. World Health Organization. Adherence to long term therapies: Evidence for action 2003 [cited 2019 September 14]. Available from: http://apps.who.int/medicinedocs/en/d/Js4883e/.
190. Lingam R, Scott J. Treatment non-adherence in affective disorders. Acta Psychitrica Scandinavica. 2002;105(3):164-72.
191. Kennedy S, Rizvi S. Agomelatine in the treatment of Major Depressive Disorder: Potential for clinical effectiveness. CNS Drugs. 2010;24(6):479-99.
192. Rossiter D. South African medicine formulary (SAMF 11). Eleventh ed. Cape Town: Health and Medical Publishing Group; 2014.
193. World Health Organization. Definition of an older or elderly person 2010 [cited 2020 January 14]. Available from: https://www.who.int/healthinfo/survey/ageingdefnolder/en/.
194. Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L. Do the findings of case series studies vary significantly according to methodological characteristics? Health Technol Assess. 2005;9(2):1-146.
195. van Petegem K. Steve Biko hospital blames patients for long queues Pretoria: The Citizen; 2019 [cited 2020 January 13]. Available from: http://citizen.co.za/news/south-africa/health/2147274/steve-biko-hospital-blames-patients-for-long-queues/.
196. World Bank. World development report 1993: Investing in health New York: Oxford University Press; 1993 [cited 2017 December 20]. Available from: https://www.openknowledge.worldbank.org/handle/10986/5976.

Appendices

Appendix 1 - Ethics approval

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/14/2020.

13/09/2018

Approval Certificate
New Application

Ethics Reference No: 508/2018

Title: Prescription patterns and drug duplication in specialist out-patient clinics at a tertiary hospital in the greater Tshwane metropolitan area

Dear Musawenkosi Ncube

The **Amendment** as described in your documents specified in your cover letter dated 28/08/2018 received on 28/08/2018 was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 12/09/2018.

Please note the following about your ethics approval:
- Ethics Approval is valid for 1 year
- Please remember to use your protocol number (**508/2018**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

*** Kindly collect your original signed approval certificate from our offices, Faculty of Health Sciences, Research Ethics Committee, Tswelopele Building, Room 4.59 / 4.60.*

Dr R Sommers; MBChB; MMed (Int); MPharMed,PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 46 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2016 (Department of Health).

Research Ethics Committee
Room 4-60, Level 4, Tswelopele Building
University of Pretoria, Private Bag X323
Arcadia 0007, South Africa
Tel +27 (0)12 356 3084
Email deepeka.behari@up.ac.za
www.up.ac.za

Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/11/2020.

9 October 2019

Approval Certificate
Annual Renewal

Ethics Reference No.: 508/2018
Title: Prescription patterns and drug duplication in specialist out-patient clinics at a tertiary hospital in the greater Tshwane metropolitan area

Dear Mr MG Ncube

The **Annual Renewal** as supported by documents received between 2019-09-19 and 2019-10-09 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 2019-10-09.

Please note the following about your ethics approval:

- Renewal of ethics approval is valid for 1 year, subsequent annual renewal will become due on 2020-10-09.
- Please remember to use your protocol number (508/2018) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers
MBChB MMed (Int) MPharmMed PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2016 (Department of Health)

Research Ethics Committee
Room 4-03, Level 4, Tswelopele Building
University of Pretoria, Private Bag X323
Arcadia 0007, South Africa
Tel +27 (0)12 356 3084
Email deepeka.behari@up.ac.za
www.up.ac.za

Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

Appendix 2 - Permission letter: CEO Steve Biko Academic Hospital

Permission to access Records / Files / Data base at Steve Biko Academic Hospital

TO:
The [CEO] Chief Executive Officer of Steve Biko Academic Hospital

Re: Permission to do research at Steve Biko Academic Hospital

TITLE OF STUDY: Prescription patterns and drug duplication in specialist out-patient clinics at Steve Biko Academic Hospital

This study is approved by the relevant Head of Department [HOD]: Steenkamp Signature: PROF V STEENKAMP

This request is logged with you in terms of the requirements of the Promotion of Access to Information Act, No. 2 of 2000

I am a researcher / student at the Department of Pharmacology at the University of Pretoria /Steve Biko Academic Hospital I am working with Dr. Andre Marais . I herewith request permission on behalf of all of us to conduct a study on the above topic on the hospital / clinic grounds. This study involves access to patient records. This study involves clinical research

The researchers request access to the following information: clinical files, record books and data bases.

