PROCUREMENT AND EXPENDITURE OF MEDICINES USED FOR MENTAL, NEUROLOGICAL AND SUBSTANCE USE DISORDERS: A SECONDARY ANALYSIS OF THE 2017/2018 GAUTENG PHARMACEUTICAL DATABASE

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MASTER OF MEDICINE
in the discipline of PSYCHIATRY.

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DECLARATION

I, Jade Catheryne Bouwer, declare that this research report is my own work. It is being submitted in partial fulfilment of the requirements for the degree of Master of Medicine in the discipline of Psychiatry, at the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg.

It has not been submitted for any degree or examination at this or any other university.

Signature: 

Date: 8 September 2020

DEDICATION

To God be all the glory.

To my father Clive Holland, who passed away suddenly during my training, thank you for always believing I could achieve anything I set out to do. You were always my one constant.

"People – like trees – can grow and achieve their full integrated capacity, meaning and purpose."

Professor Bernard Janse van Rensburg

April 1960 – April 2020

ABSTRACT

Background

Access to essential medicines is necessary for an effective, efficient, and equitable health care system. Analysis of the procurement of and expenditure on medicines may assist in the planning of sustainable access. The procurement of medicines for mental, neurological, and substance use (MNS) disorders in South Africa has to date received little research attention.

Aim

To examine the procurement of and expenditure on medicines used to treat MNS disorders in Gauteng province for the 2017/2018 financial year.

Method

A secondary analysis of the Gauteng provincial pharmaceutical database was undertaken. Defined daily doses (DDD) and cost per 1000 population served were calculated to compare procurement across service levels and facilities.

Results

MNS medicines accounted for 3.73% of total provincial medicine expenditure. More than three-quarters of this amount was spent on anti-epileptic medicines (47.5%) and antipsychotics (30.9%). Over 90% of the total DDD issued were issued at general healthcare clinics and hospitals. Chi square contingency testing revealed significant differences in procurement among facilities at each service level.

Conclusion

Medicine for the treatment of MNS disorders, primarily epilepsy, psychosis, and bipolar disorder, accounted for less than 4% of total medicine expenditure. Inconsistency in procurement between sites suggests differences in patient populations and treatment approaches. Future studies using patient-linked data are recommended to evaluate medicine utilisation according to treatment outcomes.

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CONTENTS

GLOSSARY AND LIST OF ABBREVIATIONS

ATC: Anatomic, therapeutic and chemical

CHo: Central hospital

CMHS: Community mental health services

Cost/1000: Cost per 1000 population served per district (i.e. headcount)

DALYs: Disability adjusted life years

DDD: Defined daily dose

DDD/1000: DDD per 1000 population served per district (i.e. headcount); this presents medicine consumption. It may provide a rough estimate of the proportion of the study population treated with a particular medicine or medicine group.

DHIS: District Health Information Services

DHo: District hospital

EML: Essential medicines list

HC: Headcount: this includes the measure of patients attending clinic facilities; it is also used to represent the population served per district (i.e. clinic headcount and PDE).

HIC: High-income country

HIV/AIDS: Human immunodeficiency virus/acquired immune deficiency syndrome

LMIC: Low- and middle-income country

MNS: Mental, neurological and substance use

NDOH: National Department of Health

NEML: Non-EML

PDE: Patient day equivalent: a measure of the average number of patients in hospital (in- and outpatient) per day

PHC: Primary health care

RHo: Regional hospital

SDG: Sustainable Development Goal

SHo: Specialised hospital

STG: Standard treatment guideline

THo: Tertiary hospital

TQEML: Tertiary and quaternary EML

UHC: Universal health coverage

Vertical lookup: A Microsoft Excel function which searches for a value in the first column of a table and returns the value in the same row in the index number position

WHO: World Health Organization

YLDs: Years lived with disability

YLLs: Years of life lost

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Chapter 1 : INTRODUCTION

Background

Access to essential medicines is one of the six building blocks of an effective, efficient and equitable health care system identified by the World Health Organization (WHO) (1), and is included in Sustainable Development Goal (SDG) 3.8 as being integral to achieving universal health coverage (UHC) (2). The WHO describes an essential medicine as one which satisfies a population's priority health care needs (3) and has developed an essential medicines list (EML) to guide low- and middle-income countries (LMICs). An EML (4,5) serves to facilitate access to medication on the basis of four factors: rational selection, affordability, availability, and appropriate use. All four factors rely on sound health care, management, and medicine supply systems. While an appropriate budget is a pre-requisite, sustainable financing depends on the careful selection of affordable, effective and safe medicines as well as their appropriate use.

Health information systems constitute another WHO building block (1). Through the monitoring of various parameters, systems can provide valuable information to assist decision-makers with regard to policy implementation, governance, service delivery and financing. Procurement databases provide an indirect indication of disease profiles, medicine consumption, and spending (6). Additionally, using the WHO's classification system, standardised medicine utilisation and comparison studies can be undertaken (4).

Medicine usage should reflect the burden of disease (7). Mental, neurological and substance use (MNS) disorders are commonly grouped together due to similarities in aetiology, disease progression, treatment approach and outcome (4). Despite the disease burden of MNS disorders almost doubling between 1990 and 2010 (7), the allocation of resources toward mental health care remains inadequate, with a treatment gap in excess of 75% in LMICs (4,8). To improve mental health coverage and treatment outcomes, the WHO's Comprehensive Mental Health Action Plan 2013–2020 proposes the appropriate use of evidence-based treatment guidelines together with access to essential medicines (5,9,10).

South Africa is committed to the concept of UHC and has ensured the alignment of its National Drug Policy of 1996 with the WHO essential medicines guidelines (11). To achieve this, South Africa has its own EML and standard treatment guidelines (STGs), which incorporate medicines for MNS disorders, and which are constantly revised (12). Monitoring and evaluation of medicine consumption could be useful in informing these STGs, and in ensuring the rational and sustainable provision of medicines.

Literature Review

Universal health coverage (UHC) is a United Nations goal intended to ensure that essential health services are readily available to all without being financially burdensome (2,13). The primary purpose of a health system is to improve health (1). While health systems are unquestionably reliant on efficient governance, adequate funding and staffing, essential medicines are pivotal to a health system in promoting UHC (14). Procurement of medicines should be captured on health system databases for analysis so as to allow sustainable and rational use to be monitored. A database of this kind was established in Gauteng in 2016 and allows for some analysis of spending.

Universal health coverage and access to medicines

The concept of health as a human right was introduced in 1946 (15). The United Nations amended this in 2002 to include mental health and to provide for the highest attainable physical and mental health service delivery. Access to essential medicines became a core feature of this right. The definition of essential medicines was also reformulated by the WHO from being those of the utmost importance to those which satisfy priority health care needs. This highlighted the importance of quality and equitable health care, but also drew attention to the fact that inappropriate use could waste resources and threaten the financial sustainability of health systems.

Wirtz et al. (15) trace the evolution of essential medicines policies from being a core element of basic primary health care, directed toward the management of acute conditions, to being shaped by financing and political investments in the wake of the HIV/AIDS epidemic. Access to medicines thus expanded to include those used in the treatment of communicable diseases. However, it was only with the need to expand

the footprint of UHC as an SDG that essential medicines policies were reframed to provide not only for acute and communicable illnesses, but for chronic, non-communicable diseases as well.

Rational selection of medicines for MNS disorders

MNS disorders contribute substantially to mortality and have detrimental outcomes on the economic and social well-being of sufferers and their families (4,7). The indirect costs (loss of productivity, absenteeism, loss of income) are estimated to far outweigh the direct costs of mental illness (8). For the year 2001/2002 in South Africa, lost income attributable to severe anxiety and depression disorders was estimated at R28.8 billion, over 60 times the approximately R472 million spent on mental health care for adults for the same year (5,16). While effective multi-modal interventions may be delivered across all health service levels, evidence-based medicine treatment is essential to facilitate improved care outcomes (4). The clinical use of these medicines should be guided by STGs to ensure safe and rational use of available resources (12,17).

Choosing EML medicines for MNS disorders can be difficult, as there are multiple participant and research complexities complicating clinical trials (4,9,12,18). Mental health conditions are a highly heterogeneous set of disorders. Participants in clinical trials are often rigidly selected, however, with those with multimorbidity and very severe illness possibly being excluded, which may lead to poor generalisability of results. Moreover, obtaining consent from participants may raise concerns regarding capacity or the risk of exposing them to further stigma. Pharmaceutical trials may be influenced by sponsor bias, and findings of treatment approach studies may reveal overlapping efficacy and tolerability profiles with little longitudinal data showing clear benefit of one over another. Utilising results from head-to-head comparisons together with those of network meta-analyses, which provide an indirect assessment of comparative effectiveness, observational studies and expert opinion may be needed to inform EML decision-making. EMLs may therefore be appropriate for real-world clinical practice in terms of medication suitability and range.

Affordability of medication

When essential medicines with proven efficacy and safety are affordable and available, they could act as one of the most cost-effective components of a health system, with positive health effects both in the immediate and long term (14,19). Thus, cost-effectiveness is an important consideration in the selection of medicines for EMLs. With regard to MNS disorders, medicines often have overlapping indications as well as tolerability and side effect profiles, blurring clear treatment benefit. Procurement of older treatment options, which are available as generic products, may reduce treatment costs, as newer psychotropics often carry high procurement costs. However, newer, slightly more expensive medicines with fewer extra-pyramidal side effects may prove more affordable than the addition of an anticholinergic agent to a first-generation antipsychotic. Furthermore, an important consideration is that acceptability to the patient according to individual response and tolerability may promote greater treatment adherence, minimising the risk of relapse and the high costs of repeated hospital admissions (20).

Availability of medication

Despite the high burden of disease, many LMICs spend less than 1 to 2% of their budgets on the management of MNS disorders (7,19,21). Historically, specialised psychiatric facilities serving a smaller proportion of the patient population have been prioritised, with most funds and resources per capita being spent on inpatient care (21,22). However, it has been shown that it is generally more cost effective to treat patients at a community and primary health care level, where care is integrated, than in hospitals (21).

Figure 1.1 illustrates the relative organisation of services for mental health care as conceived by the WHO (23). Most patients can be managed at the self- and community-care level, where the cost-burden is lowest. As greater expertise is required, service delivery becomes more specialised. At these levels, the cost-burden is greater, but the demand is lower. Community mental health services, at the same service delivery level as psychiatric facilities in general hospital settings, allow for greater accessibility and sustainability of health care to users at lower cost than an inpatient setting (24). Their function is to provide care for those recently discharged

from an acute inpatient facility, facilitate hospital referrals, oversee primary health care (PHC) practice, and promote health awareness through outreach and community liaison.

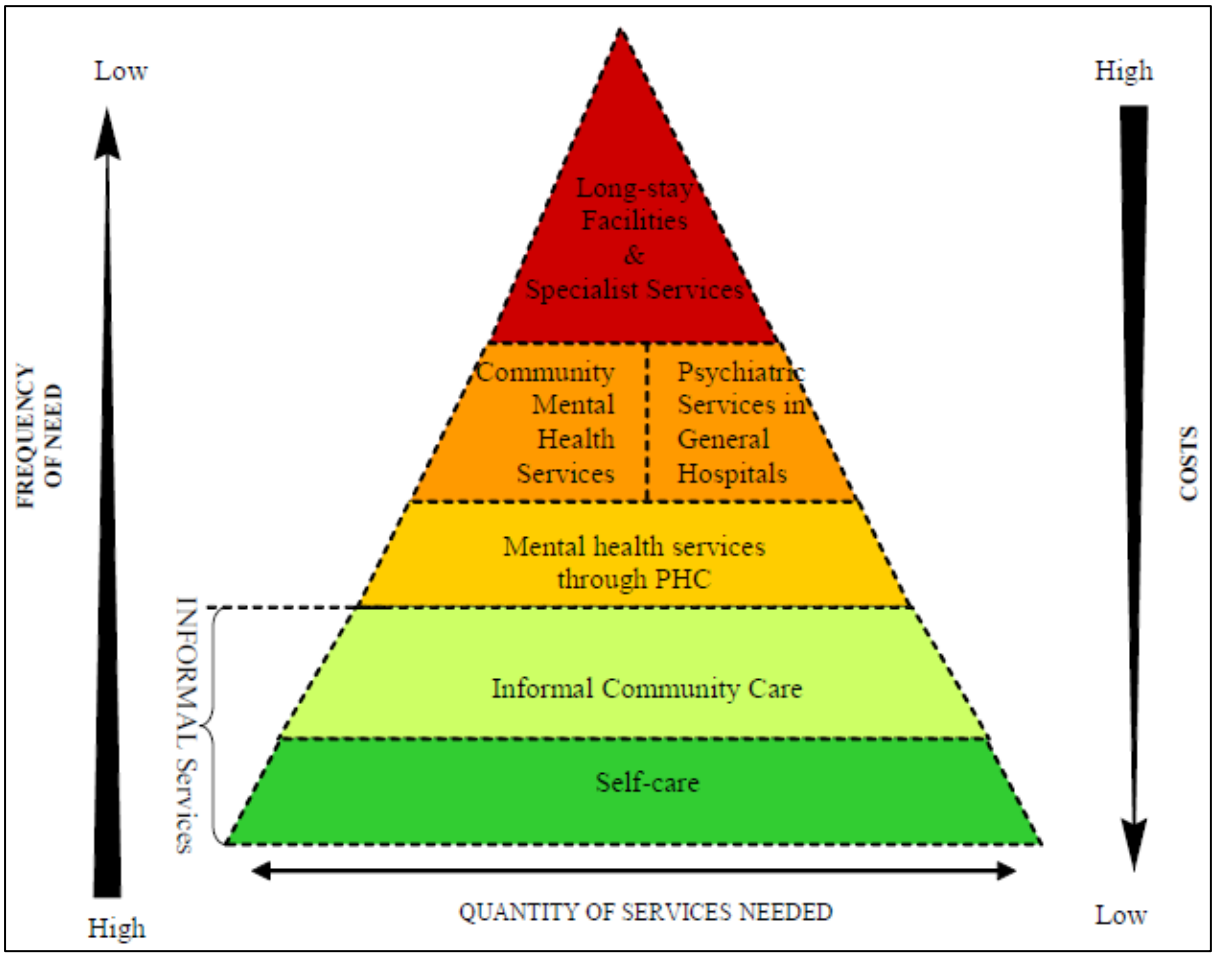

Figure 1.1: WHO organisation of services for mental health
(source: The optimal mix of services: WHO pyramid framework https://www.who.int/mental_health/policy/services)(23)

In order to improve health, all components of a health system need to function optimally (1). Preventive, promotive, curative and rehabilitative interventions should be available at various service levels within the health sector, as no single health intervention can meet the needs of an entire population (24). While health care planners should consider the WHO hierarchical model when seeking to optimise service delivery and health coverage (4,20,22), it has been noted that the scaling up of community services and integration of mental health into PHC (23) in no way

negates the value of specialist psychiatric services geared toward inpatient care, but seeks to avoid over-utilisation of highly specialised facilities at great expense (25).

