Sales of over-the-counter codeine-containing medicines in South Africa, 2019-2020: a retrospective observational study

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DECLARATION

I, Federica Maria Giuricich, declare that this dissertation is my own, unaided work. It is being submitted in fulfilment for the degree of Master of Pharmacy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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Federica Maria Giuricich

Signed at Parktown, Johannesburg, in South Africa, on the 15th day of October 2024.

ETHICAL DECLARATION

I, Federica Maria Giuricich, am registered with the University of the Witwatersrand, Johannesburg, for the degree of Master of Pharmacy and have read the University's current research ethics guidelines. An ethical waiver was granted for the purposes of this study (Appendix A).

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Federica Maria Giuricich

Signed at Parktown, Johannesburg, in South Africa, on the 15th day of October 2024.

DEDICATION

“I can do all things through Christ who strengthens me.”

Philippians 4:13

“… with God all things are possible.”

Matthew 19:26

Deo Gratias.

†

ABSTRACT

Introduction and Rationale

Codeine-containing medicines (CCMs), used mostly for its analgesic properties, with its addictive potential, contributes to irrational drug use in South Africa (SA). Furthermore, many CCMs are affordable and some available as over-the-counter (OTC) medicines, thus increasing risks of misuse. This leads to misconceptions of codeine's safety due to its easy accessibility. Analysing OTC CCM sales trends and associations in SA, can provide valuable information for policy reform.

Aim

The study aimed to review the factors contributing to CCMs. The dissertation further aimed to describe the sales trends of OTC CCMs using a retrospective observational analysis of an IQVIA dataset. The dataset included sales data from retail pharmacies across all provinces in SA for the period of 1 January 2019 to 31 December 2020.

Objectives

I. To conduct a review of the factors contributing to CCM sales.

II. *Objective **II** was divided into parts **a** and **b**.*
   a. To describe the sales trends of OTC CCMs across all provinces in SA.
   b. To assess any difference between the effect of the severe acute respiratory syndrome-related coronavirus 2 (Covid-19) pandemic on the sales trends of OTC CCMs across all provinces in SA.

III. To determine the contributing factors associated with OTC CCM sales in the South African provinces of Gauteng, Mpumalanga and the North-West, identified as "codeine hotspots".

Methodology

A quantitative retrospective observational analysis of South African codeine-sales data, from an IQVIA dataset was used for analyses, using STATA®, to determine the sales trends and associations significantly associated with OTC CCM sales across all provinces in SA. An overview of the factors contributing to CCM sales was discussed. Pearson chi-square tests were used to determine evidence to support the presence of any associations between the analysed variables. Descriptive results were plotted in

graphs to depict the trends and effects associated with OTC CCM sales. Univariate and multiple linear regressions were also conducted to determine the strengths of the contributing factors associated with OTC CCM sales in the three South African “codeine hotspot” provinces (Gauteng, Mpumalanga and the North-West).

Results

In total, 36 065 459 OTC CCM script line items were analysed. Cumulatively, the top five OTC CCM products sold, accounted for approximately 60% of the total percentage distribution of all the analysed products. These included Adco-Dol® (40s) (21.34%), Mybulen® (30s) (12.80%), Gen-Payne® (30s) (10.78%), Adco-Dol® (20s) (10.02%) and Accurate® (40s) (7.93%). Gauteng (40.95%) descriptively displayed the greatest amount of OTC CCM sales, with the Northern Cape (2.35%) showing the least amount of OTC CCM sales. Sales were greatest through cash payments in chain pharmacy groups, at the onset of winter. March 2020 demonstrated a significant sales spike, before plummeting in April 2020, indicative that sales were higher before Covid-19, with significant differences (p<0.001). Of the “codeine hotspot” provinces (Gauteng, Mpumalanga and the North-West), linear regressions showed significant results, with Gauteng displaying increased OTC CCM sales (p<0.001), particularly with the sale of generic (p<0.001) oral liquid products (p<0.001), acquired with cash (p<0.001) and purchased as smaller pack sizes (p<0.001).

Conclusion

From this study's findings, codeine use is still greatly prevalent in SA. Legitimate and irrational use of OTC CCMs is affecting the burden of medicine misuse and abuse in SA. The purchase of oral liquid form OTC CCM products is on the rise, particularly amongst the adolescent generation, as an easy and affordable illicit drug. Purchasing affordable OTC CCMs with cash and in smaller pack sizes is prevalent in SA’s top three “codeine hotspot” provinces (Gauteng, Mpumalanga and the North-West). It is therefore recommended that enhanced education, knowledge, and codeine policy reform surrounding the control of access to OTC CCMs is warranted to help combat irrational CCM misuse in SA.

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95% CI	95% Confidence interval
Cap	Capsules
CCMs	Codeine-containing medicines
Covid-19	Severe acute respiratory syndrome-related coronavirus 2
CY	Cytochrome
DDD	Defined daily dose
DSP	Designated service provider
Eft	Effervescent tablets
EML	Essential Medicines List
ES	Extra strength
FDA	Food and Drug Administration
GDP	Gross domestic product
HCP	Healthcare professional
ID	Identification document
MRSCA	Medicines and Related Substances Control Amendment Act 90 of 1997
NAPPI	National pharmaceutical product index
OR	Odds ratio
OTC	Over-the-counter
Paed	Paediatric
PIT	Pharmacist-initiated therapy
POPIA	Protection of Personal Information Act
R_x	Prescription
SA	South Africa
SAHPRA	South African Health Products Regulatory Authority
SAMF	South African Medicine Formulary
SEP	Single exit price
Susp	Suspension
Syr	Syrup
Tab	Tablets
UK	United Kingdom
UNODC	United Nations Office on Drugs and Crime
USA	United States of America
WHO	World Health Organisation

CHAPTER 1: INTRODUCTION

1.1. Background

An *opioid* is a term used to classify a wide range of substances that are commonly used for their analgesic properties (UNODC, 2019). The 21st century has been burdened with the global public health threat of the opioid crisis (Harker *et al.*, 2020). This crisis refers to the widespread and escalating public health risk attributed to the uncontrollable and increased use of opioids for non-medical reasons (McCabe *et al.*, 2017), further exacerbated by the cost-effectiveness of codeine (UNODC, 2019). Additionally, there are large gaps in the international legislative guidelines for the control of opioids, many of which are inconsistent among countries (UNODC, 2019). The use of codeine often begins for legitimate and medically therapeutic reasons, as prescribed and advised by healthcare professionals (HCPs) (Foley *et al.*, 2017). However, this can eventually transition into illegitimate use, leading to potential misuse, abuse and addiction to codeine products (Wells *et al.*, 2019; Hockenhull *et al.*, 2022).