We intend to publish the findings of the study in a professional journal and/ or to present them at professional meetings like symposia, congresses, or other meetings of such a nature.

We intend to protect the personal identity of the patients by assigning each individual a random code number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely

Print Name: MASUMENG DEMBE Signature:
Principal Investigator

Permission to do the research study at this hospital / clinic and to access the information as requested, is hereby approved, on condition that there will be no cost to the hospital.

Title and name of Chief Executive Officer: Dr ES Mangwane

Name of hospital / clinic: Steve Biko Academic Hospital

Signature: Date: 20/06/18

2018 -06- 20
Official Stamp

Appendix 3 - Declaration of Helsinki

Special Communication

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added) 59th WMA General Assembly, Seoul, Republic of Korea, October 2008 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

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

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights

Appendix 4 - Statistical raw data

26 Jun 2019, 15:07:30

```
. tab scripts

    scripts |      Freq.     Percent        Cum.
------------+-----------------------------------
          0 |        187       77.92       77.92
          1 |         53       22.08      100.00
------------+-----------------------------------
      Total |        240      100.00

. tab tot_drugs if scripts == 0

  tot_drugs |      Freq.     Percent        Cum.
------------+-----------------------------------
          1 |         20       10.70       10.70
          2 |         28       14.97       25.67
          3 |         32       17.11       42.78
          4 |         22       11.76       54.55
          5 |         16        8.56       63.10
          6 |         20       10.70       73.80
          7 |         18        9.63       83.42
          8 |          7        3.74       87.17
          9 |          8        4.28       91.44
         10 |          3        1.60       93.05
         11 |          3        1.60       94.65
         13 |          1        0.53       95.19
         14 |          5        2.67       97.86
         15 |          1        0.53       98.40
         16 |          1        0.53       98.93
         19 |          2        1.07      100.00
------------+-----------------------------------
      Total |        187      100.00

. * % with 5 or more

. display (85/187)*100
45.454545

. display 100 - 54.55
45.45



. * Number of items per script

. display 929/187
4.9679144


. list drug tot_pres use_per

     +-----------------------------------+
```

drug	tot_pres	use_per
diazepam	3	.3229279
oxazepam	1	.1076426
clobazam	1	.1076426
lorazepam	1	.1076426
hydroxyzine	1	.1076426
meth_phen	1	.1076426
amitrip	38	4.09042
fluoxet	20	2.152853
venlafax	2	.2152853
trazodone	2	.2152853
citalopram	14	1.506997
olanzap	1	.1076426
aripipraz	1	.1076426
risperid	11	1.184069
lamotrig	15	1.614639
valpr_acid	21	2.260495
topiram	3	.3229279
gabapentin	4	.4305705
carbamaz	9	.9687836
clonazep	8	.861141
phenytoin	1	.1076426
carb_lev	2	.2152853
metoclop	6	.6458558
prometh	3	.3229279
morphine	2	.2152853
paracet	40	4.305705
ibuprofen	14	1.506997
tramadol	51	5.489774
ketorolac	1	.1076426
diclofenac	4	.4305705
brufen	7	.7534984
aspirin	35	3.767492
allopurinol	5	.5382131
colchicine	3	.3229279
baclofen	3	.3229279
pyridost	4	.4305705
loratidine	2	.2152853
promethazine	2	.2152853
cetirizine	1	.1076426
ondansetron	5	.5382131
digoxin	1	.1076426
amiodarone	1	.1076426
verapamil	2	.2152853
doxazosin	6	.6458558
atenolol	6	.6458558