However, there remain substantial barriers to adequate access to and use of medicines for MNS disorders within each level. These include supply and demand constraints and monitoring challenges (4). Limitations on medicine availability include limited budgets, the absence of guidelines governing procurement and prescribing habits, and geographic restrictions hindering accessibility of services to those in more rural settings (26). Furthermore, medication stock-outs influence the morbidity and mortality of mental illnesses (4). Underutilisation of resources due to poor awareness of illness or the treatment thereof, associated stigma, or discrimination affecting health-seeking behaviours may skew the inferred need for treatment, while side effects of treatment or functional decline associated with illness itself may restrict medication use (4,27).

Appropriate use of medication

When used judiciously, medicines can contribute to the overall health and well-being of populations in a sustainable manner. However, it is estimated that over half of prescribed medicines in LMICs are used inappropriately (14). Only 30 to 40% of patients are treated according to guidelines. Reasons identified include unreliable procurement and supply systems, too few trained prescribers, and prescribers having inadequate knowledge of STGs. Recommendations for correcting these shortcomings include the improvement of healthcare policies, aided by the establishment of national EMLs with more efficient procurement and supply protocols, more stringent adherence to evidence-based STGs, with monitoring of such medicine utilisation (14,28).

An additional consideration relating to the appropriate use of medication is the issue of polypharmacy. While there is validity in combining two or more agents for the enhanced targeting of symptoms or for minimising side effects, psychiatric polypharmacy not only propels medication spending, but promotes the off-label use of medications and risks therapeutic duplication (29). The evidence-base supporting this practice is small, however, and the aim is not to avoid polypharmacy altogether, but rather to practise rational prescribing.

Monitoring and evaluation

Efficient procurement of medicines and rational prescribing based on STGs contribute to the rational use of a country's financial resources and may be monitored through pharmaco-epidemiological research.

In LMICs, the general lack of reliable data and the inability to test and monitor this has been recognised as a particular obstacle to ensuring medicine supply (14). The Lancet's Commission on Essential Medicines (15) proposed that governments and health systems should create and maintain information systems for routine monitoring of data on the affordability of essential medicines so as to manage medicine costs, availability and procurement trends. Medicine utilisation studies should be performed on pharmaceutical databases to allow for service provision and access to medicine to be monitored and compared both nationally and internationally (4,27). Inferences drawn from these data sources may also inform decision-making regarding treatment guidelines and further adjustments to the EML.

Pharmaco-epidemiological research

The interpretation of medication procurement can provide a range of information (30): retrospective and descriptive studies may identify trends in prescribing patterns, the volume of prescriptions of certain medicines may indicate clinical value of medicines, and quantity sold may indicate medication consumption. Additionally, patient-linked databases may indicate dosages prescribed and indication of medicine use, although prescription does not automatically translate into treatment adherence. The estimation of burden of disease from database studies can be difficult, but the analysis of medicine procurement in terms of quantity and the average maintenance adult dose per day together with population studies may indirectly allow for the approximation of burden of disease. Such information may then be compared with current treatment guidelines to assess quality of management (6,8,31).

Psychotropic medicine utilisation patterns have been studied, primarily in high-income countries (HICs), where health care data is routinely captured (4,5,17). The presence of such databases presents opportunities for descriptive studies in these populations, which may cast light on extent of medication use, validate defined daily doses, identify long-term adverse effects and establish in-utero safety (6,32). In countries where

patient-level data is available, studies have succeeded in showing medicine appropriateness and extent of use for common mental illnesses, disease profiles and prevalence. The analysis of databases has cast light on resource and patient distribution and differences in total medicine expenditure, while comparisons of disease prevalence and procurement patterns have helped assess adherence to treatment guidelines.

WHO classification systems

The WHO has established an internationally recognised anatomical therapeutic chemical (ATC) classification system in terms of which all medicines are assigned a unique code based on the nature of the medication. Medicines are grouped according to the physiological organ system on which they act. Subgroups are determined by chemical, pharmacological and therapeutic properties. Letters and numbers are used to denote these groupings. The complete structure of the code is illustrated in the following example of haloperidol (17):

N = nervous system (1st level, anatomical main group)

N05 = psycholeptics (2nd level, therapeutic subgroup)

N05A = antipsychotics (3rd level, pharmacological subgroup)

N05AD = butyrophenone derivatives (4th level, chemical subgroup)

N05AD01 = haloperidol (5th level, chemical substance)

Medicine consumption is recorded using the defined daily dose (DDD), which is a dosage value assigned by the WHO. This value is based on an assumed average maintenance dose per day for each medicine when used for its main indication in adults (17). While the DDD may not always reflect typically prescribed doses of medicines, it provides a defined statistical measure of medicine usage. Use of the ATC/DDD system allows standardisation of medicine groupings and a uniform utilisation measurement. This makes comparisons of medicine use between countries, regions, and other health care settings possible. Currently, there is no direct way to accurately monitor medication utilisation and prescribing. Interpretation of DDDs procured at various sites and across time may provide an indirect reflection of the volumes of medicines being prescribed.

Furthermore, relating the DDDs procured to the population served and total costs makes further comparisons possible. For example, a low DDD/1000 headcount served suggests that smaller doses of medicines are being prescribed or that medicines are being prescribed less frequently, whereas a high DDD/1000 headcount served suggests greater population coverage (i.e. the provision of treatment to a larger number of patients), if standard doses are prescribed. A low cost/DDD reflects that a medicine is inexpensive for a standard dose, making affordability comparison possible. Thus, high expenditure may be due to either a large total quantity of a medicine procured, a high DDD prescribed, or high cost/DDD. The classification system and DDDs are dynamic and therefore subject to revision according to new information or identification of inaccuracy (7,17,33).

Mental health in the South African setting

Although South Africa is a World Bank upper middle-income country, there is a substantial equality gap; a large proportion of the population live in poverty, with a high prevalence of HIV/AIDS and other communicable diseases contributing significantly to mortality (34). Multiple societal-level socio-economic risk factors, such as high rates of crime and interpersonal violence, road traffic accidents and substance abuse, predispose individuals to mental illness and disability.

A recent South African costing analysis by Docrat et al. (2019) (35) found that an average of 5% of the total public health budget was spent on mental health in the 2016/2017 financial year, with high levels of inequity between provinces and between service levels. The largest proportion of these funds (86%) was spent on inpatient care, and almost half at specialist psychiatric hospital level. The analysis furthermore revealed an estimated mental health treatment gap of 91% and indicated gaps in the knowledge base relating to health goals, service delivery and true MNS disease burden estimates, which were largely attributed to a paucity of mental health data.

Burden of disease in South Africa

The top ten burden of disease causes in South Africa for 2015 (7,33) are shown in Table 1.1. Although depression appears to be the only prominent mental disorder, the bidirectional relationship between MNS disorders and HIV/AIDS, interpersonal

violence, trauma, chronic pain and other conditions should not be overlooked (5). Overall, neuropsychiatric disorders are believed to be the third most prevalent contributors to the burden of disease in the country (4,5,27).

Table 1.1: 2015 global burden of disease findings for South Africa

	1	2	3	4	5	6	7	8	9	10
YLDs	HIV	Back & neck pain	Sensory deficits	MDD	DM	Skin disease	Iron deficiency	Migraine	Asthma	Anxiety
DALYs	HIV	DM	IPV	LRTI	TB	Road injuries	IHD	Back & neck pain	Stroke	Diarrhoea
YLLs	HIV	IPV	LRTI	Road injuries	TB	IHD	DM	Stroke	Diarrhoea	Neonatal preterm delivery

Source of data: (36–38). YLDs = years lived with disability; DALYs = disability adjusted life years; YLLs = years of life lost; HIV = human immunodeficiency virus; DM = diabetes mellitus; IPV = interpersonal violence; LRTI = lower respiratory tract infection; MDD = depression; TB = tuberculosis; IHD = ischaemic heart disease

Standard treatment guidelines and essential medicine list

South Africa has its own locally relevant national EML and STGs (12). Development of the EML and STGs started in the late 1990s (11,27) and both have continuously evolved to align with SDG 3.8 and the move toward UHC.

The National Department of Health (NDOH) STGs and EML guide patient care and medicine prescribing from the PHC to non-academic specialist (regional hospital) service levels. At the university-linked facilities, management is additionally influenced by various guidelines such as the British NICE guidelines (39), the Maudsley Prescribing Manual (40), the SASOP treatment guidelines (41), and the tertiary and quaternary EML.

Mental health care services in South Africa

South Africa has endeavoured to scale up mental health care in accordance with SDG 3.8 (2) so as to promote UHC and strengthen mental health care systems (35).

At present, South Africa's health care service delivery is the responsibility of two service providers: state-owned enterprises funded by national health care budgets, and the private sector financed by medical aid schemes and out-of-pocket spending (42). 84% of the population are estimated to be reliant on state-funded health care,

despite only 40% overall health funding provision (35), which serves to highlight the importance of judicious medicine procurement and rational use in the presence of an efficiently managed health care system. An appreciation of the vertical and horizontal relationship of mental health care services (24) may allow a more integrated approach to service delivery, with better use of available resources.

Mental health care services in Gauteng province

Community mental health services (CMHS) have been established in the southern Gauteng region in an endeavour to narrow the treatment gap and meet the service needs of those with mental illness (43), and to promote sustainable, affordable and equitable health care. These facilities have been established at the discretion of individual District Health Directors in affiliation with the University of the Witwatersrand (43,44).

Mental health care in Gauteng is provided at all recommended WHO levels (Figure 1.1.) with clearly defined routes of referral (44). PHC is provided by primary care practitioners, with limited CMHS offering ambulatory care to people with psychiatric disorders from PHC clinics, although these are staffed by specialist mental health professionals. Provision for medications prescribed at these CHMSs are provided for in the EML. Some district and regional hospitals have psychiatric wards and are mostly staffed by medical officers. Subsequent referral proceeds to acute psychiatric units in general hospitals (tertiary and university-linked central academic hospitals), with three stand-alone psychiatric hospitals at the top tier. Specialist psychiatric hospitals function independently of general hospital psychiatric units, which are grouped under ‘Hospital Services’ management (personal communication from the Directorate of Pharmaceutical services). Service usage is monitored as part of district health information systems (DHIS) data and expenses overseen by the individual districts (45).

Motivation for the study

Notwithstanding the 20-year history of an EML process in South Africa, there is a paucity of pharmaco-epidemiological analysis. To inform this study, a PubMed search was performed on 11/01/2018 to identify South African research on psychotropic

prescribing patterns. The terms “psychotropic prescribing”; “psychotropic”; “drug register”; “pharmacy database” AND “mental illness” AND “Africa” were used, with no restrictions. No public-sector studies of a district or provincial database analysis were found. Nevertheless, the National Mental Health and Policy Framework and Strategic Plan (NMHPF) recommends provision of essential medicines as well as continual monitoring and evaluation of medicine usage as part of quality improvement (5,10).

In Gauteng, while there is no patient-linked data, pharmaceutical procurement and expenditure is captured by the Medical Supplies Depot in the MEDSAS database, which provides a record of all medications procured by public health sector facilities in the province. Facility headcounts and patient day equivalents may be used to monitor service utilisation. This data is captured in the DHIS database. Data is captured at each facility site, either through tick registers or electronically. By combining the data from the MEDSAS and DHIS databases, it is possible to evaluate medicine procurement and expenditure in terms of the population served by the relevant facilities. Although this is not a direct indication of utilisation, it does create an understanding of procurement patterns and serves as a useful baseline for further analysis. This may also provide insight into the type of disorders being treated.

Aim and Objectives

The aim of this study was to investigate the patterns of procurement of and expenditure on medicines for MNS disorders (as per the ATC classification) in Gauteng province for the 2017/18 financial year across the service levels at different facilities.

The study objectives were:

1. To evaluate the proportion of provincial medication expenditure on medicines for MNS disorders.
2. To describe the profile of medicines procured by the province for MNS disorders and their relative costs both according to their ATC classification and considering their EML status.
3. To compare procurement (in DDD/1000 population served) and expenditure (in cost/1000 population served) between institutions within each service level.
4. To make recommendations for further research.

Hypothesis

It was hypothesised that there would be no significant differences in prescribing patterns between the institutions within each service level. The reason for this assumption is that prescribing practice in the public health care sector in South Africa is governed by the EML and STGs. As the facilities are all managing similar conditions within their respective service level, the medications used should be similar.

Chapter 2 : METHODS

Study Design

A secondary analysis of the Gauteng Pharmaceutical database for the 2017/2018 financial year was conducted. The study parameters are described according to the Reporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement (46).

Study Setting

The five districts into which Gauteng province is divided (Ekurhuleni, City of Johannesburg, Sedibeng, Tshwane and West Rand) constituted the setting for this study. The total population of Gauteng at the last national census, conducted in 2011, was 12 272 263 (45). The facilities per district and service level are presented in Table 2.1. 'District clinics' represent PHC and specialist level CMHS. Medications at this level are ordered from a central regional pharmacy depot.

Table 2.1: Gauteng facilities per district and service level

District	Level of Care	Institution
City of Johannesburg	District Clinic	• COJ Regional Pharmacy
	District Hospital	• Bheki Mlangeni Hospital • South Rand Hospital
	Regional Hospital	• Edenvale Hospital • Rahima Moosa Mother and Child Hospital
	Tertiary Hospital	• Helen Joseph Hospital
	Central Hospital	• Charlotte Maxeke Johannesburg Academic Hospital • Chris Hani Baragwanath Academic Hospital
	Specialised Hospital	• Tara H. Moross Centre (Psychiatric) • Sizwe Hospital (MDR TB)
Ekurhuleni	District Clinic	• Ekurhuleni Regional Pharmacy
	District Hospital	• Bertha Gxowa Hospital
	Regional Hospital	• Far East Rand Hospital • Pholosong Hospital • Tambo Memorial Hospital • Thelle Mogoerane Hospital
	Tertiary Hospital	• Tembisa Hospital
Sedibeng	District Clinic	• Sedibeng Regional Pharmacy
	District Hospital	• Kopanong Hospital • Heidelberg Hospital
	Regional Hospital	• Sebokeng Hospital
Tshwane	District Clinic	• Tshwane Regional Pharmacy
	District Hospital	• Tshwane District Hospital • Pretoria West Hospital • Jubilee Hospital • Odi Hospital • Bronkhorstspruit Hospital
	Regional Hospital	• Mamelodi Hospital
	Tertiary Hospital	• Kalafong Hospital
	Central Hospital	• Dr George Mukhari Academic Hospital • Steve Biko Academic Hospital
	Specialised Hospital	• Weskoppies Hospital (Psychiatric) • Tshwane Rehabilitation Centre (Physical disabilities) • Cullinan Care Centre Hospital (Intellectual disabilities)
West Rand	District Clinic	• West Rand Regional Pharmacy
	District Hospital	• Carletonville Hospital • Dr Yusuf Dadoo Hospital
	Regional Hospital	• Leratong Hospital
	Specialised Hospital	• Sterkfontein Hospital (Psychiatric)

COJ = City of Johannesburg; MDR TB = multi-drug-resistant tuberculosis

Study Population

The study population comprised medicines used for MNS disorders in the ATC classes N03 to N07 in Gauteng province for the year 2017/18. Figure 2.1 illustrates the three levels of source information, according to the RECORD Statement (46). The source population is representative of where the database population is derived from and is the population for which the study makes inferences. This information was obtained from the 2011 Gauteng census (45). The database population is a subgroup of the source population. For this study, the database population included total medicine procurement and expenditure in the province for the 2017/2018 financial year as captured by the MEDSAS database. The study population was then derived from the database population using codes and algorithms and included medicines for MNS disorders.