In recent years, there has been a significant increase in deaths and hospitalisations related to opioid overdoses. Between 1999 to 2011, the mortality rate in the United States of America (USA), almost quadrupled, primarily attributable to the misuse and abuse of opioid analgesics (Jayawardana *et al.*, 2021). With this, the American average life expectancy declined from 78.9 years in 2014 to 78.6 years in 2017, due to opioid overdoses (UNODC, 2019). A South African study on hospital admissions related to over-the-counter (OTC) codeine-containing medicine (CCM) usage, found that the mean length of stay in hospital for each patient was approximately six days, with just over 10% of this group requiring intensive care treatment (Mill *et al.*, 2018). This study further reported that of all the analysed hospitalisations, each patient consumed daily, on average, 28 OTC CCM tablets for a mean period of approximately 600 days, prior to the need for hospital admission (Mill *et al.*, 2018).

One of the largest contributing factors to the opioid crisis in South Africa (SA), is the ease of accessibility. In SA, a prescription is not required for the sale of Schedule 0

(S0), S1 and S2 medicines, as they are classified as OTC products and can be sold to any person above the age of 12-years-old upon request from a registered dispenser (MRSA, 1965). Certain opioids, like codeine, can also be used for their antitussive and anti-diarrhoeal properties (Schiller *et al.*, 1982; Bolser and Davenport, 2007). Widely available OTC medicines in SA, encourage patients to self-medicate, allowing patients to feel empowered in autonomy by taking responsibility for their health (Padayachee, 2020). Self-medicating behaviours may be beneficial; however, it may also potentially escalate the danger of medicine misuse, especially opioids like codeine, considering their addictive properties (Van Hout and Norman, 2016). In addition, with the OTC availability of some CCMs, many individuals mistakenly assume that all CCMs are low-risk and completely safe to use (Padayachee *et al.*, 2020).

Individuals seeking support during opioid withdrawal or tapering may resort to any means to obtain products like codeine (being a potent opioid), to alleviate withdrawal symptoms (Cooper, 2013a). The increasing popularity of HCPs' suspicions leading to the refusal of prescriptions or sale of codeine products, further escalate black-market codeine sales, exacerbating the opioid crisis (Van Hout *et al.*, 2014). Black-market schemes, provide easy access to codeine products without HCP surveillance or monitoring (Grzybowski, 2004). However, this raises concerns about the potential misuse of codeine for non-therapeutic purposes, highlighting the importance of vigilant regulation and oversight (Van Hout *et al.*, 2014).

Globally, countries (such as the United Kingdom (UK) and the USA) whereby the regulation of CCMs to prescription-only status, has led to increased fraudulent prescriptions and a surge in black-market sales of CCMs (Grzybowski, 2004). However, the World Health Organisation (WHO) has recognised opioids, including codeine, as essential medicines for pain management and thus advocates against rescheduling all CCMs to prescription-only (Jayawardana *et al.*, 2021; Richards *et al.*, 2021). Nevertheless, ongoing debates and discussions are essential to refine the regulatory framework in SA regarding the potential up-scheduling of all OTC CCMs to prescription-only status. The South African public healthcare sector is often described as an "abuse of human rights", due to a shortage of HCPs, and being grossly under-resourced and underfunded, leading to poor and unsafe practices (Brauns and Wallis,

2014). This sector serves more than 80% of the South African population but lacks the necessary funds to adequately serve this population (van Rensburg, 2014). Consequently, overburdened and ill-equipped public health facilities result in longer waiting times, overcrowding and the inability to adequately attend to large patient numbers with minimal resources at disposal (van Rensburg, 2014; Padayachee *et al.*, 2019).

Affecting approximately 20% of the adult population, pain is recognised as a global health concern (Jayawardana *et al.*, 2021). If pain is not treated, it most often negatively impacts the individual's quality of life and can lead to potentially life-threatening situations (Jayawardana *et al.*, 2021). Studies have shown that untreated pain is highly prevalent in developing countries, due to limited access to proper pain relief products (UNODC, 2019; Jayawardana *et al.*, 2021). Opioids, like codeine, are frequently used to reduce moderate to severe pain (Carney *et al.*, 2018). As codeine is a potent opioid with structural similarities to its active metabolite, morphine, CCM products possess a considerable risk for user dependence, misuse and potential abuse (Dada *et al.*, 2015).

In SA, many protocols have been adopted to aid in preventing irrational codeine OTC misuse. The intention to adopt a S2 register in pharmacies, legislatively required, is to aid pharmacies in documenting patients' details such as identification numbers and physical addresses, when purchasing a S2 OTC medicine. This is to identify patterns of patient usage and hinder abuse of a potentially addictive substance. However, compliance with this requirement is often lacking in practice. Due to the absence of a national centralised codeine database, individuals can visit multiple pharmacies concurrently to obtain OTC codeine products (Voigt, 2022), and this is known as 'pharmacy hopping' (Van Hout and Norman, 2016). This 'pharmacy hopping' phenomenon can result in fragmented patient care, potential drug interactions and challenges in monitoring medication adherence, ultimately posing risks to patient safety and overall healthcare outcomes (Van Hout, 2014a). As recognised by the South African Health Products Regulatory Authority (SAHPRA), the lack of control over the sale of widely available CCMs promulgated SAHPRA adjusting the sales regulations of CCMs in 2019 to align with international codeine guidelines. Table 1.1

highlights the updated established South African regulatory restrictions on the maximum daily dosage for consideration in CCM sales in SA (Government Gazette No. 254, 2016).

Table 1.1: Regulatory restrictions on the daily maximum dosage of CCM sales in SA.

Dosage Form	Maximum amount of codeine (mg)	Maximum daily dose (mg)
*S0-S2 OTC codeine-combination analgesics		
Oral solid	≤10 per dosage unit	80
Oral liquid	≤10 per 5 mL dosage unit	80
S3-S5 codeine-combination analgesics		
Oral solid	>10 per dosage unit	-
Oral liquid	>10 per 5 mL dosage unit	-

*S = schedule

In SA, oral solid OTC CCMs are sold for a maximum treatment period of five days and no more than one pack per customer per day. The oral liquid OTC CCM pack size may not exceed 100 mL sold per customer per day (Government Gazette No. 254, 2016). If a CCM contains only codeine as the single active ingredient (with no other added active ingredients), regardless of dosage or strength, this medicine is classified as a S6 substance in a South African pharmacy (MRSA, 1965; Voigt, 2022). Schedule 6 medicines are considered moderate to high risk for potential abuse and a new non-repeatable prescription is necessary on every account of dispensing a limited 30-day supply at most (MRSA, 1965).

Given codeine's classification as an ingredient with abuse potential, South African OTC CCMs typically incorporate low doses of codeine. The scheduling of medicines in SA is overseen by SAHPRA, with classifications determined according to the safety profiles of each medicine (MRSA, 1965). The scheduling of these products determines the conditions under which these medicines can be prescribed and dispensed.

Codeine is found in many single-ingredient and multi-ingredient analgesic OTC products in South African retail pharmacies (Padayachee *et al.*, 2023). Self-medicating practices and the wide availability of OTC CCMs may result in the increased use of codeine, leading to increased risks of tolerance and dependence amongst these

products (UNODC, 2019). This relates to the concern of having widely accessible OTC CCMs. Although it may boost overall sales, it may lead to increased misuse and thus, harm patients' health.