46. | propanolol 4 .4305705 |
47. | carvedilol 28 3.013994 |
48. | hydralazine 2 .2152853 |
49. | amlodipine 34 3.659849 |
50. | enalapril 45 4.843918 |
    |---|
51. | losartan 2 .2152853 |
52. | ver_pam 2 .2152853 |
53. | nitroglyc 8 .861141 |
54. | isosorb_mon 15 1.614639 |
55. | bezafibrate 2 .2152853 |
    |---|
56. | artovastatin 2 .2152853 |
57. | simvastatin 48 5.166846 |
58. | ezetimibe 2 .2152853 |
59. | tranex_acid 1 .1076426 |
60. | iron_iii 3 .3229279 |
    |---|
61. | folicacid 19 2.04521 |
62. | warfarin 9 .9687836 |
63. | clopidogrel 1 .1076426 |
64. | salbutamol 3 .3229279 |
65. | ipratropiumbr 2 .2152853 |
    |---|
66. | becl_dipr 3 .3229279 |
67. | pancreat 3 .3229279 |
68. | ranitid 1 .1076426 |
69. | omepraz 1 .1076426 |
70. | calc_carb 9 .9687836 |
    |---|
71. | lansopraz 43 4.628633 |
72. | sucralfate 5 .5382131 |
73. | hyon_but 1 .1076426 |
74. | lactulose 7 .7534984 |
75. | sennosid 1 .1076426 |
    |---|
76. | sod_phos 3 .3229279 |
77. | loperamide 1 .1076426 |
78. | furosemide 14 1.506997 |
79. | spironaloct 4 .4305705 |
80. | acetazolam 1 .1076426 |
    |---|
81. | hctz 36 3.875134 |
82. | tams_hcl 1 .1076426 |
83. | actraphane 13 1.399354 |
84. | actrapid 19 2.04521 |
85. | insum_comb 1 .1076426 |
    |---|
86. | protaphane 14 1.506997 |
87. | glimpirid 3 .3229279 |
88. | metformin 16 1.722282 |
89. | glibenclam 2 .2152853 |
90. | gluc_strips 23 2.47578 |
    |---|
91. | levothyr 17 1.829925 |
92. | prednisone 5 .5382131 |

```
 93. |      dexameth          6   .6458558 |
 94. |     conj_estr          1   .1076426 |
 95. |      anastroz          4   .4305705 |
     |----------------------------------------|
 96. |       tamoxif          7   .7534984 |
 97. |       pyridox          2   .2152853 |
 98. |     vitb_comp         19    2.04521 |
 99. |         vit_d          4   .4305705 |
100. |     sod_chlor          2   .2152853 |
     |----------------------------------------|
101. |     potass_cl         18   1.937567 |
102. |      mg_sulph          6   .6458558 |
103. |     calc_gluc          1   .1076426 |
104. |      imatinib          1   .1076426 |
105. |     cisplatin          2   .2152853 |
     |----------------------------------------|
106. |     methotrex          2   .2152853 |
107. |    hydroxurea          3   .3229279 |
108. |       fluor_5          3   .3229279 |
109. |  azathioprine          4   .4305705 |
110. |     interf_1b          1   .1076426 |
     |----------------------------------------|
111. |     tot_drugs        929        100 |
     +----------------------------------------+

. log close
      name:  <unnamed>
       log:  C:\Data_15\musa.log
  log type:  text
 closed on:  26 Jun 2019, 15:57:41

___  ____  ____  ____  ____ (R)
 /__    /   ____/   /   ____/
___/   /   /___/   /   /___/   Release 15.1   Copyright 1985-2017 StataCorp LLC
  Statistics/Data Analysis            StataCorp
                                      4905 Lakeway Drive
                                      College Station, Texas 77845 USA
                                      800-STATA-PC        http://www.stata.com
                                      979-696-4600        stata@stata.com
                                      979-696-4601 (fax)

-------------------------------------------------------------------------------------------------------------------------------
----------------------
```