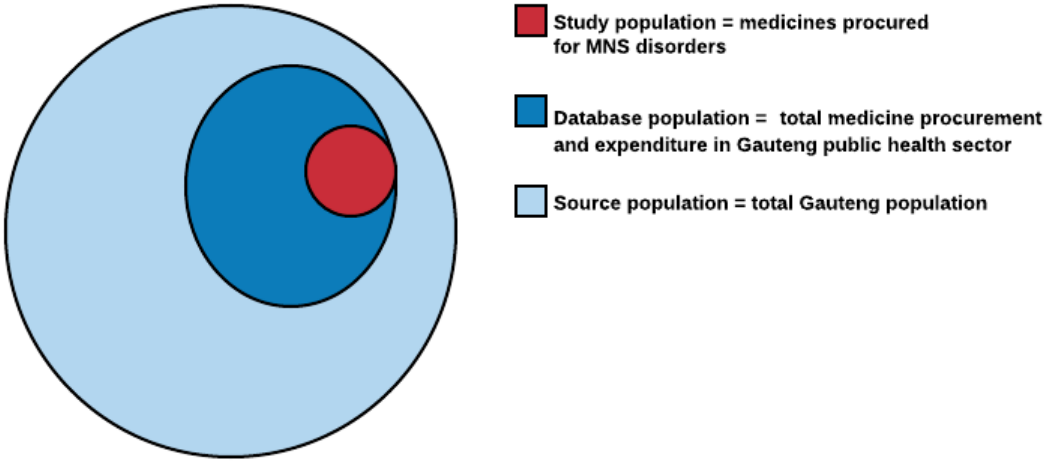

Figure 2.1: Population hierarchy for medicine procurement and expenditure (adapted from Fig 1 in RECORD 2015)
(46) (open access with reproduction in any medium permitted)

Inclusion criteria

To be included in the study population, the medicine had to be used in the treatment of MNS disorders (ATC classes N03 to N07) and procured by Gauteng for the public health care sector. Medications included in this study were grouped according to the third ATC classification level. The groupings are as follows:

Table 2.2: ATC 3rd level classification and description

ATC 3rd Level	Description
N03A	Anti-epileptics
N04A	Anticholinergics
N04B	Dopaminergics
N05A	Antipsychotics
N05B	Anxiolytics
N05C	Hypnotics and Sedatives
N06A	Antidepressants
N06B	Psychostimulants
N07B	Drugs used in Addictive Disorders

Exclusion criteria

Medicines procured on behalf of contracted care (e.g. Life Healthcare Esidimeni) were excluded, as were medicines belonging to the N class used for anaesthetic (N01), analgesic (N02) or specialised neurological services. This included specific third-level groupings of medicines related to the above ATC classes, such as N06C (psycholeptics and psychoanaleptics in combination), N06D (anti-dementia drugs), N07A (parasympathomimetics), N07C (antivertigo preparations), and N07X (other nervous system drugs).

Data Collected

Data collected from the MEDSAS database for each medicine comprised the item description, medicine strength, pack size, unit (e.g. tablet, capsule, vial), cost, and quantity procured by Gauteng facilities.

The DDD for each medicine was obtained from the WHO Collaborating Centre for Drug Statistics Methodology website (47) website and the EML status from the NDOH STGs (48).

The DHIS database was used for the population served by each district and institution. This data was available to the Directorate of Pharmaceutical Services and provided by one of the research supervisors, Mrs S. Govender. As there was no data specific to mental health care service utilisation, the data collected from the DHIS database consisted of total headcounts for PHC facilities and patient day equivalents (PDEs) for hospitals (these will jointly be referred to as “headcounts”).

In order to evaluate the procurement of medicines for MNS disorders in the context of total medicine procurement, an analysis presented in the Gauteng Provincial Pharmacy and Therapeutics Committee (GPPTC) report (49), which is in the public domain on request from the Gauteng Directorate of Pharmaceutical Services, was used. This report was used to accommodate restrictions in the range of data for which permission was granted (see note under ethical considerations).

Data Preparation/Cleaning

With the assistance of Mrs Govender, all data from the MEDSAS and DHIS databases was cleaned to ensure that the figures were summed correctly, with duplicates removed and data arranged according to health care facility, service level, and district. A new data sheet was created in Microsoft Excel™ with data extrapolated by vertical lookups. This included all facilities and their headcounts, as well as procurement data organised according to ATC classification, EML status, unit costs and DDD values.

Data Analysis

To compare the patterns of use across the different service levels and institutions, the procured DDD/1000 population served and cost/1000 population served were calculated.

In order to calculate the DDD/1000 population served, the DDD/pack of medicine was first calculated by dividing the product of the tablet or capsule strength and the pack size by the DDD value:

1. DDD/pack = (tablet strength x pack size)/DDD value

This value was then multiplied by the quantity of packs procured to obtain the total DDD issued:

2. DDD issued = DDD/pack x quantity procured

Lastly, the DDD issued was divided by the total population served according to the calculated headcounts from the DHIS database and multiplied by 1000 to obtain the DDD/1000:

3. DDD/1000 = (DDD issued/headcount) x 1000

Calculating all medications in terms of their DDD/1000 allowed for all like medications of the same preparation to be added together (e.g. all risperidone tablets could be added together, and all risperidone syrups could be added together, regardless of strength or pack size).

Total cost was obtained from the raw data. In order to calculate the cost/1000 population served, the total cost was divided by the total population served according to the DHIS database. This value was then multiplied by 1000:

1. Cost/1000 = (Total cost/headcount) x 1000

A custom program was written in the Go Programming Language® to process and aggregate the raw data. This allowed for the generation of tables and graphs of the DDD/1000 and cost/1000, in accordance with the study objectives.

Descriptive statistics were used to analyse the total DDD, cost/1000 and DDD/1000 per medicine, service level and facility.

Statistical analyses were conducted using R software (50). Tests were two-tailed probability values, and statistical significance accepted when $\alpha \leq 0.05$. Chi-squared (χ^2) contingency tables were used to analyse consistency in the procurement of each medication by the different service levels and institutions in terms of the DDD/1000 and the cost/1000 population served. Since the values generated were large and introduced error in the chi-squared calculation, the data was converted to percentages of the DDD/1000 and cost/1000 scores. The use of percentages was possible since the variables were scaled and independently generated at each service level and district.

Ethical Considerations

The protocol for this study was approved unconditionally by the Human Research Ethics Committee at the University of the Witwatersrand (protocol number M180612) (Appendix A).

Permission to conduct the research utilising DHIS and MEDSAS data was also granted by the Gauteng Deputy Director of the Research and Epidemiology Directorate, Dr Bridget Ikalafeng (Appendix B). As permission to conduct the research did not include analysis of the ATC classes other than the N class, the relative expenditure on medicines for MNS disorders was extracted from the GPPTC report (49).

Chapter 3 : RESULTS

MNS Medication Expenditure

R3 551 613 657.22 was spent on total medication procurement in Gauteng province for the 2017/2018 year. Of this, R132 323 280.26 was spent on the study population (those medicines which met the inclusion criteria). This represented 3.73% of total provincial procurement expenditure.

The GPPTC Report (49) published the breakdown of the relative proportion of medicine expenditure per ATC class in Gauteng from January 2017 to March 2018 (Table 3.1). Although this represents a longer period than that covered by the study, it should not affect the relative proportion of expenditure. According to the GPPTC report, 6% of the total health expenditure amount was spent on ATC Class N, comprising all nervous system medications, including medicines used for anaesthesia, analgesia and specialised neurological disorders, and contracted mental health care (e.g. Life Healthcare Esidimeni), all of which were excluded from this study.

Table 3.1: Gauteng pharmaceutical expenditure by ATC class from Jan 2017 to Mar 2018

ATC class	Contents	Percentage spend
A	Alimentary tract and metabolism	5%
B	Blood and blood forming organs	7%
C	Cardiovascular system	4%
D	Dermatologicals	2%
G	Genito-urinary system and sex hormones	1%
H	Systemic hormonal preparations, excluding sex hormones and insulin	1%
J	Anti-infectives for systemic use (Anti-virals for systemic use)	65% (68%)
L	Antineoplastic and immunomodulating agents	3%
M	Musculoskeletal system	1%
N	Nervous system	6%
P	Anti-parasitic products, insecticides and repellents	0%
R	Respiratory system	3%
S	Sensory organs	1%
V	Various	1%

Source: GPPTC Report, 2018 (49), used with permission.

The bulk of the expenditure (65%) was on anti-infectives for systemic use. Of this, 13% was spent on vaccines and 68% (i.e. 44% of total expenditure) on systemic anti-viral agents, including medicines for the treatment of HIV/AIDS. While spending on

HIV/AIDS should not be compromised, the GPPTC report (49) focuses on efforts to rationalise antimicrobial prescribing, which accounted for 9% of spending on systemic anti-infectives. When considered as a percentage of the total spending over the 15-month period, expenditure on antimicrobials equated to 5.85%, which is very close to the combined spending on anaesthetic, pain, neurological and psychiatric medications (i.e. to spending on the entire N class of medicines).

Medicine Profile and Relative Costs

Table 3.2 summarises the total quantity and cost of medicines procured for MNS disorders according to their ATC classification, with the DDD/1000 and cost/1000 headcount of each of these illustrated in Figure 3.1. Of the medicines procured, 73.43% of the total expenditure was on EML medicines, 18.65% on non-EML and 7.92% on TQ-EML medicines.

Class N03A (antiepileptic medicines) accounted for almost half (47.49%) of the total expenditure, amounting to R62 837 005.12. More than half of this (R36 694 548.87) was spent on sodium valproate and valproic acid tablets, injections, and syrup, with over 8 million DDDs procured. Although sodium valproate and valproic acid had the highest cost/1000 headcount served, this was not markedly greater than the DDD/1000 (Figure 3.2). This reflects high procurement quantities at moderate cost.
Anticholinergics (the N04A group), used primarily for the management of neuroleptic-induced parkinsonism, constituted 3.6% of the total expenditure. Although a low cost/DDD, over 2 million DDDs were procured for the year, suggesting extensive coverage. Dopaminergics (N04B), used to treat Parkinson's disease, accounted for 1.82% of total MNS expenditure, with just over 600 000 DDDs procured by the province.

The N05A group (antipsychotics) was the second biggest cost driver (30.92%) of total expenditure. While their cost/DDD was low (R0.53), over 5 million DDDs of risperidone tablets were procured. Amisulpride tablets, in comparison, had a higher cost/DDD with a smaller DDD/1000 procured. Amisulpride tablets were the most expensive of this group. The low DDD/1000 reflects less population coverage at greater expense. While risperidone has EML status for doctor prescribing at all service levels, amisulpride (on

the TQEML) is only available for specialist prescribing at tertiary academic hospitals and psychiatric institutions.

Oxazepam tablets, probably used in the management of insomnia, were the highest procured DDD/1000 of the N05B (anxiolytic) group. Lorazepam injections had the highest cost/DDD of this group resulting in a high cost/1000 headcount served with a relatively low DDD/1000 procured (Figure 3.1).

Amitriptyline was the most procured of the N06A (antidepressant) group in terms of both DDD/1000 and cost/1000. Its primary indication is not, however, for the treatment of depression, and it is not a first line agent for this disorder. Rather, it is on the EML for doctor prescribing at all service levels for multiple indications, including neuropathic pain, migraine and depression associated with insomnia (48). The high DDD/1000 suggests a high population coverage.

Despite not being on the EML, long-acting methylphenidate hydrochloride capsules, used for the treatment of attention deficit hyperactivity disorder (ADHD), accounted for 3.89% of the total spend on MNS disorders. It was the highest DDD/1000 procured item of the N06B (stimulant) group with the third lowest cost/DDD. This suggests greater coverage of this medication. Caffeine citrate, although not on the EML and not used for MNS conditions in South Africa, is allocated to class N06B as a stimulant, and had the highest cost/DDD of all medicines included in the study.

Methadone was the only N07B medicine procured. It is on the EML for the treatment of opiate withdrawal, but not for opiate substitution therapy.

Table 3.2: Quantity and cost of medicines procured for the treatment of MNS disorders according to their ATC classification in Gauteng for 2017/2018

Medicine (ATC 4th Level)	EML Status	Total Cost	% Spend	DDD Procured	Cost/DDD
		R132 323 280.26			
ATC N03A (Anti-epileptics) in order of expenditure					
Sodium Valproate & Valproic Acid Tabs.	EML	R24 156 389.00	18.26%	7615077.07	R3.17
Sodium Valproate Syrup	EML	R6 844 078.23	5.17%	479800.00	R14.26
Phenytoin Sodium Tabs. & Caps.	EML	R6 540 038.68	4.94%	2977266.67	R2.20
Carbamazepine Tabs.	EML	R5 739 571.68	4.34%	3410840.00	R1.68
Sodium Valproate Inj.	Non-EML	R5 643 972.05	4.27%	14968.27	R377.06
Lamotrigine Tabs.	EML	R3 150 386.50	2.38%	1011125.00	R3.12
Clonazepam Tabs.	EML	R3 048 352.80	2.30%	736888.13	R4.14
Phenytoin Sodium Inj.	EML	R1 908 685.62	1.44%	100425.83	R19.01
Clonazepam Inj.	EML	R1 881 798.00	1.42%	12112.50	R155.36
Pregabalin Caps.	Non-EML	R937 089.02	0.71%	134484.00	R6.97
Levetiracetam Tabs.	Non-EML	R918 934.87	0.69%	170995.00	R5.37
Carbamazepine Syrup	EML	R760 095.00	0.57%	31750.00	R23.94
Gabapentin Caps.	Non-EML	R608 706.09	0.46%	72705.56	R8.37
Topiramate Tabs.	TQEML	R310 680.95	0.23%	104550.00	R2.97
Vigabatrin Tabs.	Non-EML	R126 505.50	0.10%	3750.00	R33.73
Phenobarbitone Tabs.	EML	R81 967.50	0.06%	276722.40	R0.30
Sodium Valproate Crushable Tabs.	EML	R48 037.50	0.04%	4066.67	R11.81
Phenobarbitone Inj.	EML	R43 689.54	0.03%	1408.00	R31.03
Clonazepam Drops	EML	R25 486.72	0.02%	1121.88	R22.72
Ethosuximide Syrup	Non-EML	R24 101.22	0.02%	624.00	R38.62
Carbamazepine CR Tabs.	Non-EML	R22 583.56	0.02%	8496.00	R2.66
Oxcarbazepine Tabs.	Non-EML	R13 783.00	0.01%	750.00	R18.38
Valproic Acid Caps.	EML	R2 072.09	0.00%	366.67	R5.65
ATC N04A (Anticholinergics) in order of expenditure					
Orphenadrine Hydrochloride Tabs.	EML	R4 533 386.35	3.43%	2045820.00	R2.22
Biperiden Hydrochloride Tabs.	EML	R134 801.39	0.10%	32429.60	R4.16
Biperiden Inj.	EML	R62 800.36	0.05%	889.50	R70.60
Trihexyphenidyl (Benzhexol) Hydrochloride Tabs.	Non-EML	R448.29	0.00%	40.00	R11.21
ATC N04B (Dopaminergics) in order of expenditure					
Carbidopa & Levodopa Tabs.	EML	R1 514 433.44	1.14%	432141.67	R3.50
Amantadine Hydrochloride Caps.	Non-EML	R905 962.20	0.68%	171600.00	R5.28
Ropinirole Tabs.	EML	R4 335.12	0.00%	588.00	R7.37
Pramipexole Dihydrochloride Monohydrate Tabs.	EML	R787.10	0.00%	50.00	R15.74
ATC N05A (Antipsychotics) in order of expenditure					
Amisulpride Tabs.	TQEML	R7 167 553.24	5.42%	382563.75	R18.74
Risperidone Syrup	EML	R5 633 746.75	4.26%	167232.00	R33.69
Flupenthixol Decanoate oily Inj.	EML	R3 624 916.92	2.74%	620200.00	R5.84
Zuclopenthixol Decanoate Inj.	EML	R3 142 434.51	2.37%	518166.67	R6.06
Risperidone Tabs.	EML	R2 805 580.78	2.12%	5326764.00	R0.53
Quetiapine Fumarate ER Tabs.	Non-EML	R2 430 210.20	1.84%	269512.50	R9.02
Olanzapine Tabs.	EML	R2 367 881.43	1.79%	1976538.00	R1.20
Clozapine Tabs.	EML	R2 193 767.06	1.66%	565400.00	R3.88
Aripiprazole Tabs.	TQEML	R2 120 999.64	1.60%	60690.00	R34.95
Lithium Carbonate Tabs.	EML	R2 015 009.25	1.52%	2147364.31	R0.94
Risperidone Powder for Inj.	Non-EML	R1 736 241.26	1.31%	33620.37	R51.64
Paliperidone Palmitate PR Inj. Prolonged Release	Non-EML	R1 416 923.04	1.07%	31980.00	R44.31