The United Nations Office on Drugs and Crime (UNODC) reported that African countries like SA are currently at risk of high usage of codeine-based cough syrups for non-medical reasons (UNODC, 2019). Several factors and influences contribute to this finding, many of which stem from the adolescent youth of the 21st century (Tettey *et al.*, 2020). Being relatively inexpensive, accessible and widely available, OTC codeine cough syrups in South African pharmacies are on the rise in sales for recreational and non-medical reasons (Agnich *et al.*, 2013). As custodians of medicine, South African pharmacists are becoming more aware and concerned about the substantial increase of such cough syrup sales to individuals under the age of 18-years-old (Carte Blanche, 2018). The youth are purchasing these syrups to reach a euphoric state on codeine concoctions, such as 'Purple Drank', that are often constituted of candy, flavoured beverages, sometimes alcohol, and the OTC codeine cough syrup (Van Hout, 2014b).

On the 11th March 2020, the severe acute respiratory syndrome-related coronavirus 2 (Covid-19) pandemic was globally declared (Dubey *et al.*, 2020). Various measures and protocols were implemented worldwide to attempt to contain the outbreak and prevent disease transmission (Dubey *et al.*, 2020; Benschop *et al*., 2021). In SA, a national lockdown was introduced, beginning on the 27th March 2020, which included curfews and strict quarantine regulations (South African Government, 2020; Molebatsi *et al.*, 2021). These restrictions greatly affected individuals, particularly in psychosocial behaviours, leading to feelings of uncertainty, helplessness, loneliness, worthlessness, boredom and increased stress, anxiety and depression (Dubey *et al.*, 2020; Karas *et al.*, 2020; Çaki *et al*., 2021; Molebatsi *et al.*, 2021). Lifestyle patterns, social activities and consumer habits were also disrupted (Dubey *et al.*, 2020; Çaki *et al*., 2021).

During the first phase of the Covid-19 restrictions in SA, alcohol and tobacco were classified as non-essential goods and their sales were temporarily banned to try and reduce Covid-19 transmission through cigarette sharing and to decrease alcohol/tobacco-related trauma cases being referred to hospitals (Mapanga *et al.*,

2023). This altered individuals' patterns of alcohol and tobacco usage (Chen, 2020). Anxiety and depression during the pandemic increased the risk of addictive substance use for coping mechanisms (Chen, 2020; Benschop *et al*., 2021; Gittins *et al*., 2022). These bans on alcohol and tobacco products in SA, limited the use of these substances to help manage unwanted psychosocial behaviours (Benschop *et al*., 2021). Consequently, substances such as codeine, substituted alcohol and tobacco to achieve the "euphoric" emotions (Gittins *et al*., 2022; Mapanga *et al.*, 2023). In this period, codeine products were purchased either for legitimate medical reasons to treat symptoms of the Covid-19 infection or for recreational and illicit purposes to alleviate psychosocial distress (Benschop *et al*., 2021; Gittins *et al*., 2022; Mapanga *et al.*, 2023).

In SA, certain provinces are more prone to codeine prevalence and use than others (Nyoni *et al.*, 2022). Such provinces are labelled as "codeine hotspots" and include the South African provinces of Gauteng, Mpumalanga and the North-West (Nyoni *et al.*, 2022). Although contributing factors to the irrational use of CCMs are most prevalent in rural communities, urban communities are not excluded from this. Contributing factors may include unemployment (83.2%), a low level of education (62.6%), high transport costs and poverty (Harker *et al.*, 2020). Due to the high unemployment rates in rural Mpumalanga and the North-West, high migration levels to Gauteng may result. However, CCM misuse habits may follow the rural inhabitants to job-seeking provinces, comparable to Gauteng which has an increased availability of CCMs, thereby potentially continuing CCM misuse habits with semigration to other provinces (Nyoni *et al.*, 2022).

1.2. Problem statement and Rationale

This dissertation is both crucial and relevant as it highlights a significant public health concern regarding the usage of OTC CCMs in SA. Existing literature indicates that SA, as a developing nation, is significantly affected by the global opioid crisis and experiences prevalent codeine misuse (Harker *et al.*, 2020). Understanding the sales trends and associations contributing to the consumption of OTC CCMs is essential due to the risks associated with their misuse, dependence, abuse and impact on societal influences. Furthermore, by examining the impact of the Covid-19 pandemic on OTC

CCM sales trends, the study can offer valuable insights into the resilience and adaptability of the South African pharmaceutical market in response to external crises. The differences in OTC CCM sale trends before and during the Covid-19 pandemic in SA, were assessed to determine if psychosocial factors exacerbated the codeine crisis.

Gauteng, Mpumalanga and the North-West have been identified as the top three South African provinces with the highest prevalence and potential misuse of codeine over the years, characterised by differing economic backgrounds (StatsSA, 2016; Nyoni *et al.*, 2022). The inclusion of these "codeine hotspots" enriches the study's relevance and potential impact, enabling a deeper exploration of the socioeconomic factors associated with codeine misuse, and an understanding of the multifaceted nature of the issue within the South African context. Understanding the intricate relationships among codeine trends, societal influences and healthcare protocols is vital for fostering a safer and more resilient pharmaceutical environment in SA. This understanding is essential for policymakers, HCPs and regulatory authorities to develop informed strategies and interventions aimed at promoting responsible medication use, safeguarding public health and mitigating potential harm associated with the overuse of OTC CCMs (Richards *et al.*, 2021).

1.3. Aim

The study aimed to review the factors contributing to CCMs. The dissertation further aimed to describe the sales trends of OTC CCMs using a retrospective observational analysis of an IQVIA dataset. The dataset included sales data from retail pharmacies across all provinces in SA for the period of 1 January 2019 to 31 December 2020.

1.4. Objectives

The objectives of the study are stipulated below.

I. To conduct a review of the factors contributing to CCM sales.

II. *Objective **II** was divided into parts **a** and **b**.*

    a. To describe the sales trends of OTC CCMs across all provinces in SA.

b. To assess any difference between the effect of the Covid-19 pandemic on the sales trends of OTC CCMs across all provinces in SA.

III. To determine the contributing factors associated with OTC CCM sales in the South African provinces of Gauteng, Mpumalanga and the North-West, identified as “codeine hotspots”.

1.5. Synopsis

Chapter One

Provides background information for this study. This chapter explores the global opioid crisis, with a specific focus on South African codeine regulations. It discusses how the widespread and easy accessibility of codeine significantly contributes to public health concerns regarding the misuse of OTC CCMs in SA. This chapter also includes the rationale, aim and the objectives of the study.

Chapter Two

Explains the methodology and study design undertaken in this research project. This chapter includes the process undertaken to conduct the literature review, meeting the requirements for **objective I**. It also discusses the statistical processes that were undertaken to achieve **objectives II** and **III** of this study.

Chapter Three

Provides an overview of the factors contributing to CCM sales. The review of **objective I**, further highlights both the medical and recreational uses of codeine which contribute to codeine sales, and associated uses, misuse and abuse of codeine.