2 Aug 2019, 10:48:00

```
. for var sed_hypnMS - imm_stimMS: tab X if (count == 2 | count == 3) & (X == 2 | X == 3)

->  tab sed_hypnMS if (count == 2 | count == 3) & (sed_hypnMS == 2 | sed_hypnMS == 3)
no observations

->  tab cns_stimMS if (count == 2 | count == 3) & (cns_stimMS == 2 | cns_stimMS == 3)
no observations
```

```
->  tab anti_deprMS if (count == 2 | count == 3) & (anti_deprMS == 2 | anti_deprMS == 3)

anti_deprMS |      Freq.     Percent        Cum.
------------+-----------------------------------
          2 |         14      100.00      100.00
------------+-----------------------------------
      Total |         14      100.00

->  tab anti_psychMS if (count == 2 | count == 3) & (anti_psychMS == 2 | anti_psychMS == 3)
no observations

->  tab anti_epilMS if (count == 2 | count == 3) & (anti_epilMS == 2 | anti_epilMS == 3)

anti_epilMS |      Freq.     Percent        Cum.
------------+-----------------------------------
          2 |          7      100.00      100.00
------------+-----------------------------------
      Total |          7      100.00

->  tab anti_parkMS if (count == 2 | count == 3) & (anti_parkMS == 2 | anti_parkMS == 3)
no observations

->  tab anti_vertMS if (count == 2 | count == 3) & (anti_vertMS == 2 | anti_vertMS == 3)

anti_vertMS |      Freq.     Percent        Cum.
------------+-----------------------------------
          2 |          1      100.00      100.00
------------+-----------------------------------
      Total |          1      100.00

->  tab analgesMS if (count == 2 | count == 3) & (analgesMS == 2 | analgesMS == 3)

  analgesMS |      Freq.     Percent        Cum.
------------+-----------------------------------
          2 |         18      100.00      100.00
------------+-----------------------------------
      Total |         18      100.00

->  tab nsaidsMS if (count == 2 | count == 3) & (nsaidsMS == 2 | nsaidsMS == 3)

   nsaidsMS |      Freq.     Percent        Cum.
------------+-----------------------------------
          2 |          2      100.00      100.00
------------+-----------------------------------
      Total |          2      100.00

->  tab anti_goutMS if (count == 2 | count == 3) & (anti_goutMS == 2 | anti_goutMS == 3)
no observations


->  tab musc_relMS if (count == 2 | count == 3) & (musc_relMS == 2 | musc_relMS == 3)
no observations

->  tab cholinegicsMS if (count == 2 | count == 3) & (cholinegicsMS == 2 | cholinegicsMS == 3)
```

no observations

-> tab antihistMS if (count == 2 | count == 3) & (antihistMS == 2 | antihistMS == 3)
no observations

-> tab serot_antMS if (count == 2 | count == 3) & (serot_antMS == 2 | serot_antMS == 3)
no observations

-> tab pos_inotrMS if (count == 2 | count == 3) & (pos_inotrMS == 2 | pos_inotrMS == 3)
no observations

-> tab antiarrhMS if (count == 2 | count == 3) & (antiarrhMS == 2 | antiarrhMS == 3)
no observations

-> tab anti_hypMS if (count == 2 | count == 3) & (anti_hypMS == 2 | anti_hypMS == 3)

anti_hypMS	Freq.	Percent	Cum.
2	7	100.00	100.00
Total	7	100.00	

-> tab anti_anggentsMS if (count == 2 | count == 3) & (anti_anggentsMS == 2 | anti_anggentsMS == 3)

anti_anggentsMS	Freq.	Percent	Cum.
2	3	100.00	100.00
Total	3	100.00	

-> tab hipolipidMS if (count == 2 | count == 3) & (hipolipidMS == 2 | hipolipidMS == 3)

hipolipidMS	Freq.	Percent	Cum.
2	1	100.00	100.00
Total	1	100.00	

-> tab haemostMS if (count == 2 | count == 3) & (haemostMS == 2 | haemostMS == 3)
no observations

-> tab haemanMS if (count == 2 | count == 3) & (haemanMS == 2 | haemanMS == 3)

haemanMS	Freq.	Percent	Cum.
2	3	100.00	100.00
Total	3	100.00	

-> tab anti_coagMS if (count == 2 | count == 3) & (anti_coagMS == 2 | anti_coagMS == 3)
no observations