Haloperidol Tabs. & Caps.	EML	R1 086 513.41	0.82%	1205396.25	R0.90
Haloperidol Inj.	EML	R1 008 591.53	0.76%	28896.25	R34.90
Zuclopenthixol Acetate Inj.	EML	R978 076.54	0.74%	42283.33	R23.13
Chlorpromazine Hydrochloride Tabs.	EML	R581 588.40	0.44%	233060.33	R2.50
Quetiapine Fumarate Tabs.	Non-EML	R238 097.31	0.18%	51937.50	R4.58
Fluphenazine Decanoate Inj.	EML	R180 004.86	0.14%	178250.00	R1.01
Clothiapine Inj.	Non-EML	R78 932.80	0.06%	2047.00	R38.56
Olanzapine Powder for Inj.	Non-EML	R74 962.10	0.06%	510.00	R146.98
Flupenthixol Tabs.	Non-EML	R29 162.98	0.02%	750.00	R38.88
Pimozide Tabs.	Non-EML	R5 123.11	0.00%	212.50	R24.11
ATC N05B (Anxiolytics) in order of expenditure					
Lorazepam Inj.	EML	R1 588 152.16	1.20%	39616.00	R40.09
Oxazepam Tabs.	EML	R634 041.11	0.48%	490380.00	R1.29
Lorazepam Tabs.	EML	R440 633.01	0.33%	212520.00	R2.07
Diazepam Tabs.	EML	R191 178.00	0.14%	167700.00	R1.14
Buspirone Hydrochloride Tabs.	Non-EML	R189 954.21	0.14%	30320.00	R6.26
Clobazam Tabs.	Non-EML	R182 146.00	0.14%	35000.00	R5.20
Diazepam Inj.	EML	R58 005.13	0.04%	25160.00	R2.31
Alprazolam Tabs.	TQEML	R10 088.88	0.01%	16200.00	R0.62
Hydroxyzine Dihydrochloride Inj.	Non-EML	R1 586.88	0.00%	400.00	R3.97
ATC N05C (Hypnotics & Sedatives) in order of expenditure					
Midazolam Inj.	EML	R763 146.22	0.58%	123214.33	R6.19
Midazolam (As Maleate) Tabs.	EML	R896.00	0.00%	160.00	R5.60
ATC N06A (Antidepressants) in order of expenditure					
Amitriptyline Hydrochloride Tabs.	EML	R3 255 345.24	2.46%	5619584.00	R0.58
Citalopram Hydrobromide Tabs.	EML	R1 280 575.58	0.97%	4972590.00	R0.26
Fluoxetine Caps.	EML	R1 026 602.20	0.78%	4906548.00	R0.21
Venlafaxine Hydrochloride Caps.	TQEML	R849 670.85	0.64%	539347.50	R1.58
Trazodone Caps.	Non-EML	R541 320.57	0.41%	25333.33	R21.37
Sertraline Hydrochloride Tabs. & Caps.	Non-EML	R267 076.80	0.20%	91510.00	R2.92
Mianserin Hydrochloride Tabs.	Non-EML	R252 890.19	0.19%	39970.00	R6.33
Clomipramine Hydrochloride Tabs.	Non-EML	R230 000.00	0.17%	28750.00	R8.00
Duloxetine Caps.	Non-EML	R110 242.80	0.08%	23002.00	R4.79
Mirtazapine Tabs.	Non-EML	R53 858.52	0.04%	6240.00	R8.63
Bupropion Hydrochloride Tabs.	TQEML	R20 399.00	0.02%	1500.00	R13.60
Imipramine Hydrochloride Tabs.	Non-EML	R2 960.50	0.00%	600.00	R4.93
ATC N06B (Psychostimulants) in order of expenditure					
Methylphenidate Hydrochloride LA Caps.	Non-EML	R5 143 839.43	3.89%	916700.00	R5.61
Caffeine Citrate Inj.	Non-EML	R2 095 579.20	1.58%	156.00	R13 433.20
Methylphenidate Hydrochloride Tabs.	EML	R1 810 446.46	1.37%	725090.00	R2.50
Methylphenidate Hydrochloride ER Tabs.	Non-EML	R243 365.40	0.18%	14256.00	R17.07
Atomoxetine Hydrochloride Caps.	Non-EML	R150 474.60	0.11%	1417.50	R106.15
Caffeine Powder	Non-EML	R570.00	0.00%	2500.00	R0.23
ATC N07B (Drugs used in Addictive Disorders) in order of expenditure					
Methadone Hydrochloride Syrup	EML	R17 958.83	0.01%	1009.60	R17.79

ATC = Anatomical, therapeutic and chemical class; EML= essential medicines list; NEML = non-EML; TQEML = tertiary and quaternary EML; DDD = defined daily dose; Tabs = tablets; Caps = capsules; Inj. = injection; LA = long acting; ER = extended release

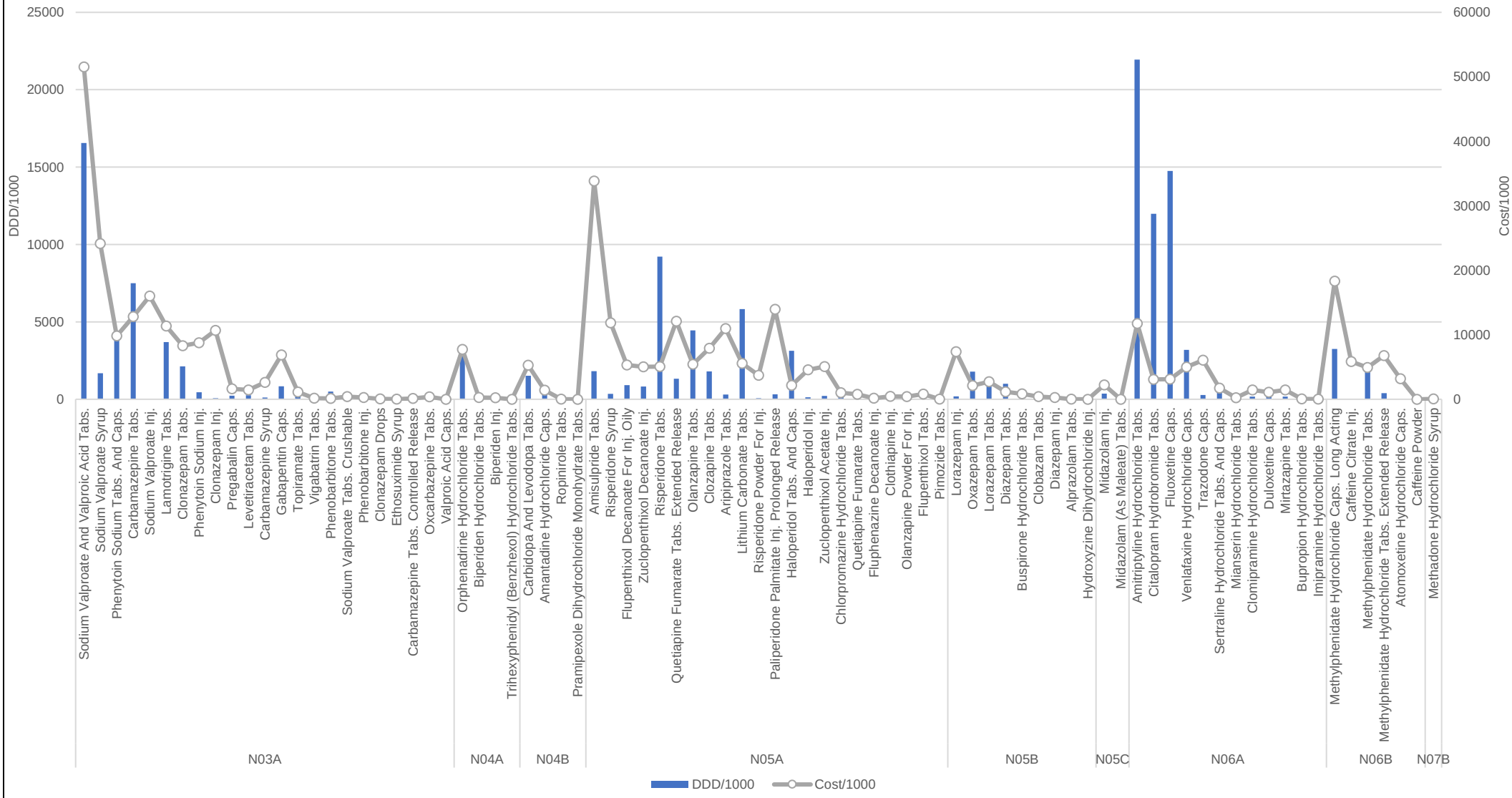

Figure 3.1: DDD/1000 and cost/1000 of medicines procured for MNS disorders in Gauteng for 2017/2018

Procurement Patterns across the Districts and Service Levels

The total costs and DDDs of medicines for MNS disorders procured by general health care facilities in each district are presented in Table 3.3. General facilities spent 89.7% of their total expenditure on medicines, which accounted for 93.7% of the overall DDDs procured (Table 3.3). Specialised hospitals procured 6.3% of the total DDD, spending 10.3% of the total medicine expenditure amount (Table 3.4). Results of the chi-square consistency test for each service level within each district are also presented in Table 3.3. Whilst COJ served the largest population and recorded the greatest headcount overall, the chi-square test revealed no significant differences between the districts in total headcount in relation to the district general population. There was also no difference in the percentage of the total headcount served at district clinics and district hospitals, but the relative proportions served at regional and at tertiary and central (grouped together in the table) academic hospitals were significantly different. Total procurement costs differed significantly between districts at all service levels. There was no significant discrepancy in DDD issued between the districts at PHC clinic service level, although the proportion of DDD issued at this level was highest in Sedibeng and lowest in Tshwane. In relation to the total population served by each district, including all service levels, Tshwane had the highest cost/1000 and Sedibeng the highest DDD/1000.

Table 3.3: Cost and DDD of medicines issued to general health facilities for the treatment of MNS disorders by Gauteng district, service level and headcount served in 2017/2018

	COJ	Ekurhuleni	Sedibeng	Tshwane	West Rand	χ^2	df	p
District Pop (2011)	4 434 827	3 178 470	916 484	2 921 488	820 995			
HC served	10 049 491	7 148 680	2 161 353	6 255 309	2 195 153			
HC/Total Pop	2.27	2.25	2.36	2.14	2.67	0.07	4	0.999
% HC/DC	75	80	80	70	78	0.93	4	0.920
% HC/DHo	2	2	6	7	6	5.04	4	0.283
% HC/RHo	2	13	14	2	16	**19.91**	**4**	**0.001**
% HC/TCHo	21	5	NA	21	NA	**10.89**	**2**	**0.004**
Total Cost	R46 851 785.12	R22 382 637.15	R9 958 050.96	R31 583 258.63	R7 862 515.56			
TCost%DC	47	60	75	38	61	**14.36**	**4**	**0.006**
TCost%DHo	4	3	14	10	20	**19.69**	**4**	**0.001**
TCost%RHo	4	28	11	5	19	**30.54**	**4**	**<0.001**
TCost%TCHo	45	9	NA	47	NA	**27.17**	**2**	**<0.001**
Total DDD issued	18 816 594.12	10 656 682.55	5 077 018.89	11 132 950.65	3 759 226.95			
TDDD%DC	62	73	80	52	60	7.51	4	0.111
TDDD%DHo	3	3	13	15	25	**28.88**	**4**	**<0.001**
TDDD%RHo	3	20	7	4	15	**22.33**	**4**	**<0.001**
TDDD%TCHo	32	4	NA	29	NA	**21.82**	**2**	**<0.001**
Cost/1000 HC	R4 662.11	R3 131.02	R4 607.32	R5 049.03	R3 581.76	**624.09**	**4**	**<0.001**
DDD/1000 HC	1872.39	1490.72	2349.00	1779.76	1712,51	**218.38**	**4**	**<0.001**
Cost/DDD	R2.49	R2.10	R1.96	R2.84	R2.09	0.23	4	0.994

COJ = City of Johannesburg; Pop = population; HC = headcount; DC = district clinics; DHo = district hospitals; RHo = regional hospitals; TCHo = tertiary and central hospitals; T = total; DDD = Defined daily dose.

The specialised hospitals are divided into two groups. The first group comprised rehabilitation centres: Cullinan Rehabilitation Centre (providing long-stay medium care for severe intellectual disability), Tshwane Rehabilitation Hospital (providing physical rehabilitation for chronic injuries and strokes) and Sizwe Tropical Disease Hospital (for treatment of patients with certain infectious diseases). The second group was made up of the three specialised psychiatric hospitals in the province: Sterkfontein Hospital, the Tara H. Moross Centre and Weskoppies Hospital. These facilities all serve the entire Gauteng population. Table 3.4 shows the differences in cost and DDD between the two groups. Although the high cost/1000 and DDD/1000 at specialised psychiatric hospitals are attributable to the fact that the entire headcount is made up of psychiatric patients, the high cost/DDD suggests that the use of more expensive medicines is also a contributing factor.