Chapter Four

Reports on the descriptive, quantitative findings of **objectives IIa** and **IIb**. This objective used the IQVIA dataset to describe sales trends of OTC CCMs in SA and to determine the effect of the Covid-19 pandemic on these sales. The results are presented in tables and appropriate graphs to provide an overview of the sales of codeine across all nine provinces in SA during 2019-2020. Additionally, a discussion and analysis of the results of **objective II** are presented.

Chapter Five

Reports on the inferential results of **objective III**. This objective also used the IQVIA dataset to determine any associations of various analysed variables that may have contributed to the sale of OTC CCMs, specific to three South African provinces (Gauteng, Mpumalanga and the North-West) identified as “codeine hotspots”. The results are presented in tables and relevant graphs. In addition to these results, a discussion and analysis of the findings of **objective III** is provided.

Chapter Six

Concludes this dissertation by providing a summary of the main findings and outcomes of the study. It also addresses the study’s strengths, limitations and proposes recommendations for future research concerning OTC CCMs in SA.

CHAPTER 2: METHODOLOGY

2.1. Background

The study was a quantitative retrospective, observational analysis of codeine-sales data in SA from an IQVIA dataset (**objectives II** and **III**). A retrospective, observational study reviews established database records to analyse topics of interest that have already occurred (de Sanctis *et al.*, 2022). These studies are useful since they provide a comprehensive observational examination of medical database records that are rapidly obtainable and in a large corpus of data (Abbott *et al.*, 2016). The dataset was an established dataset containing secondary raw data, extracted from 1 January 2019 to 31 December 2020, covering a 24-month period. The University of the Witwatersrand purchased the raw data directly from IQVIA, whereby the researcher had direct access to such data from the IQVIA webpage. No patient identifiers were included in this dataset shared.

Known as the 'Human Data Science Company', IQVIA is a global company that offers healthcare technology to its clients, which specifically drives the obtainment of pharmacy data from multiple sources to produce a wide range of datasets to aid in data collection studies (Tran *et al.*, 2020). The dataset was used to investigate various statistics of OTC CCM sales across SA. The results, including trends and associations, were drawn by calculating descriptive and inferential statistics (Mann, 2003). Summarised quantitative results were used to discuss the findings of existing literature studies.

2.2. Objective I Methodology

In fulfilment of **objective I** of this study, **Chapter 3** is a review that explores the factors contributing to codeine-containing medicine sales. This review is valuable to the expanding repertoire of methods employed for synthesising evidence, specifically to the literature investigating factors contributing to the increase of CCM sales (Mann, 2003).

2.2.1. Review approach

A narrative review approach was applied to construct this overview. Several sources were analysed and summarised which was essential for compiling the literature for this overview (Jesson and Lacey, 2006). Narrative reviews are retrospective evaluations of existing literature, synthesising relevant literature into a structured form on a particular topic (Ferrari, 2015; Snyder, 2019; Agarwal *et al.,* 2023). These reviews offer advantages as they encompass a wide range of study designs and conduct thorough searches across multiple databases to gather evidence related to the topic under review (Colquhoun *et al.*, 2014; Munn *et al.*, 2018).

The chosen topic in **objective I** is well-suited for this review as it is broad enough to encompass various factors contributing to the sale of CCMs, while also being specific enough to allow readers to understand and enhance their knowledge on the chosen topic (Snyder, 2019; Agarwal *et al.,* 2023). Another method used to identify relevant literature for this review was to examine the reference lists of included articles and scan them for additional literature relevant to this review (Snyder, 2019). Additionally, utilising a broad time period of article publication in the review, allowed the researcher to understand the published work in the field and its evolution over time (Agarwal *et al.,* 2023).

2.2.2. Search strategy

To create this review, an electronic search strategy was adopted to include articles from reputable and scientific electronic resource databases, which applied to the review's inclusion criteria. Most of the resources employed were accessed through the Google Scholar search engine, which redirected the researcher to various scientific resource databases, including, but not limited to the following listed below:

- PubMed
- ResearchGate
- Science Direct–Elsevier
- Scopus

The following keywords/key phrases, among others, were utilised when scoping the various search engines for the literature review:

- Codeine
- Codeine abuse
- Codeine addiction
- Codeine and environment
- Codeine and healthcare professionals
- Codeine and lack of medical reviews
- Codeine and mental health
- Codeine and South Africa
- Codeine drug utilisation
- Codeine misuse factors
- Codeine use and sales
- Codeine use in age and gender
- Irrational codeine prescribing
- Non-therapeutic codeine factors
- Reasons for codeine abuse
- Reasons for codeine sales
- Recreational codeine use
- Social media and codeine education
- Therapeutic codeine variables

2.2.3. Eligibility criteria

The articles cited in this review were selected based on the specific inclusion and exclusion criteria, which were applied throughout the search, screening and review stages of this overview. This eligibility process is illustrated in Figure 2.1. Although a broad time period was selected, recent articles contained the most relevant information regarding various influential motives for increased CCM sales. However, older literature is useful for comparing newer and older generation patterns on codeine, considering various contributing factors for the potential of generational variances.