-> tab plat_aggrMS if (count == 2 | count == 3) & (plat_aggrMS == 2 | plat_aggrMS == 3)
no observations

```
->  tab bronchodMS if (count == 2 | count == 3) & (bronchodMS == 2 | bronchodMS == 3)
no observations

->  tab anti_asthMS if (count == 2 | count == 3) & (anti_asthMS == 2 | anti_asthMS == 3)
no observations

->  tab digestMS if (count == 2 | count == 3) & (digestMS == 2 | digestMS == 3)
no observations

->  tab antacidsMS if (count == 2 | count == 3) & (antacidsMS == 2 | antacidsMS == 3)

 antacidsMS |      Freq.     Percent        Cum.
------------+-----------------------------------
          2 |          4      100.00      100.00
------------+-----------------------------------
      Total |          4      100.00

->  tab anti_spasMS if (count == 2 | count == 3) & (anti_spasMS == 2 | anti_spasMS == 3)
no observations

->  tab laxativesMS if (count == 2 | count == 3) & (laxativesMS == 2 | laxativesMS == 3)
no observations

->  tab antidiarrhMS if (count == 2 | count == 3) & (antidiarrhMS == 2 | antidiarrhMS == 3)
no observations

->  tab diureticsMS if (count == 2 | count == 3) & (diureticsMS == 2 | diureticsMS == 3)

diureticsMS |      Freq.     Percent        Cum.
------------+-----------------------------------
          2 |          4      100.00      100.00
------------+-----------------------------------
      Total |          4      100.00

->  tab urin_antisMS if (count == 2 | count == 3) & (urin_antisMS == 2 | urin_antisMS == 3)
no observations

->  tab insulinsMS if (count == 2 | count == 3) & (insulinsMS == 2 | insulinsMS == 3)
no observations

->  tab anti_diabMS if (count == 2 | count == 3) & (anti_diabMS == 2 | anti_diabMS == 3)

anti_diabMS |      Freq.     Percent        Cum.
------------+-----------------------------------
          2 |          1      100.00      100.00
------------+-----------------------------------
      Total |          1      100.00

->  tab gluc_testMS if (count == 2 | count == 3) & (gluc_testMS == 2 | gluc_testMS == 3)
no observations

->  tab thyroidMS if (count == 2 | count == 3) & (thyroidMS == 2 | thyroidMS == 3)

  thyroidMS |      Freq.     Percent        Cum.
------------+-----------------------------------
          2 |          1      100.00      100.00
```

```
------------+-----------------------------------
      Total |          1      100.00

->  tab corticostMS if (count == 2 | count == 3) & (corticostMS == 2 | corticostMS == 3)
no observations

->  tab oestrogMS if (count == 2 | count == 3) & (oestrogMS == 2 | oestrogMS == 3)
no observations

->  tab horm_inhMS if (count == 2 | count == 3) & (horm_inhMS == 2 | horm_inhMS == 3)
no observations

->  tab vitamMS if (count == 2 | count == 3) & (vitamMS == 2 | vitamMS == 3)

    vitamMS |      Freq.     Percent        Cum.
------------+-----------------------------------
          2 |          1      100.00      100.00
------------+-----------------------------------
      Total |          1      100.00

->  tab mineralsMS if (count == 2 | count == 3) & (mineralsMS == 2 | mineralsMS == 3)

 mineralsMS |      Freq.     Percent        Cum.
------------+-----------------------------------
          2 |          1      100.00      100.00
------------+-----------------------------------
      Total |          1      100.00

->  tab cytostaticsMS if (count == 2 | count == 3) & (cytostaticsMS == 2 | cytostaticsMS == 3)
no observations

->  tab imm_suprMS if (count == 2 | count == 3) & (imm_suprMS == 2 | imm_suprMS == 3)
no observations

->  tab imm_stimMS if (count == 2 | count == 3) & (imm_stimMS == 2 | imm_stimMS == 3)
no observations

. tab clinic

     clinic |      Freq.     Percent        Cum.
------------+-----------------------------------
          1 |          7        3.26        3.26
          2 |         26       12.09       15.35
          3 |         59       27.44       42.79
          4 |         60       27.91       70.70
          5 |         25       11.63       82.33
          6 |         38       17.67      100.00
------------+-----------------------------------
      Total |        215      100.00


. tab comb

       comb |      Freq.     Percent        Cum.
------------+-----------------------------------
        120 |          1        0.94        0.94
```

```
       123 |        1       0.94       1.89
       130 |        4       3.77       5.66
       140 |        1       0.94       6.60
       230 |       10       9.43      16.04
       234 |        1       0.94      16.98
       240 |        7       6.60      23.58
       250 |        2       1.89      25.47
       260 |        4       3.77      29.25
       340 |       26      24.53      53.77
       345 |        1       0.94      54.72
       350 |        9       8.49      63.21
       360 |        7       6.60      69.81
       450 |        5       4.72      74.53
       460 |       19      17.92      92.45
       560 |        8       7.55     100.00
-----------+-----------------------------------
     Total |      106     100.00
```

```
___  ____  ____  ____  ____ (R)
/__    /   ____/   /   ____/
___/   /   /___/   /   /___/   Release 15.1   Copyright 1985-2017 StataCorp LLC
  Statistics/Data Analysis            StataCorp
                                      4905 Lakeway Drive
                                      College Station, Texas 77845 USA
                                      800-STATA-PC        http://www.stata.com
                                      979-696-4600        stata@stata.com
                                      979-696-4601 (fax)
```