Table 3.4: Cost and DDD of medicines procured for the treatment of MNS disorders by specialised Gauteng hospitals in 2017/2018

	Specialised Rehabilitation Centres	Specialised Psychiatric Hospitals
Total Population (Census 2011)	12 272 264	12 272 264
Headcount (2017/18)	131 999	504 838
Headcount/Total Population	0.01	0.04
Total Cost	R395 812.95	R13 289 219.89
Total DDD issued	179 173.40	3 132 354.87
Cost/1000	R2 998.61	R26 323.73
DDD/1000	1357.38	6 204.67
Cost/DDD	R2.21	R4.24

DDD = defined daily dose

Figure 3.2 illustrates the DDD/1000 and cost/1000 for each ATC class per service level. For the sake of simplicity, subclasses (e.g. N04A and N04B) were collapsed into a single class (N04). Specialised hospitals included the non-psychiatric hospitals and are shaded grey because of the unique populations served at these institutions. District clinics procured the smallest DDD/1000 for all medicine classes at the least cost/1000, despite serving the majority of the population. Of the general facilities, district hospitals procured the largest DDD/1000 of all medicine classes, with the largest DDD/1000 of the N03 group and N06 group procured overall. N05 medicines were procured at the largest DDD/1000 and at the highest cost/1000 at specialised hospitals. This group largely comprises antipsychotics, suggesting the use of more expensive medicines at higher dosages. Methadone (N07) was procured in the smallest DDD/1000 and at the lowest cost/1000 across all districts at general hospital level. It was not procured at all by district clinics or specialised hospitals.

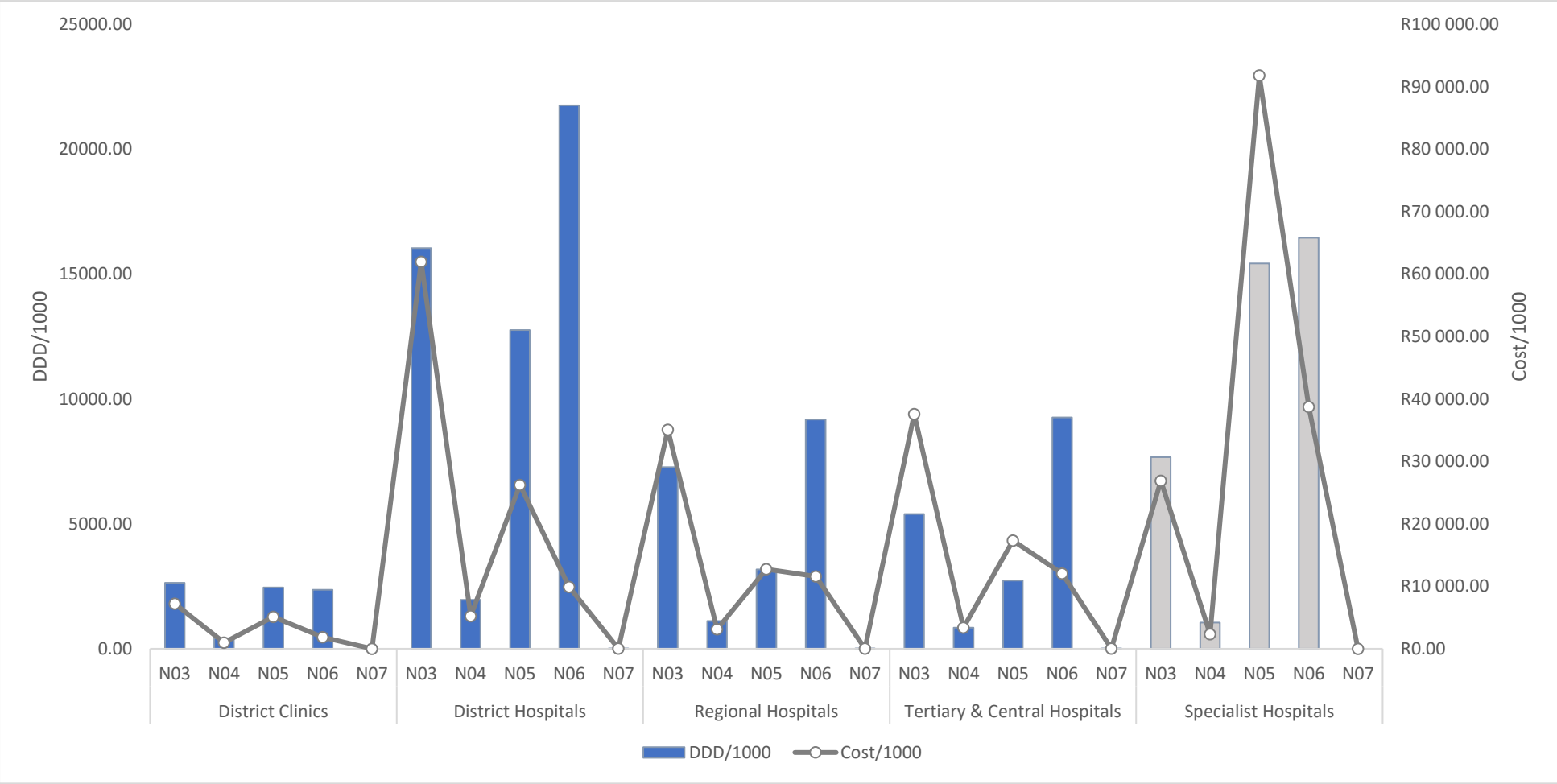

Figure 3.2: DDD/1000 and cost/1000 for medicine classes per service level in Gauteng for 2017/2018

Figures 3.3 to 3.8 illustrate the DDD/1000 and cost/1000 for ATC classes N03A (antiepileptics), N05A (antipsychotics), N05B (anxiolytics), N06A (antidepressants) and N06B (psychostimulants) for the different facilities at each service level. The accompanying outputs for the chi-squared contingency analysis are presented in Table 3.5, where significant findings are indicated in bold. For the sake of simplicity, N04 (anticholinergics and dopaminergics), N05C (midazolam) and N07B (methadone) were not included in this analysis, as they were procured in small quantities. Furthermore, anticholinergics (N04A) and midazolam (N05C) are not specific to mental disorders (48). Figures 3.3 to 3.8 are accompanied by Table 3.5, which presents the outputs of the chi-square contingency testing between districts and service levels.

Figure 3.3 shows trends in the DDD/1000 and cost/1000 of included procured medicines across the district. The differences in DDD/1000 procured were all found to be significant (Table 3.5) except in the case of anxiolytics (N05B) ($p=0.064$) at district clinic level and anxiolytics ($p=0.134$) and psychostimulants (N06B) ($p=0.055$) at tertiary hospital level. The only non-significant difference in cost/1000 related to the procurement of antidepressants (N06A) ($p=0.3$) at district clinic level.

In the case of the district hospitals (Figure 3.4), Tshwane district was found to have procured the highest DDD/1000 and cost/1000 for all medicine classes (N06A in particular). Chi-square testing showed the differences in cost/1000 and DDD/1000 to be statistically significant for all ATC classes at district hospital level. At regional hospital level (Figure 3.5), Ekurhuleni is shown to have procured the highest DDD/1000 of all included classes except psychostimulants (N06B), the latter being procured in the greatest quantity by City of Johannesburg. Differences in DDD/1000 and cost/1000 were statistically significant for all ATC classes.

Figure 3.6 shows the findings relating to DDD/1000 and cost/1000 for tertiary hospitals, with the exclusion of Sedibeng and West Rand, as they do not have tertiary-level facilities. At tertiary level, most of the psychiatric units have at least one specialist psychiatrist overseeing patient management. Chi-square contingency analysis

revealed that while the DDD/1000 of anxiolytics (N05B) procured did not differ significantly between the districts ($p=0.134$), the cost/1000 did ($p<0.001$), with the highest cost/1000 being incurred by City of Johannesburg (R368.96/1000). The procured DDD/1000 of psychostimulants (N06B) did not differ significantly either ($p=0.055$). However, the cost/1000 did ($p<0.001$), with the highest cost/1000 incurred by Ekurhuleni (R1 195.92/1000). City of Johannesburg had the highest expenditure for antiepileptic agents (N03A) and procured the largest DDD/1000 of antidepressants (N06A).

Figure 3.7 shows the procurement of and expenditure on medicines for central hospitals represented per facility within two districts: City of Johannesburg and Tshwane. These each have a designated psychiatric inpatient and outpatient facility overseen by consultant psychiatrists and serve as training facilities for registrars affiliated to major universities in the province. While antiepileptics (N03A) were procured in the highest DDD/1000 for Charlotte Maxeke Johannesburg Academic Hospital, Steve Biko Academic Hospital incurred the highest cost/1000 for this class. Chi-square contingency testing was statistically significant ($p<0.001$) for both the DDD/1000 and cost/1000 for all ATC classes.

Similarities and differences in DDD/1000 and cost/1000 at specialist hospital level are presented in Figure 3.8. As previously mentioned, these facilities serve the entire province, but are located in the City of Johannesburg, Tshwane and West Rand districts. Cullinan Care Centre (a medium-care, long-stay housing facility for intellectually impaired patients) and Tshwane Rehabilitation Hospital (for trauma and stroke rehabilitation, amongst others) were included, as data analysis showed these facilities to be procuring considerable quantities of medications relevant to this study. Sizwe Tropical Diseases Hospital was excluded, as it is concerned primarily with the treatment of drug-resistant tuberculosis. The Tara H. Moross Centre procured the highest DDD/1000 at the highest cost for each of the included ATC classes. Statistical analysis revealed significant differences ($p<0.001$) in DDD/1000 and cost/1000 procured for each ATC class between facilities.

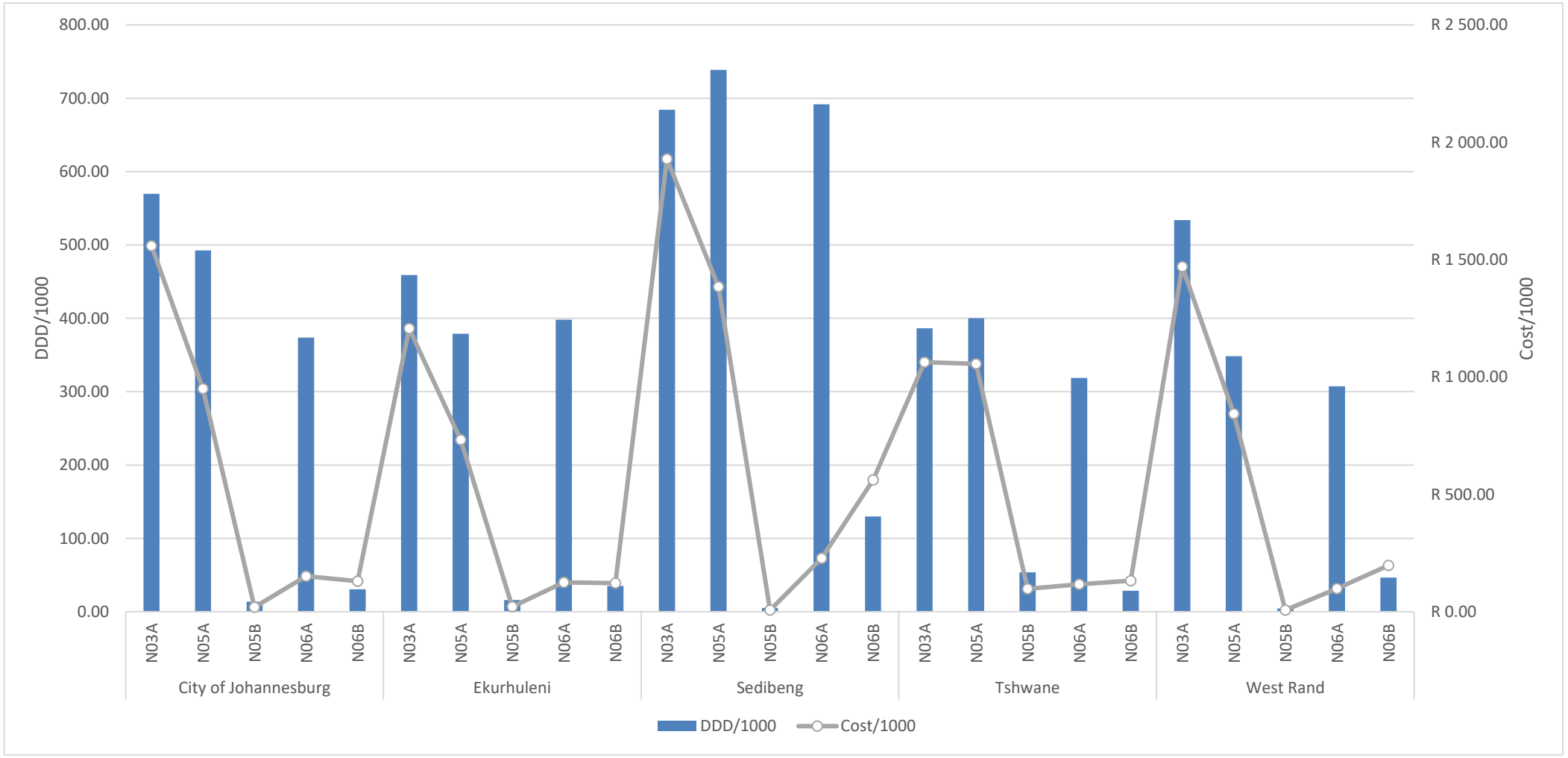

Figure 3.3: DDD/1000 and cost/1000 of medicines procured at district clinic level in Gauteng for 2017/2018

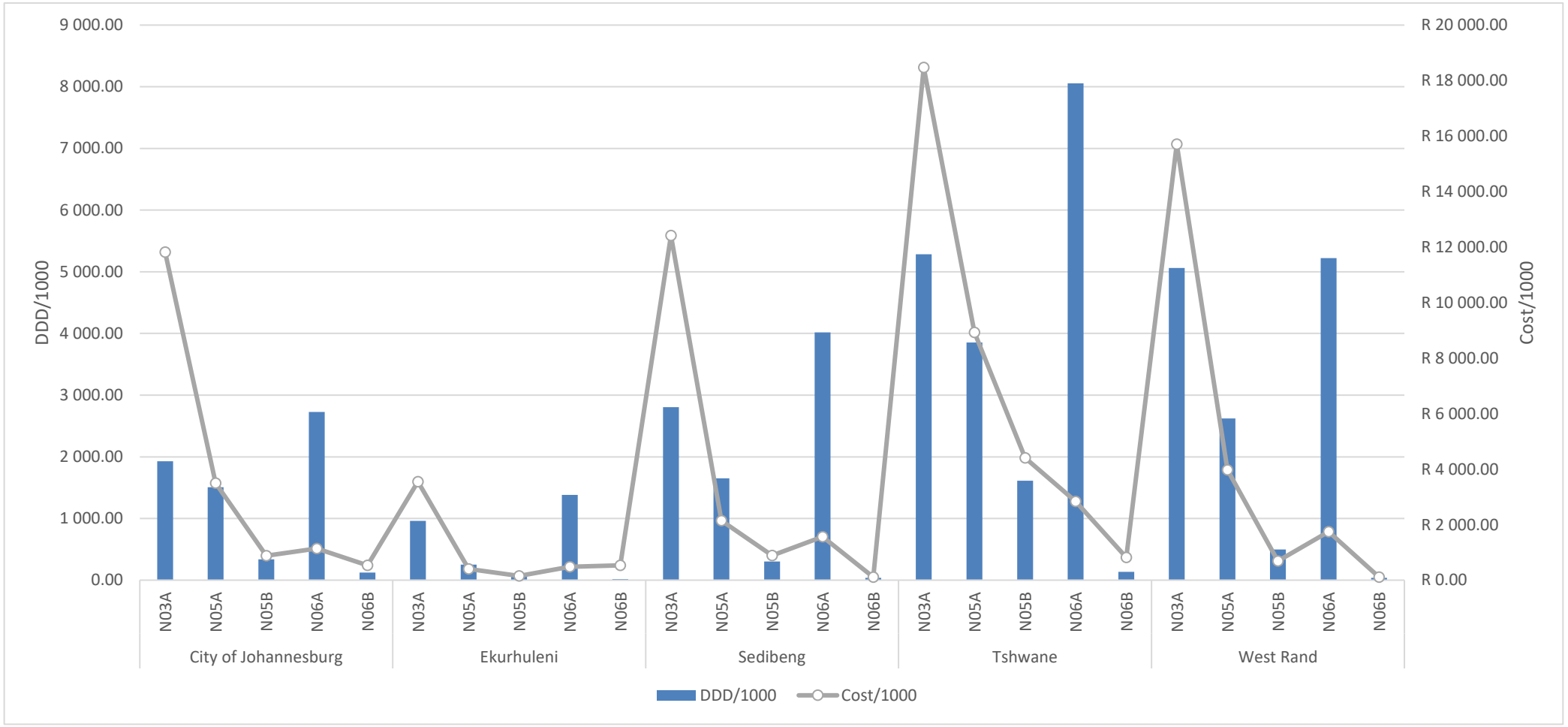

Figure 3.4: DDD/1000 and cost/1000 of medicines procured at district hospital level in Gauteng for 2017/2018