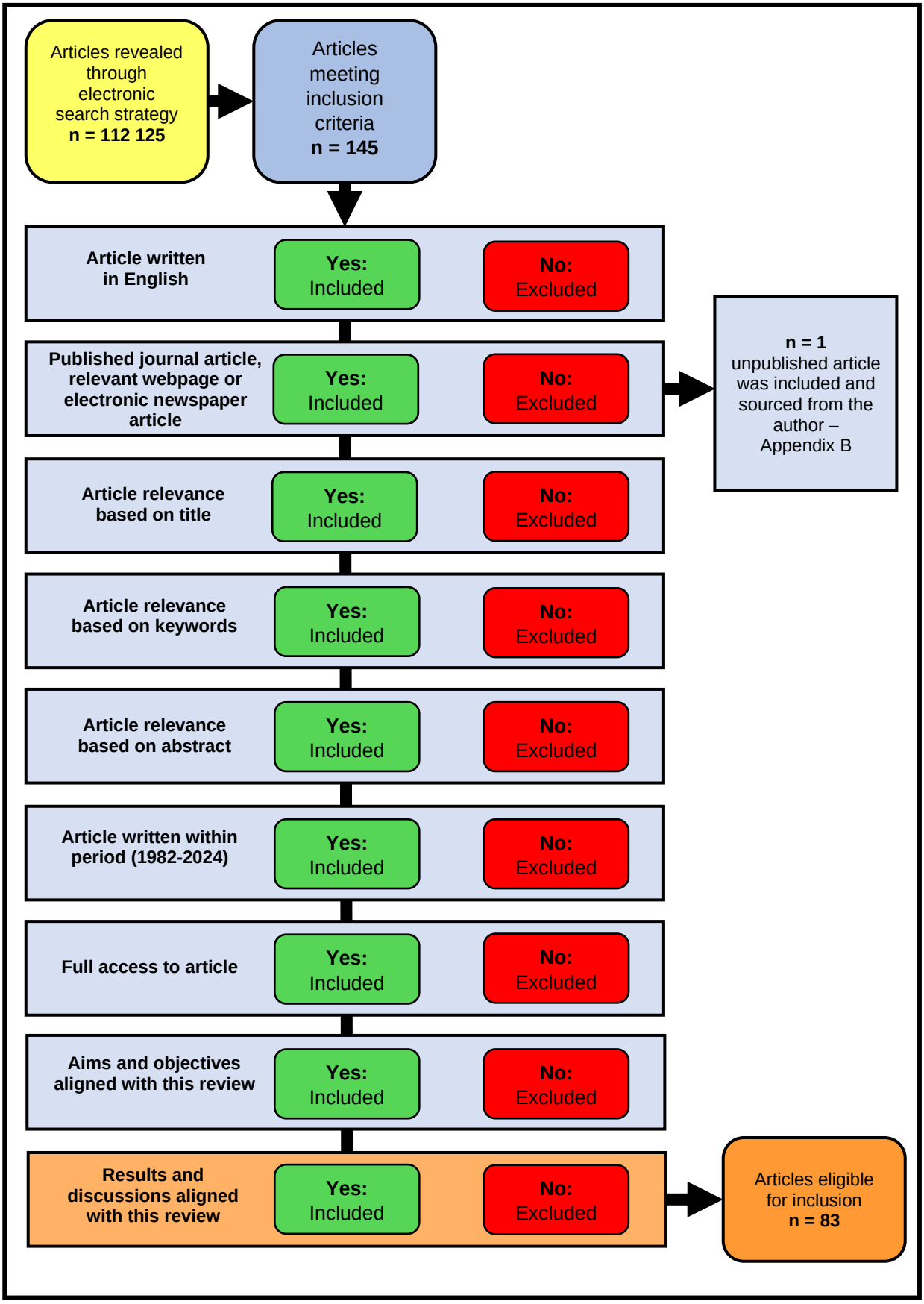


Figure 2.1: Article eligibility screening flow diagram.

Full-text reviews on each article (n=83 articles) were performed, whereby the article was analysed, evaluated, summarised and discussed. A data extraction table was developed and data from the articles were extracted and represented into this summary table used to create this review (Appendix C).

Quantitative, qualitative, mixed-methods literature, including but not limited to geospatial analyses, comparative analyses, pharmacoepidemiologic studies, narrative reviews and scoping reviews were employed in this review. The quantitative literature included but was not limited to statistical findings and defined daily dose (DDD) studies. A defined daily dose is a useful tool to describe the amount of a certain drug being prescribed, namely codeine. To include an overview of the amount of codeine dispensed in a population, it is advised to represent a DDD statistic per 1 000 inhabitants per day of that population (Fredheim *et al.*, 2009). Qualitative literature was included, and not limited to surveys and interviews.

2.3. Objectives II and III Methodology

Objectives II and **III** of the study encompassed the use of the IQVIA dataset. The same dataset was used for both objectives, however, each objective exported a different datasheet to analyse, depending on the variables and statistical tests required for each respective objective.

2.3.1. Dataset

Following approved ethical clearance (Appendix A), the researcher exported relevant variable data from the IQVIA dataset webpage into Microsoft Office Excel® spreadsheets. Version 2401 of Microsoft Office Excel® was used. The same process of data extrapolation occurred for each objective's datasheet. The use of Microsoft Office Excel® spreadsheets allowed the researcher to prepare the data to allow for easy transferral of such data into statistical software, STATA® (version 17). With the data in such software, the process of calculating descriptive and inferential statistics for the data analyses and integration of the study was undertaken. The webpage containing the raw IQVIA data was secured with a unique username and password protection with restricted access to the researcher and supervisors of the

study. All Microsoft Office Excel® spreadsheets were stored on a password-protected device with the backups of the spreadsheets stored on a password-protected OneDrive®, with access restricted to only the researcher and supervisors of the study.

The IQVIA dataset utilised for the study consisted of 36 065 459 script line items which were OTC CCM products in SA. Script line items refer to the number of packs or bottles sold of a particular product. These products were either single-codeine or combination-codeine active ingredient products. The IQVIA dataset extended across all nine provinces in SA, spanning over 720 regions. This dataset also extended over an estimated 2 500 South African retail pharmacies. These retail pharmacies included community pharmacies such as chain pharmacy groups, independent pharmacies and independent pharmacy groups.

2.3.2. Data Analysis

Both **objective II** and **objective III** required the process of data analyses, to derive findings based on the study's topic and aim. The purpose of the analyses were to additionally generate results that could further be examined and discussed in relation to the overall aim and objectives of the study. Before the process of analysing the data occurred, the respective datasheets needed to undergo data preparation. Data preparation for both objectives was conducted similarly, with most aspects of the data preparation process being applied to both objectives. Throughout the analyses, Pearson chi-square tests were frequently used to determine if there was evidence to support the presence of any associations between variables and if so, how statistically significant these results were (Trochim, 2020). The *p*-value was used to determine the probability of the significance of the findings (Hoare and Hoe, 2013). A *p*-value *(p)*<0.05 was considered statistically significant throughout this study.

2.3.2.1. Data Preparation

The study used secondary data from the IQVIA dataset that needed to first undergo data preparation. Data preparation is crucial before analysing data as it prepares the data in a structural and organised manner such that it can be readily and appropriately analysed (Soibelman and Kim, 2002). Data preparation was done in Microsoft Office

Excel®, whereby cleaning, coding and organising of the data was executed. Figure 2.2 provides a summarised overview of the steps undertaken to prepare the data for data analysis.

Steps 1-7 pertain to the data preparation for both **objectives II** and **III**. Step 8 specifically relates to **objective II** and the final steps of the figure; steps 9-11 relate to **objective III** respectively. Once data preparation occurred, the data was then transferred into the statistical data software, STATA® (version 17) for data analysis to begin.

2.3.2.2. Objective II

Descriptive statistical trends and statistics were used to describe **objectives IIa** and **IIb**. Following data preparation, the Microsoft Office Excel® spreadsheet included just under 500 000 rows of data that were analysed. Descriptive statistics described the basic overview of trends and relationships found in the variables of **objectives IIa** and **IIb**. Descriptive statistics were useful in analysing **objective II**, since it provided an overview of South African OTC CCM sales data over a two-year period. These statistics also provided results that were logical, meaningful and effective in overviewing an entire country's results (all nine provinces of SA) on a specific topic, such as South African OTC CCM sales (Vetter, 2017). These statistics simplified substantial data in the dataset into samples, and then into quantitative measures to aid the researcher in describing the relationships found within an overview context of South African codeine sales (Trochim, 2020).

The types of descriptive statistical tests that were run for **objectives IIa** and **IIb**, were best chosen according to the type of data presented in the chosen variables. Percentages and measures of frequency distribution were appropriately used to analyse this data (Hayes, 2022). Once the statistical analysis had been done in STATA®, the researcher represented and reported the results in appropriate graphs and tables, using Microsoft Office Excel®. Supplementary tables of the results found in the graphs were also added to the appendices of the study to show the detailed statistical findings of the graphs.