---

7 Aug 2019, 16:03:52

```
. summ script_cost if script_cost ~= 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
 script_cost |       187    899.7667    1852.679      14.42    21983.6

. ci means script_cost if script_cost ~= 0

    Variable |       Obs        Mean    Std. Err.      [95% Conf. Interval]
-------------+---------------------------------------------------------------
 script_cost |       187    899.7667    135.4813       632.4892    1167.044

. summ tot_cost if incl == 0 & tot_cost ~= 0

    Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
    tot_cost |        80    2103.205    2925.843     325.66   22551.74

. ci means tot_cost if incl == 0 & tot_cost ~= 0
```

```
    Variable |       Obs        Mean    Std. Err.       [95% Conf. Interval]
-------------+--------------------------------------------------------------
    tot_cost |        80    2103.205    327.1192        1452.09    2754.319

___  ____  ____ ____  ____ (R)
/__    /  ____/   /   ____/
___/   /   /___/   /   /___/   Release 15.1   Copyright 1985-2017 StataCorp LLC
  Statistics/Data Analysis            StataCorp
                                      4905 Lakeway Drive
                                      College Station, Texas 77845 USA
                                      800-STATA-PC        http://www.stata.com
                                      979-696-4600        stata@stata.com
                                      979-696-4601 (fax)

------------------------------------------------------------------------------------------------------------------------ ----------

------------------------------
```

Appendix 5 - Participants affected by drug duplication

	Gender	Age	Clinics attended
1	Female	74	MOPD + oncology
2	Female	83	MOPD + oncology
3	Female	79	MOPD + oncology
4	Male	46	MOPD + neurology
5	Female	88	MOPD + diabetes
6	Female	32	MOPD + neurology
7	Female	64	MOPD + neurology + oncology
8	Female	65	MOPD + neurology
9	Female	71	MOPD + oncology
10	Male	46	MOPD + neurology
11	Female	80	MOPD + neurology
12	Female	59	MOPD + oncology
13	Female	53	Diabetes + psychiatry
14	Male	42	Diabetes + MOPD
15	Male	62	Diabetes + neurology + MOPD
16	Female	69	Diabetes + MOPD
17	Male	79	Diabetes + oncology
18	Female	71	Neurology + psychiatry
19	Male	82	Neurology + oncology
20	Female	21	Neurology + psychiatry
21	Male	35	Neurology + MOPD
22	Female	29	Neurology + MOPD
23	Female	32	Neurology + psychiatry
24	Male	31	Neurology + psychiatry
25	Female	60	Neurology + MOPD
26	Female	50	Neurology + MOPD
27	Female	80	Psychiatry + MOPD
28	Male	73	Psychiatry + neurology
29	Male	51	Psychiatry + neurology
30	Female	53	Psychiatry + MOPD
31	Female	51	Psychiatry + neurology
32	Female	50	Psychiatry + neurology
33	Female	64	Oncology + neurology
34	Female	51	Oncology + neurology
35	Male	69	Oncology + MOPD
36	Female	30	Oncology + psychiatry
37	Female	56	Oncology + psychiatry
38	Male	66	Oncology + psychiatry
39	Male	31	Oncology + neurology