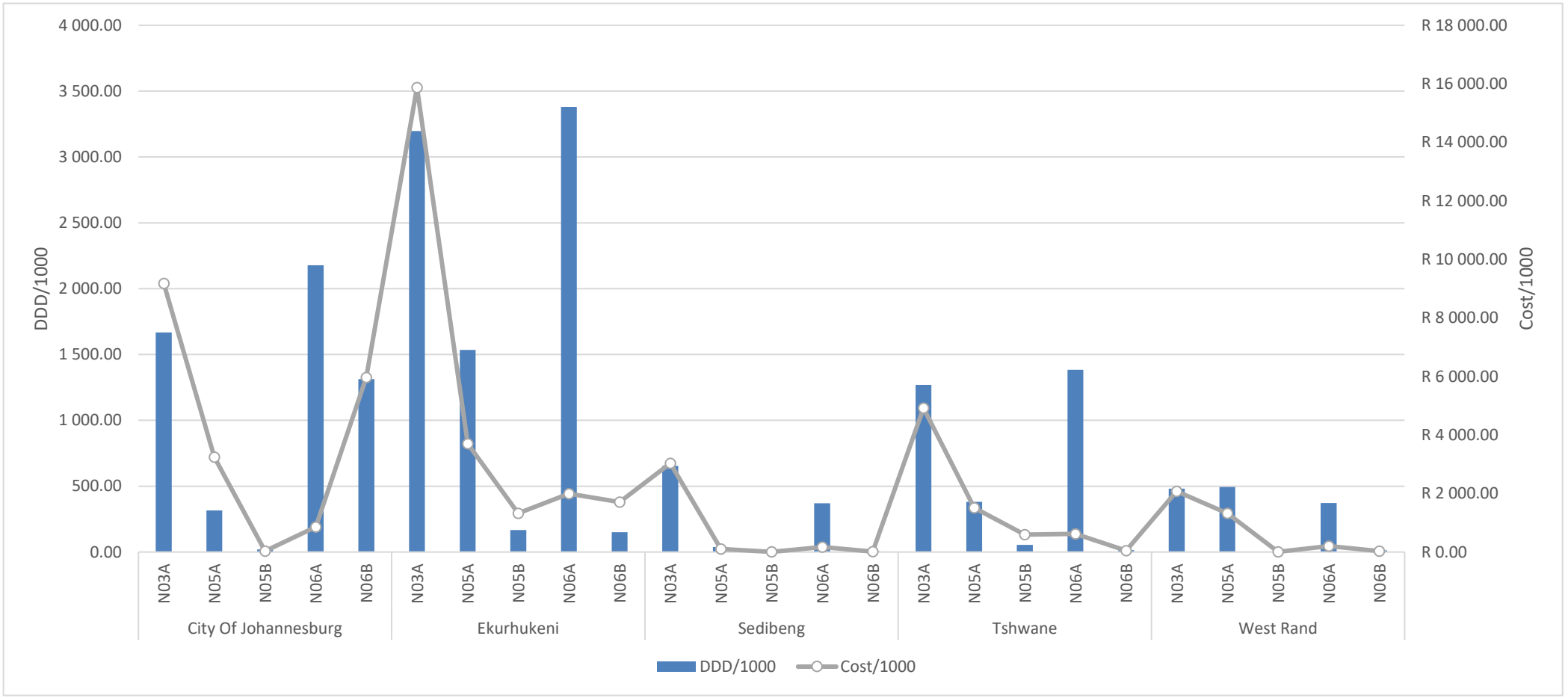

Figure 3.5: DDD/1000 and cost/1000 of medicines procured at regional hospital level in Gauteng for 2017/2018

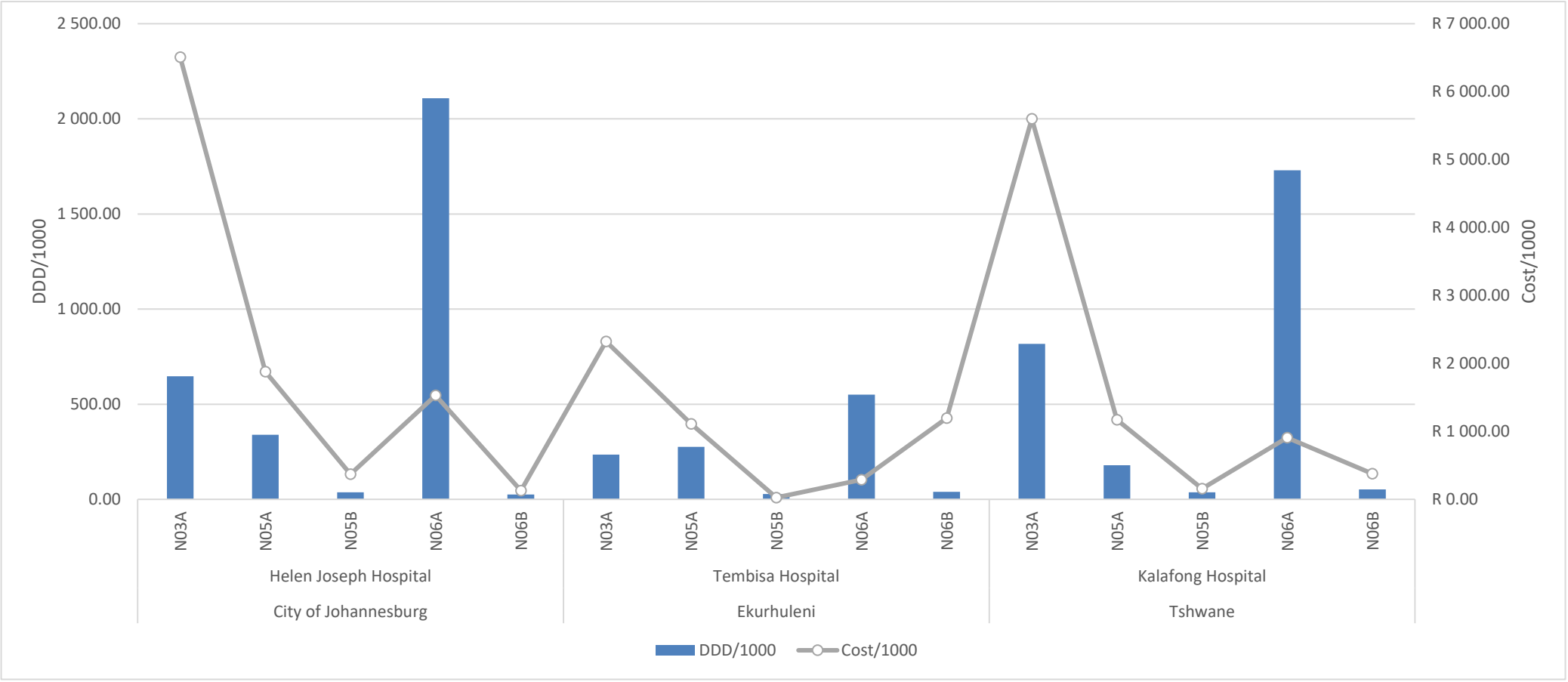

Figure 3.6: DDD/1000 and cost/1000 of medicines procured at tertiary hospital level in Gauteng for 2017/2018

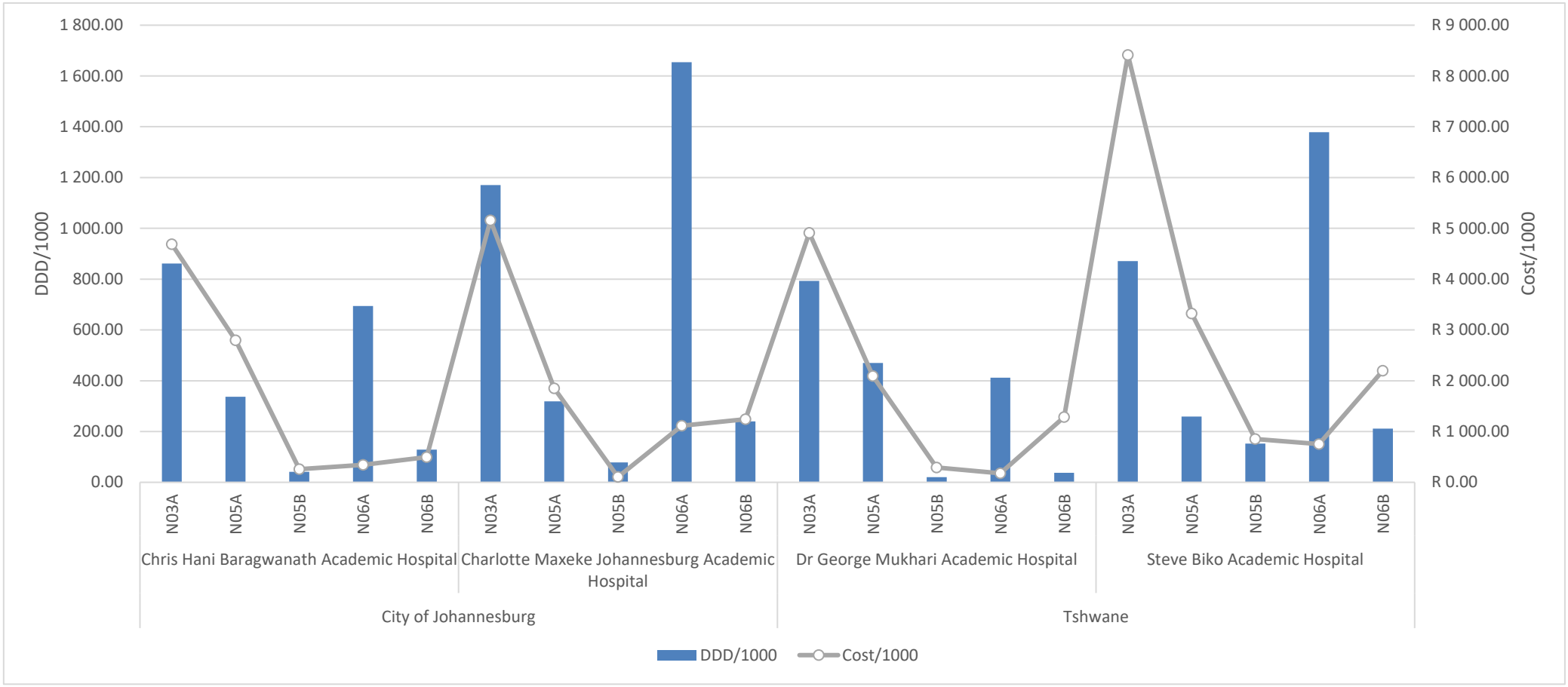

Figure 3.7: DDD/1000 and cost/1000 of medicines procured at central hospital level in Gauteng for 2017/2018

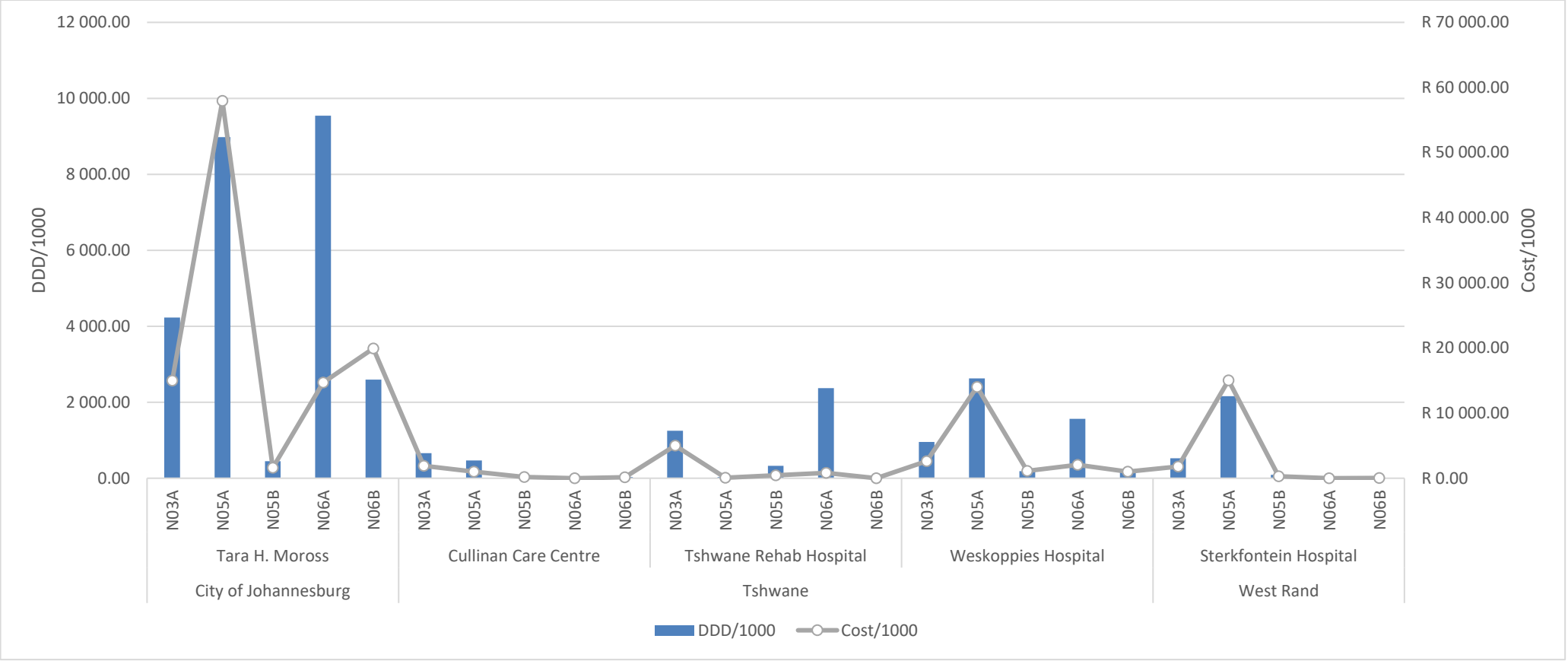

Figure 3.8: DDD/1000 and cost/1000 of medicines procured at specialist hospital level in Gauteng for 2017/2018

Table 3.5: Statistical output of the DDD/1000 and cost/1000 of ATC classes at each service level across Gauteng province in 2017/2018 (Significant outcomes are indicated in bold.)