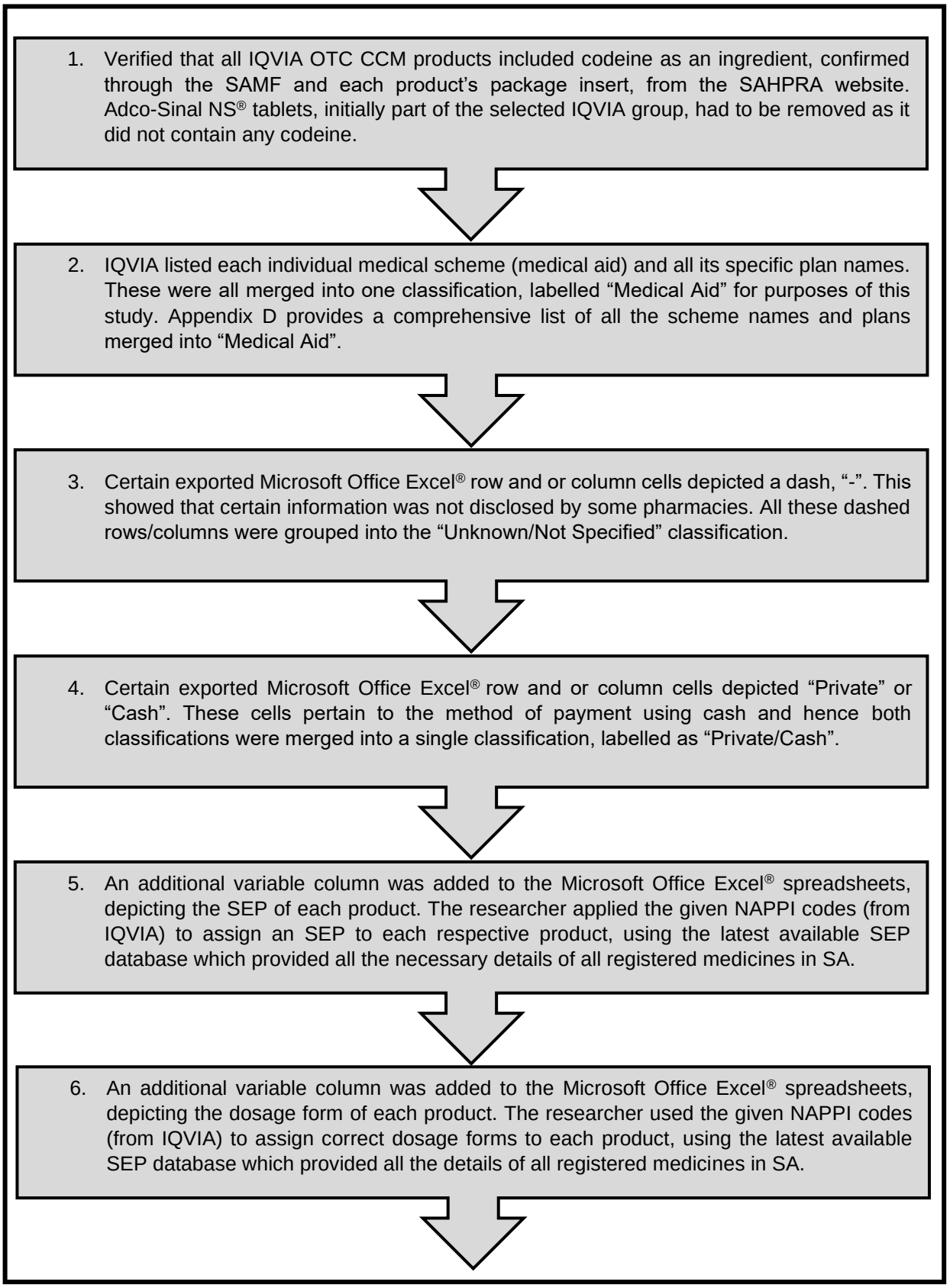
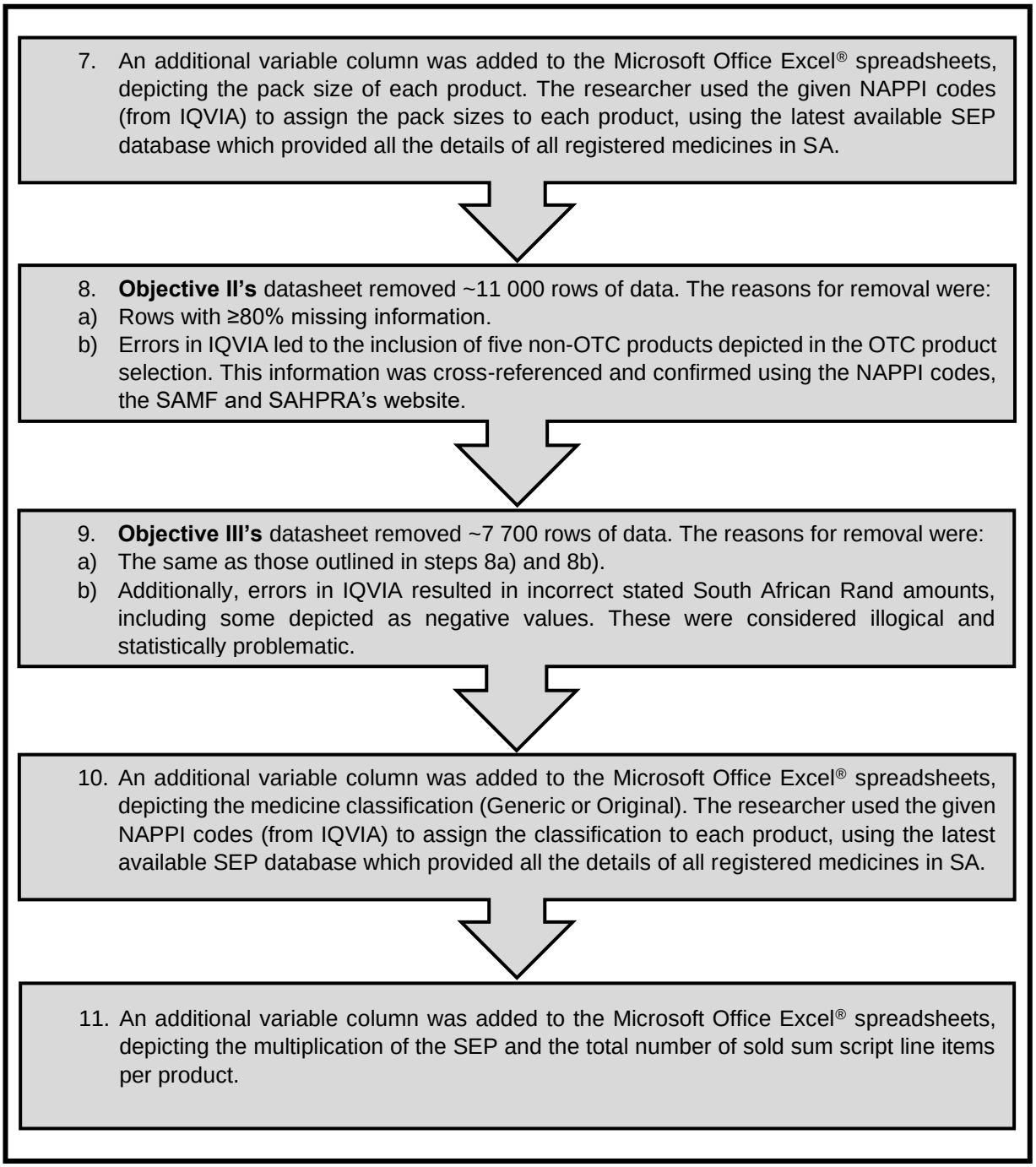


Figure 2.2: Data preparation steps.



OTC = over-the-counter; SAMF = South African Medicine Formulary; SAHPRA = South African Health Products Regulatory Authority; NAPPI = National pharmaceutical product index; SEP = Single exit price

Figure 2.2 continued: Data preparation steps.

Following the completion of data integration, a thorough analysis of the results occurred. Subsequently, the integration and analysis were synthesised into a comprehensive written report. In conjunction with the results analysis, pertinent trends

were discussed, and possible existing literature reasons were added to contribute to the findings of the results.

2.3.2.3. Objective III

Inferential statistics were used to ascertain associations found in the factor variables of **objective III**. Inferential statistics allowed the researcher to determine associations between the variables analysed in **objective III** found in the codeine-sales data within the South African province populations of Gauteng, Mpumalanga and the North-West (Trochim, 2020; Chappelow, 2022). These findings allowed the researcher to understand the various associations found in the results that contributed to the increase or decrease of codeine sales across these provinces. The results also allowed for more use-of-codeine research to understand the importance of CCM usage and factors that correlate to its findings.

The datasheet used to analyse the results of **objective III** contained approximately 99 000 Microsoft Office Excel® rows. Certain inferential tests and analyses were run based on the types of variables and the nature of the data provided in the datasheet for **objective III**.

A univariate linear regression analysis and a multiple linear regression (also known as an 'Adjusted linear regression') analysis was conducted in this objective. These regressions studied the relationships between the dependent variable and the independent variable(s) of the data to determine the extent of any significant associations within the analysed variables (Schneider *et al.,* 2010). Within the results of the regressions, estimate coefficients (β), 95% confidence intervals (95% CI) and *p*-values were present to support the findings of the regressions.

The univariate model looked at each individual variable and its effect in isolation (Bou and Satorra, 2017). Instead, the multiple linear regression model adjusted the effects of the variables, incorporating all variables together, to estimate the strengths of the found associations (van Heerden *et al.*, 2009; Bou and Satorra, 2017). Discussing the results to comparative literature is more informative in discussing the multiple linear regression findings. Despite finding some results to be minimally significant and others

not significant at all, a brief report on these findings in the study was included. These analyses provided valuable results on which variables increased OTC CCM sales and which variables decreased OTC CCM sales, amongst the three South African provinces. These analyses were useful for researchers to understand and quantify relationships between one or more predictors and their outcomes, specifically pertaining to the factors associated to the sale of OTC CCM products (Solutions, 2024). Following the completion of inferential statistical tests run on the datasheet for **objective III**, the researcher summarised the results into appropriate tables and figures. Data integration and analysis of the findings occurred. Furthermore, a comprehensive discussion was formulated for the results corresponding to available literature based on this objective's results.

2.4. Ethical clearance

A dataset with raw secondary data was obtained directly from IQVIA, which was used for data analyses in this study. The dataset did not include any personal identifiers of patients therefore data received had no associations with any patient identifiers. Therefore, an ethics waiver clearance was sought from the University of the Witwatersrand's Human Research Ethics (Medical) Committee. This waiver, therefore, fully complied with the Protection of Personal Information Act (POPIA) (South African Government, 2013). The waiver was granted on the 21st August 2023 (Appendix A). Following the approval for clearance of the ethics waiver, data analysis of the IQVIA dataset commenced.

2.5. Bias, validity and reliability

Bias, validity and reliability are important aspects for evaluating the quality of research. By addressing these elements of a study, HCPs and policymakers can critically assess the study's findings when considering their application in practice or policy reform (Smith and Noble, 2014).

2.5.1. Bias

Bias can be defined as “systematic error introduced into sampling or testing by selecting or encouraging one outcome or answer over overs” (Pannucci and Wilkins, 2010). Bias can occur at any stage of research and directly affects the validity and reliability of the study, with misinterpretations of the data having profound consequences on the outcomes of the study (Pannucci and Wilkins, 2010; Smith and Noble, 2014). Table 2.1 provides an outline of various biases present in a study and how these biases can be avoided.

Table 2.1: Types of biases and strategies to minimise biases (Smith and Noble, 2014).

Type of bias	Definition	Strategy to minimise the bias
Design bias	A poor study design and disparities between the aims and methods of the study. Researcher’s beliefs may favour the aim and hypothesis of the study.	The study was designed according to a retrospective observational study with congruency present amongst the aims, objectives and methods of the study. No patient identifiers were present in the study and an ethical waiver clearance was approved for the study.
Implementation bias	When the approved protocol, which clearly outlines the methods and analyses of the study, is not adhered to.	The approved protocol, methodologies and analyses were strictly adhered to.
Data collection bias	The researcher’s personal beliefs influence the data collection process of the study.	All data provided from the IQVIA database was applied according to the inclusion and exclusion criteria of the study.
Analysis bias	When the researcher searches and analyses data that confirms their hypotheses, ignoring data that contradicts their personal beliefs.	All data was appropriately cleaned, coded and statistically analysed according to the methodology for each objective.
Reporting bias	Only statistically significant results are reported and discussed.	All data resulting from analyses (whether statistically significant or not) was reported and discussed, as per the study’s objectives.

2.5.2. Validity

Validity can be defined as “the extent to which a concept is accurately measured in a quantitative study” (Heale and Twycross, 2015). In this quantitative study, validity is assessed using statistical tests and calculating the significance of findings (including *p*-values and confidence intervals) (Smith and Noble, 2014). Validity in research is important to display the integrity and application of the chosen methods, and their precision in which the results of the study are accurately reflected (Smith and Noble,

2014). Table 2.2 depicts the threats to validity and how these threats can be accounted for.

Table 2.2: Threats to validity and strategies to minimise the threats (Heale and Twycross, 2015).

Threat	Definition	Strategy to minimise the threat
Content validity	The methodologies of the study are sufficient and thorough to meet all the study's objectives.	All objectives were appropriately addressed through each methodology, ensuring comprehensive content coverage.
Construct validity	The selected methods must be able to produce results that aligned with the study's objectives.	The correct types of methods were chosen for each objective, to be able to appropriately report on the findings of each objective.
Criterion validity	The chosen methods must be able to adequately achieve the results of the study.	The study's methods were appropriately chosen to allow the results to accurately reflect the outcomes of the study.