		DDD/1000			Cost/1000		
Service Level	**ATC class**	**χ^2**	**df**	**p**	**χ^2**	**Df**	**p**
District Clinic (Figure 3.3)	N03A	**51.21**	**4**	**<0.001**	**31.18**	**4**	**<0.001**
	N05A	**21.34**	**4**	**<0.001**	**25.13**	**4**	**<0.001**
	N05B	8.89	4	0.064	**19.15**	**4**	**<0.001**
	N06A	**23.76**	**4**	**<0.001**	7.1	4	0.13
	N06B	**13.57**	**4**	**0.009**	**62.09**	**4**	**<0.001**
District Hospital (Figure 3.4)	N03A	**455.16**	**4**	**<0.001**	**1020.31**	**4**	**<0.001**
	N05A	**366.28**	**4**	**<0.001**	**1075.28**	**4**	**<0.001**
	N05B	**253.94**	**4**	**<0.001**	**829.61**	**4**	**<0.001**
	N06A	**607.73**	**4**	**<0.001**	**193**	**4**	**<0.001**
	N06B	**16.43**	**4**	**0.003**	**89.91**	**4**	**<0.001**
Regional Hospital (Figure 3.5)	N03A	**323.8**	**4**	**<0.001**	**1822.68**	**4**	**<0.001**
	N05A	**238.47**	**4**	**<0.001**	**441.76**	**4**	**<0.001**
	N05B	**38.25**	**4**	**<0.001**	**341.06**	**4**	**<0.001**
	N06A	**426.12**	**4**	**<0.001**	**288.06**	**4**	**<0.001**
	N06B	**435.34**	**4**	**<0.001**	**1702.88**	**4**	**<0.001**
Tertiary Hospital (Figure 3.6)	N03A	**165.9**	**4**	**<0.001**	**1297.75**	**4**	**<0.001**
	N05A	**61.2**	**4**	**<0.001**	**321.24**	**4**	**<0.001**
	N05B	7.04	4	0.134	**91.14**	**4**	**<0.001**
	N06A	**442.8**	**4**	**<0.001**	**322.68**	**4**	**<0.001**
	N06B	9.25	4	0.055	**296.92**	**4**	**<0.001**
Central Hospital (Figure 3.7)	N03A	**563.51**	**4**	**<0.001**	**3606.19**	**4**	**<0.001**
	N05A	**208.69**	**4**	**<0.001**	**1523.53**	**4**	**<0.001**
	N05B	**46.22**	**4**	**<0.001**	**328.03**	**4**	**<0.001**
	N06A	**639.62**	**4**	**<0.001**	**387.64**	**4**	**<0.001**
	N06B	**98.33**	**4**	**<0.001**	**928.29**	**4**	**<0.001**
Specialised Hospital (Figure 3.8)	N03A	**968.98**	**4**	**<0.001**	**3423.76**	**4**	**<0.001**
	N05A	**1905.6**	**4**	**<0.001**	**12836.02**	**4**	**<0.001**
	N05B	**131.04**	**4**	**<0.001**	**415.4**	**4**	**<0.001**
	N06A	**2579.26**	**4**	**<0.001**	**4604.9**	**4**	**<0.001**
	N06B	**929.23**	**4**	**<0.001**	**7327.5**	**4**	**<0.001**

Chapter 4 : DISCUSSION

This analysis of the Gauteng pharmaceutical database indicated that R132 323 280.26 (3.73% of the total provincial medicine expenditure) was spent by the Gauteng Department of Health on medicines procured for the treatment of MNS disorders in the 2017/2018 financial year. Anti-epileptic medicines (N03A) accounted for almost half (47.5%) and antipsychotics (N05A) for nearly a third (31%) of this expenditure. Over 90% of the total cost and DDD issued for MNS disorders was associated with general health care clinics and hospitals. The distribution of spending within Gauteng, however, was found to be inconsistent among the districts across each service level, suggesting different patient populations and possibly different approaches to treatment at various sites.

Proportion of Spending on Medicines for MNS Disorders

Information such as mental health coverage and treatment outcomes would be needed in order to comment accurately on whether spending 3.73% of the pharmaceutical budget is appropriate. While most LMICs spend less than 1 to 2% of their national budgets on mental health care (7,19,51), South Africa appears to be spending more. In Gauteng 6.2% of the total 2016/2017 health expenditure was devoted to mental health care services (excluding non-governmental organisation subsidies), which constitutes the second highest provincial MHC spending (35). Although the 6.2% of total provincial health expenditure and the 3.73% of medicine expenditure are not directly comparable, these figures suggest that the bulk of expenditure is on inpatient care and personnel costs, including those relating to allied health professionals.

When compared with other classes, the proportion of spending on MNS disorders is similar to that on alimentary tract and metabolism (5%), cardiovascular (4%), and respiratory (3%) disorders. Spending on musculoskeletal conditions appears low (1%), but this may be accounted for by the inclusion of analgesics in the N group.

The enormous burden of disease due to HIV/AIDS is apparent in the high proportion of spending on anti-virals for systemic use (44%). Table 1.1 shows that HIV was solely responsible for the most years lived with disability (YLD), disability adjusted life years (DALYs) and years of life lost (YLL) for South Africa in 2015 (36–38). While the need

to combat HIV/AIDS as aggressively as possible may preclude increased spending on mental health care coverage, the complex relationship between HIV and MNS disorders does need to be considered (5), as mental illness and HIV are highly comorbid and mutually reinforcing (51–53): up to 35% and 21% of patients with HIV are thought to have comorbid depression or anxiety respectively (51). Regarding depression, treatment improves the depressive symptoms and may improve anti-retroviral adherence and reduce HIV transmission (54,55). Treatment adherence and lifestyle outcomes are worse in HIV-infected individuals (56): in China, a population survey by Chen et al. (53) revealed a 3.6-fold increased risk of contracting HIV and 2.3-fold increased risk of syphilis among people with bipolar disorder compared with the general population. This implies that the treatment of bipolar disorder may be of benefit in the prevention of sexually transmitted infections.

Closing the treatment gap

Considering an estimated treatment gap of 75% identified by the SASH study (57), and the more recent estimated treatment gap of 91% revealed by the costing analysis conducted by Docrat et al. (35) it is likely that increased procurement is required in order to improve mental health coverage. However, the spending on HIV/AIDS, as well as competing disease priorities such as cardiovascular and respiratory conditions, limits the available budget for MNS disorders. It is therefore necessary to reduce unnecessary expenditure. For example, the sole indication for the use of anticholinergics in mental health care is for the treatment of antipsychotic-induced side effects. Rather than adding an anticholinergic agent to treat these effects, alternative options such as reducing doses when side effects emerge or switching to an agent with less propensity for side effects may be considered, and routine prescribing of anticholinergics with first-generation or intramuscular antipsychotics discouraged. A clear indication for the use of caffeine citrate, which would justify its high cost/DDD, should also be established. Nevertheless, while rational prescribing should be standard practice, it is unlikely that large savings will be achieved solely through this undertaking, and therefore other strategies will be needed if mental health coverage is to improve.

Profile and Relative Proportions of Medicines Procured

Table 3.2 illustrates that almost half of the total spending was on antiepileptic medicines (N03A), followed by spending on antipsychotics (N05A). This is indicative of coverage of more severely disruptive illnesses such as epilepsy, bipolar disorder, and psychosis. While DDD/1000 is assumed to reflect coverage in the context of the district clinics and general hospitals, it may be influenced by the prescribing of high doses in the case of individual patients.

Anti-epileptic medicines (N03A)

Sodium valproate and valproic acid tablets were the biggest single total cost item (R24 156 389) and most procured total DDD item (R24 156 389) (Table 3.2). Despite the high cost/1000 (R51 536.51/1000), it appears that high coverage was attained (high DDD/1000) (Figure 3.1). As sodium valproate is on the EML at all service levels, including PHC nurse prescribing for epilepsy and doctors prescribing for bipolar disorder, the high procurement therefore suggests a high burden of disease due to these conditions, notwithstanding a large treatment gap.

The inclusion of clonazepam in this group may skew the findings of this study, as it is classified as an antiepileptic (N03A), but it is included on the EML for the acute management of aggressive and disruptive behaviour and for severe anxiety. Since clonazepam (all formulations combined) accounted for 3.74% of total expenditure on MNS medicines, careful consideration of the need for it is necessary when prescribing. As with all benzodiazepines, it is dependency forming and not recommended in maintenance treatment of epilepsy or mental illness (48). Apart from the injectable benzodiazepine formulations, it is not known from this study whether benzodiazepines are used predominantly for acute or for chronic care.

Antipsychotics (N05A)

Of the total expenditure on MNS disorders, 31% was accounted for by antipsychotics (N05A). Risperidone was the most procured item in terms of DDD/1000, followed by olanzapine. Although it is expensive, the use of amisulpride may be warranted in that it is beneficial in treating negative symptoms and may be more efficacious than

olanzapine, with fewer metabolic side effects (58,59). Since the study, costs have been reduced (60), and so its ranking may change in subsequent years. Aripiprazole was found to have a high cost/DDD, but its cardiac and weight-limiting benefits (40) may rationalise use in select patient groups. Lithium carbonate, on the EML for the treatment of manic episodes, is included in this group. However, it is not an antipsychotic, but rather the only true mood stabiliser. The absence of a unique ATC classification for lithium carbonate may overrepresent medicine procurement for psychotic disorders, while simultaneously underrepresenting that for bipolar disorders. Regarding lithium carbonate, recent evidence has emerged confirming its anti-suicidal effects along with other beneficial properties in the treatment of bipolar disorders (61,62). The prescribing of lithium carbonate may therefore rise in the presence of available monitoring. Furthermore, the cognitive side effects and restrictions on prescribing sodium valproate to women of child-bearing age (63) should reduce its prescribing in favour of other mood stabilising agents.

Anxiolytics (N05B)

Lorazepam injection, used mainly for acute sedation, has a cost/DDD six times that of other N05B medicines, causing a high cost/1000 with limited coverage. Judicious use of lorazepam injection could be achieved by better management of aggressive patients through behavioural modification and providing a containing environment as first-line approaches, while agitation and aggression due to mood or psychotic disorders could be managed by optimising treatment and preventing relapse of the primary disorders. Oral benzodiazepines constituted 1.1% (excluding clonazepam, which is grouped under N03A). Considering their addictive nature, it is possible that frugal and cautious prescribing could reduce spending on this category.

Antidepressants (N06A)

As a group, antidepressants were the most procured medicines in terms of DDD/1000. This is in keeping with the high prevalence of anxiety and depression in South Africa (57). As previously discussed, the multiple indications for amitriptyline hydrochloride limit its validity in inferring the prevalence of depressive disorders by using its high DDD/1000 (21 939.85/1000 population, the second highest DDD/1000 procured

overall) as a reference value. While it is more efficacious than fluoxetine and citalopram for the treatment of depression (64), its side effect profile renders it less tolerable and poses a risk of toxicity in overdose, thereby possibly restricting its use as an antidepressant. Fluoxetine and citalopram have similar costs/DDD and are preferred agents of choice, recommended by STGs. It is unclear from this study whether the high DDD/1000 of amitriptyline procured was due to large dose prescriptions or greater coverage.

Although nine of the twelve types of antidepressants procured did not have EML status, overall, these were procured in small quantities. Of these, trazadone (for the treatment of depression in the presence of severe insomnia) was the most expensive; followed by buproprion hydrochloride (with beneficial effects on sleep and potentially used by some hospitals for smoking cessation). Whether or not such items should be on the EML would depend on evidence of cost-effectiveness and safety relative to the EML medicines. Data regarding local patient outcomes could contribute to such decision-making.

Psychostimulants (N06B)

Although a non-EML item, the use of long-acting methylphenidate hydrochloride tablets for the treatment of ADHD may be justified by promoting better treatment adherence (by simpler dosing schedules) and reduced stigma associated with taking treatment at school. Adequate treatment of ADHD has long-term beneficial outcomes on academic, occupational and social function (65). The high cost/DDD of methylphenidate hydrochloride extended release (Concerta) and atomoxetine hydrochloride capsules warrants further comparative studies with methylphenidate hydrochloride to establish any superior efficacy or tolerability benefits supporting their use. Caffeine citrate injection had the highest cost/DDD of all the medicines procured (R13 433.20/DDD). While it is classified as a psychostimulant (N06BC01), it is not on the EML for mental health disorders. Although it may be used in treatment of migraine headaches and in the management of preterm babies, further evaluation of its procurement is warranted in light of its cost (66,67).

Finally, while classification systems are important for the purposes of medicine consumption studies and quality control (17), broad grouping as is seen in the nervous

system grouping poses particular difficulties. Medicines may be used by different specialities for different indications, and this should be considered when interpreting relative expenditure. Misclassification of medicines may over- or underrepresent the prevalence of some disorders, and the DDD index itself may differ from DDDs used in clinical practice (58). With patient-level data furnishing indications for medicine usage and by assigning separate N groups for certain medicines, better reporting accuracy may be possible.

Procurement and Expenditure Patterns relating to MNS Medicines at the different Service Levels

This study found that 60% of the total DDD procured, which accounted for 45% of the total cost, related to the district clinic level (Table 3.3). This is consistent with the finding by Docrat et al. (2019) (35) that the majority of mental health care was provided at PHC level, and is in line with WHO recommendations (Figure 1.1). Since roughly 33% of DDDs were issued to general hospitals and only 5.9% of the total DDD procured to specialised psychiatric hospitals, findings do suggest that recommended routes of referral are being implemented (4,20,22,25,44). It must be considered, however, that in this study setting, the majority of mental health services are provided for by the CMHS rather than the PHC system, and so integration of mental health care at this level cannot be accurately commented on. Despite it appearing that the bulk of patients are being managed in an outpatient setting and the greatest cost being incurred and procurement occurring at PHC level, Docrat et al (2019) (35) found that the greatest proportion of the health care budget was allocated to the higher service level tiers, highlighting the exorbitant costs of staffing and inpatient management.

Differences in DDD/1000 procured and cost/1000 were identified within most levels (Table 3.5) despite formal STGs in use, which may be a reflection of heterogeneous prescribing habits. Statistically significant differences in the procurement and cost/1000 of medicines may reflect clinician preferences for particular medicines, with higher cost/1000 reflecting the use of more expensive medicines or medicine preparations, for example IM or IV versus oral medicines where the DDD/1000 are not significantly different. Assuming that standard doses of effective medicines are used,

a finding of higher DDD/1000 at a lower cost/1000 would suggest greater coverage, although outcome measures would be necessary to confirm effective medicine use.

The differences and similarities in DDD/1000 and cost/1000 for medicine classes per service level (Figure 3.2) highlight important concerns. First, the lowest DDD/1000 and cost/1000 procured for all classes was noted at district clinic level, despite this level serving the largest population size. Considering the estimated national mental health gap of 91% identified by Docrat et al (2019) (35), this finding suggests either poor recognition of MNS disorders by PHC practitioners or a lack of personnel capacity for treatment rather than a low prevalence of MNS disorders in this population group. Second, the findings relating to DDD/1000 and cost/1000 pertain only to medication expenditure and do not take into account additional costs of care such as occupational therapy or social grants or total inpatient costs. Acknowledging the importance of allied care could reduce high readmission rates (24% within three months of discharge), which constitute 22.2% of the 6.2% of total expenditure. Excluding expenditure at specialist hospitals, district and regional hospitals were found to have the highest medicine expenditure. This could be due either to these facilities being easier to access for acute psychiatric conditions or possibly to the existence of more facilities at these levels with larger treatment capacity. Available infrastructure and staff skill sets could be assessed for ability to manage patient loads at these levels adequately, and until appropriate community care is established, resource allocation at specialist hospitals, although utilising most of the total expenditure, cannot be redirected.

Procurement at district clinic level

Overall, it appears that Sedibeng district achieved the greatest population coverage, indicated by having the highest DDD/1000 procured (Table 3.3), particularly at district clinic level as well (Figure 3.3), where all included ATC classes except anxiolytics (N05B) were procured in the greatest quantity. This is consistent with a finding by Robertson and Szabo (2017) (43) that Sedibeng, having the highest rate of nursing and medical staffing at district clinic level, served a larger percentage of the population. The absence of tertiary, central and specialist level of care in this district may drive greater use of lower-level service delivery.

Procurement at district hospital level

District hospitals procured the highest DDD/1000 of antiepileptics (N03), anticholinergics (N04), and antidepressants (N06) (Figure 3.2). While this may suggest that district hospitals carry a high burden of care, polypharmacy cannot be excluded. Of the district hospitals (Figure 3.4), Tshwane procured the highest DDD/1000 of all medicine classes and had the greatest cost/1000 for N03A medicines. While the district is noted to have the most district hospital facilities (Table 2.1), allowing for greater service delivery capacity, it is possible that Tshwane District Hospital functions more as a regional hospital. This may also be true of Kopanong Hospital in Sedibeng. Therefore, interpretation of the significant differences in DDD/1000 and cost/1000 is difficult, and more needs to be known regarding individual staffing and responsibilities. A large proportion of expenditure on N03A at this level was attributed to the frequent use of intravenous sodium valproate. Better outpatient control of epilepsy could mitigate this spending. Methadone hydrochloride (the only N07B medicine) is on the STG for the medical management of opioid withdrawal. It was found to have been procured mostly at district hospitals, despite being one of the least procured items in DDD/1000 overall, suggesting that some detoxification is taking place at these sites. It is unclear, however, whether it is being prescribed for elective detoxification or for iatrogenic withdrawal. Methadone hydrochloride is not represented graphically. Altogether, findings suggest that this service level either over-utilises medicines, or is responsible for managing a substantial portion of disease burden reflected by high DDD/1000 procured. When considered in the context of the proportion of mental health expenditure found by Docrat et al. (35) at district hospital level, it appears that this level may be under-resourced for the burden of care experienced.

Procurement at regional hospital level

Ekurhuleni regional hospitals procured the greatest DDD/1000 of all included medicines at regional hospital level (Figure 3.5), which may be due in part to the existence of four regional hospitals. While the proportion of headcount served in Sedibeng and West Rand was higher than in other districts (perhaps because these districts do not have tertiary-level care), procurement and expenditure patterns did not reflect this increased patient burden. Rahima Moosa Mother and Child Hospital is one of the regional hospitals in City of Johannesburg. Since it has a designated, specialist-

run child and family psychiatric outpatient unit, this may account for the significant difference in DDD/1000 procured and cost/1000 of psychostimulants (N06B) at this level. Most psychostimulants are indicated for the treatment of ADHD, a common childhood disorder. This unit may also have prescribed larger amounts of antipsychotic medicines (N05A) as adjunctive treatment for behavioural problems rather than psychotic disorders. Further study could be undertaken to look specifically at items procured and indication thereof.

Procurement at tertiary hospital level

City of Johannesburg, Ekurhuleni and Tshwane districts each have one tertiary hospital. As Ekurhuleni lacks central and specialised hospitals, it is possible that regional hospitals in this district function as tertiary-level centres, with fewer up-referrals leading to lower procurement and expenditure (Figure 3.6) at this level. Although Kalafong Hospital (Tshwane) procured a significantly larger DDD/1000 of N03A than Helen Joseph Hospital (COJ), the higher cost/1000 at Helen Joseph Hospital suggests use of higher-cost items.

Procurement at central hospital level

Docrat et al. 2019 (35) found central hospitals to account for 15.8% of the total 2016/2017 expenditure. Such facilities are only available in City of Johannesburg and Tshwane districts (Figure 3.7). COJ central hospitals served a larger PDE than Tshwane (1 802 168 as opposed to 1 046 442) and procured a greater DDD/1000 of antiepileptics (N03A), antidepressants (N06A) and psychostimulants (N06B), although cost/1000 for N03A and N06B was higher in Tshwane, suggesting possible differences in treatment protocols or clinician preference. To justify use, treatment outcomes would need to be measured.

Procurement at specialist hospital level

Significant differences in DDD/1000 and cost/1000 were found for all classes at specialist level (Table 3.5). While Docrat et al. (35) found specialised hospitals to have the highest proportion of expenditure (49%), the finding of total DDD procurement of 6.3% may allude to the costs of hospital staffing and the high cost of hospital

admissions (Table 3.4). Disease profile complexity or treatment resistance could account for this level procuring the highest DDD/1000 at the highest cost/1000 for the N05 group in comparison with other service levels (Figure 3.2). As the PDEs at these facilities were smaller than at the other levels, it can be assumed not only that higher doses of medicines were prescribed, but also that the cost of these was higher. Polypharmacy at this service level could be an additional factor driving procurement and expenditure in the face of small PDEs. Findings of a study at the Tara H. Moross Centre outpatient clinic by Holzapfel and Szabo (2018) (68) showed that more than 90% of patients at the clinic were prescribed three or more medications. These findings were not isolated, but were in keeping with international trends, suggesting that while guidelines are important in approaches to patient care, treatment at this level is ultimately tailored to individual patient needs (29).

The Tara H. Moross Centre in City of Johannesburg was found to have consistently procured the largest DDD/1000 at the greatest cost/1000 of all included medication classes at this level, despite having the smallest PDE of all of the specialised psychiatric facilities (Figure 3.8). It is, however, a highly specialised facility, with a child and adolescent unit, a personality disorder unit, an eating disorders unit and a neuropsychiatric facility. Additionally, the Tara H. Moross Centre has both in- and outpatient services and provides care to private health care patients with limited funds. Nevertheless, these factors should not be assumed to justify the study findings.

Tshwane Rehabilitation Centre was found to procure the second highest DDD/1000 for antidepressants, which is perhaps attributable to the high prevalence of post-stroke depression (69). The low DDD/1000 of antidepressants procured at Sterkfontein Hospital is potentially cause for concern, given that anxiety and depression are highly comorbid with other serious mental illnesses (70,71), SSRIs are used as an adjunct in the treatment of negative schizophrenia (40), as well as recent evidence to suggest that SSRIs are potentially more effective and ethically desirable for the treatment of hypersexuality behaviours (72). The increasing use of atypical antipsychotics with their serotonergic effects may mitigate the need for SSRIs (71).

Finally, differences in trends may be attributed to the heterogeneity of the facilities themselves. Sterkfontein Hospital does not deliver outpatient care except to forensic patients on leave of absence, while Weskoppies Hospital offers both in- and outpatient general psychiatric care and has specialised units such a child and adolescent

psychiatry unit in addition to providing care and housing to long-stay patients, such as those with intellectual disability. In turn, Cullinan Care and Tshwane Rehabilitation Centres provide long-term care and serve somewhat different patient populations. Inconsistency can therefore be attributed largely to differences in population served in terms of psychopathology, age groups or clinician preferences, among other factors.

Strengths and Limitations

This study provides valuable insight into procurement and expenditure patterns in mental health care in Gauteng. Comparative studies of procurement and expenditure could promote conscientious prescribing by flagging irregular use and high costs. This could also inspire further investigation to establish appropriateness of medicine use and identify novel outcomes. Knowledge of total medication expenditure may allow for more informed budget allocation, while insight into coverage and service provision by facility may assist in guiding resource allocation.

Results were, however, limited by a number of factors. Perhaps the most substantial limitation of this study is the absence of patient-level data, hindering the ability to ascertain treatment indications and dosages. As a result, inferences cannot be made regarding high cost of procured items, rendering many of the observations made in this study anecdotal.

Whilst DDDs are available and internationally accepted, they may not represent actual clinical usage and local prescribing patterns (58). They cannot, therefore, be used to reflect the prevalence of disease accurately, but may suggest the extent of disease burden or treatment coverage. Cost/1000 cannot be used as an indicator of disease burden, as high cost/1000 could allude to more expensive medications being used, rather than greater quantities. Neither of these parameters should be assessed in isolation, however, but should rather be considered together with cost/DDD, which could give an indication as to whether there is greater coverage of medicines, resulting in higher DDD/1000, or more expensive medications being utilised, with greater cost/1000.

The overlap of medicine indications and questions concerning the accuracy of medicine classification within the ATC N group further complicate the potential for procurement patterns to act as markers for disease prevalence (e.g. the classification

of lithium carbonate under N05B). Since procurement does not equate to treatment adherence, findings do not reflect actual treatment, merely providing an indirect estimate of utilisation. Inaccuracy in data capturing of headcounts and PDEs at each facility may skew data and are not necessarily specific to individuals seeking mental health care. To improve this study, it would be helpful to assess mental health headcounts in comparison to medication use.

A comparison between exclusively psychiatric specialist hospitals was not undertaken. Additionally, chi-square testing was not repeated after removing certain hospitals – however, the descriptive analysis and graphs are self-explanatory.

Since procurement does not equate to adherence, the inability to comment on treatment adherence remains a major limitation. The purchasing of over the counter medications or subscription to traditional healing practices could also not be accounted for in this study.

Chapter 5 : CONCLUSION and RECOMMENDATIONS

To the investigator's knowledge, this study is the first of its kind in the South African public sector. Notwithstanding the limitations, the study provides valuable insights into procurement patterns of medicines for MNS disorders. Unexpectedly, despite prescribing practices in South Africa being governed by an EML and STGs and facilities managing similar conditions, prescribing patterns between the different institutions within each service level were generally found to differ significantly, suggesting variations in prescriber preference. Scope exists for further study of procurement and expenditure patterns, and the following recommendations are therefore made:

- Ideally, a patient-linked registry could provide a more objective critique of treatment indication and dose, polypharmacy and disease burden. In the absence of such, retrospective record reviews could be performed at individual sites to compare costing, policy adherence, prescribing patterns, indications and treatment outcomes. This may not only flag irrational prescribing and polypharmacy, but also potentially shed light on novel or effective treatment approaches with benefit over existing protocols for future EML and STG consideration.
- Regular evaluation of the database is recommended for the purpose of comparing procurement patterns and spotlighting irrational use. This may also assist policymakers in establishing STGs and allocating budgets. In the long term, trend analysis can aid in procurement planning by flagging items that are commonly used or frequently out of stock.
- Some updating of the ATC classification system may be indicated, for example, lithium could be placed with N03A medicines, which could be considered as anti-epileptics and mood stabilisers.

More specific to the findings of this study, the following may be useful research adjuncts:

- The frequent use of sodium valproate, and whether its use in bipolar disorder is appropriate given its teratogenicity, should be assessed, since lithium

carbonate is recommended by STGs as a first-line treatment, and was found to account for only 1.52% of total expenditure.

- As in the example of amitriptyline, local studies establishing the specific indications of medicines with more than one indication could reflect whether their use is appropriate, and limit skewing of data.
- Where NEML items are used for specific effect, closer analysis could be performed against current guidelines to evaluate potential advantage and justify use. For example, the use of trazadone at the Tara H. Moross centre (where it is probably prescribed for its sleep benefits) could be the subject of cost-comparative and outcome studies (considering safety, tolerability and efficacy) against first-line SSRIs plus a sedative to ascertain whether its use at such high cost is justified. A similar costing and outcome analysis could be applied to the routine use of an anticholinergic together with a first-generation antipsychotic versus a more expensive second-generation agent with little propensity for extrapyramidal side effects.
- Specific comparison and statistical analysis between specialised psychiatric hospitals could be undertaken.

Rational use of medicines remains an essential component of effective patient care. Since it is unlikely in our setting that more funds could be allocated to the treatment of mental illness, rational prescribing in all domains could be practised to ensure equitable distribution of funds and improve mental health coverage. Rational use does not simply imply the use of the cheapest medicine: cost and efficacy must be weighed up against each other in the context of an effective mental health care system (5). Although awareness of spending is necessary for informed decision-making in allocating appropriate funds (1), it would be unwise to use these outcomes in establishing effective care or recommending guidelines and medicine lists.

An assumption made during planning may be that guidelines will ensure similarities in procurement and expenditure trends, and certainly the reason for STGs is to encourage the use of evidence-based medicines in the hope that these will improve outcomes; however, various factors must be considered that would prevent this, namely differences in patient populations and complexity of disorders, prescriber

preferences and experience, district budget constraints and resources. Ultimately, studies assessing quality of life and patient outcomes for patients with MNS disorders should be the main consideration in establishing treatment efficacy and quality of health care.

Appendix A: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Jade Catheryne Bouwer

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180612

NAME: (Principal Investigator)	Dr Jade Catheryne Bouwer
DEPARTMENT:	Psychiatry Medical Supplies Depot - Auckland Park Chris Hani Baragwanath Hospital
PROJECT TITLE:	Procurement and expenditure of medicines used for mental, neurological and substance use disorders: a secondary analysis of the 2017/2018 Gauteng provincial pharmaceutical database
DATE CONSIDERED:	29/06/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Lesley Robertson and Mrs Shereen Govender
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/07/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore be due in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Permission to Conduct Research

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Enquiries: Dr Bridget Ikalafeng
Email: bridget.ikalafeng@gauteng.gov.za
Cell: 082 461 9354

To: Wits Ethics Chairperson

RE: Supporting Letter Pending Ethic Approval

This serves to inform you that the Department Of Health has reviewed the study of Dr Bouwer on "Procurement and Expenditure of Medicines Used for Mental Neurological and Substance Use Disorders: A Secondary Analysis of the 2017/18 Gauteng Pharmaceutical Database".

The department agrees that the study be conducted pending Ethics Approval.

Kind regards

Dr Bridget Ikalafeng
Deputy Director: Research & Epidemiology Directorate
Date: 17/05/2018

Appendix C: Plagiarism Declaration

Postgraduate Office, Faculty of Health Sciences
Wits Medical School, 7 York Road, PARKTOWN, 2193, Johannesburg • Tel: (011) 717 2745 • Fax: (011) 717 2119 • e-mail: healthpg@health.wits.ac.za

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Jade Catheryne Bouwer (Student number: 0700732J) am a student registered for the degree of MMed Psychiatry in the academic year 2020.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this in not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature:  Date: April 2020

Appendix D: Plagiarism (Turnitin) Report

Turnitin Originality Report

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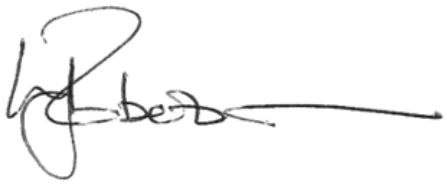

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