2.5.3. Reliability

Reliability refers to the consistency within the analytical processes of the study (Smith and Noble, 2014). Reliability also refers to "the extent to which a research instrument consistently has the same results if it is used in the same situation on repeated occasions" (Heale and Twycross, 2015). Although it is not possible to give an exact calculation of reliability, an estimate of reliability can be achieved through various measures (Heale and Twycross, 2015), and as with validity, reliability can be assessed by calculating *p*-values and confidence intervals in quantitative studies (Smith and Noble, 2014). Table 2.3 displays the threats to reliability and how these threats can be accounted for.

Table 2.3: Threats to reliability and strategies to minimise the threats (Heale and Twycross, 2015).

Threat	Definition	Strategy to minimise the threat
Homogeneity (internal consistency)	The extent to which the methods were consistently carried out, so to achieve the same results.	Each objective was carried out by an appropriate method to achieve the findings of each objective.
Stability	The study methods were designed to be able to be reproduced and repeated.	The methods were sufficiently detailed to ensure the study could be replicated.
Equivalence	The extent of consistency observed when employing the same methods.	All data were statistically analysed, based on the appropriate methods for each objective of the study.

CHAPTER 3: OBJECTIVE I REVIEW

An overview of the factors contributing to codeine-containing medicine sales.

3.1. Introduction

Codeine is a weak opioid, derived as a natural alkaloid from the resin of the *Papaver somniferum* opium poppy plant (Singu and Verbeeck, 2021). Codeine, also known as 3-methylmorhpine, is commonly used for acute and chronic analgesic purposes, as well as for its antitussive and anti-diarrhoeal properties (Carney *et al.*, 2018). Codeine is a prodrug and thus its analgesic properties result from the biotransformation of codeine to its active metabolite, morphine, via the catalyst cytochrome (CY) P450 isoenzyme CYP2D6 pathway (Singu and Verbeeck, 2021). Morphine is a strong opioid agonist that binds 200-fold greater to the mu(μ)-opioid receptor, than codeine, resulting in the potential for its addiction (Singu and Verbeeck, 2021).

The biotransformation of codeine to morphine differs in various ethnic groups due to genetic polymorphisms, which result in varying therapeutic effects in different ethnicities (Tay and Roberts, 2018). Some ethnicities are CYP2D6 poor metabolisers, suggesting that the enzyme encompasses poor codeine analgesic properties in these groups and therefore, codeine use should be avoided due to poor efficacy (Singu and Verbeeck, 2021). In comparison, other ethnicities are genetically ultra-rapid metabolisers of CYP2D6, and the biotransformation process occurs quicker and more completely in these ethnicities and this may result in symptoms of toxicity and so usage should be avoided in these groups (Singu and Verbeeck, 2021).

Codeine-containing medicines are globally more prescription-dispensed products in pharmacies, however, there are still countries in which codeine is also available OTC, such as SA (Tay and Roberts, 2018). In SA, OTC CCMs are available in numerous dosage forms, with oral tablets being the most common, followed by syrups (Richards

et al., 2021). Common codeine-product side effects include sedation, euphoria and constipation (Carney *et al.*, 2018) while products containing codeine in combination with other active ingredients, such as paracetamol and ibuprofen can result in side effects such as inflammatory bowel conditions, gastric ulcers and paracetamol hepatotoxicity (Carney *et al.*, 2018). Although codeine, a 'weak' opioid is available in many OTC preparations, it should not be misinterpreted for its high potential for addiction which may lead to abuse, misuse, tolerance and dependence (Carney *et al.*, 2018).

Globally, codeine is the most consumed opioid and is heavily contributing to the global opioid crisis (Tay and Roberts, 2018). This crisis refers to an alarmingly increased rate of opioid use for recreational and non-therapeutic reasons (Tettey *et al.*, 2020). The ongoing global opioid crisis continues to pose an overall public health threat and challenges the monitoring of usage and prevention of misuse of CCMs (Richards *et al.*, 2021).

In countries where OTC CCMs are easily accessible, there is a risk of increased misuse and dependence of these products (Norman *et al.*, 2016). Three of the most influential factors contributing to the opioid crisis include opioid overdose, increased usage of raw codeine and codeine poisoning (Van Hout *et al.*, 2014; Gisev *et al.*, 2016; Tettey *et al.*, 2020). According to Tettey *et al*. (2020), from the Centres for Disease Control and Prevention, a six-fold increase was reported in the number of opioid overdose deaths over the past 18 years (Tettey *et al.*, 2020). Usage of raw codeine, as an active pharmaceutical ingredient, also increased significantly, from 168 tonnes in 1994 to just under 250 tonnes in 2013 during the manufacturing process (Gisev *et al.*, 2016). Being available as a prescription-only product in Finland, codeine-use poisoning was the cause of suicidal death in a study from 2000-2008, whereby 40% of its study sample size and 43% of participants died from accidental codeine use (Van Hout *et al.*, 2014).

Developing countries, such as SA, commonly experience medicine shortages (Dada *et al.*, 2015). However, these countries are not spared from the global opioid crisis (Nyoni *et al.*, 2022). A study by Richards *et al*. (2021), reported sales of OTC CCMs in

31 countries over six years. In this study, SA was ranked as the country selling the largest mean volume of codeine medicines at 31 units per person (34% among all the countries), accounting for the greatest volume of OTC CCM sales (Richards *et al.*, 2021). Thus, the review aims to identify factors contributing to the sale of CCMs.

3.2. Results and discussion

Throughout the review, 'overuse,' 'misuse' and 'abuse' are commonly used to describe contributing factors that account for codeine-product sales. Whilst 'overuse' may be the overconsumption of medicine to manage a medical ailment, 'misuse' may be the legitimate but inappropriate use of medicines for a longer period than advised (Lo *et al.*, 2015; Norman *et al.*, 2016; Cooper, 2018). Overuse of codeine products does not necessarily warrant exceeded daily quantities but exceeded monthly quantities of such products, are considered overuse (Cooper, 2013a). 'Abuse' may be defined as the intentional and illegitimate excessive intake of medicines, for non-medical reasons (Lo *et al.*, 2015; Cooper, 2018).

To create a structured review, the literature was categorised into various themes, as seen in Figure 3.1. The five main themes were then further subdivided into various subthemes within each category. **Category 1** explored the legitimate use of CCMs and its effect on CCM sales. **Category 2** explored the contributing factor of increased CCM sales resulting from the misuse and abuse of such products. Patient-related factors in **Category 3**, identified what contributors influenced a patient to purchase or use CCMs, and their lack of education and awareness surrounding CCM products. **Category 4** investigated factors influencing prescribers and dispensers, to prescribe, dispense and or recommend the use of codeine products, and how such crucial professions of a community may influence CCM sales. This category also explored the lack of education and awareness that HCPs possess on CCMs, and with increased knowledge and education, this may lead to prevent misuse and irrational use of CCMs. An aspect of the regulatory framework of codeine is described in the final category, **Category 5**, which highlights the ease of access of CCM products within a community.

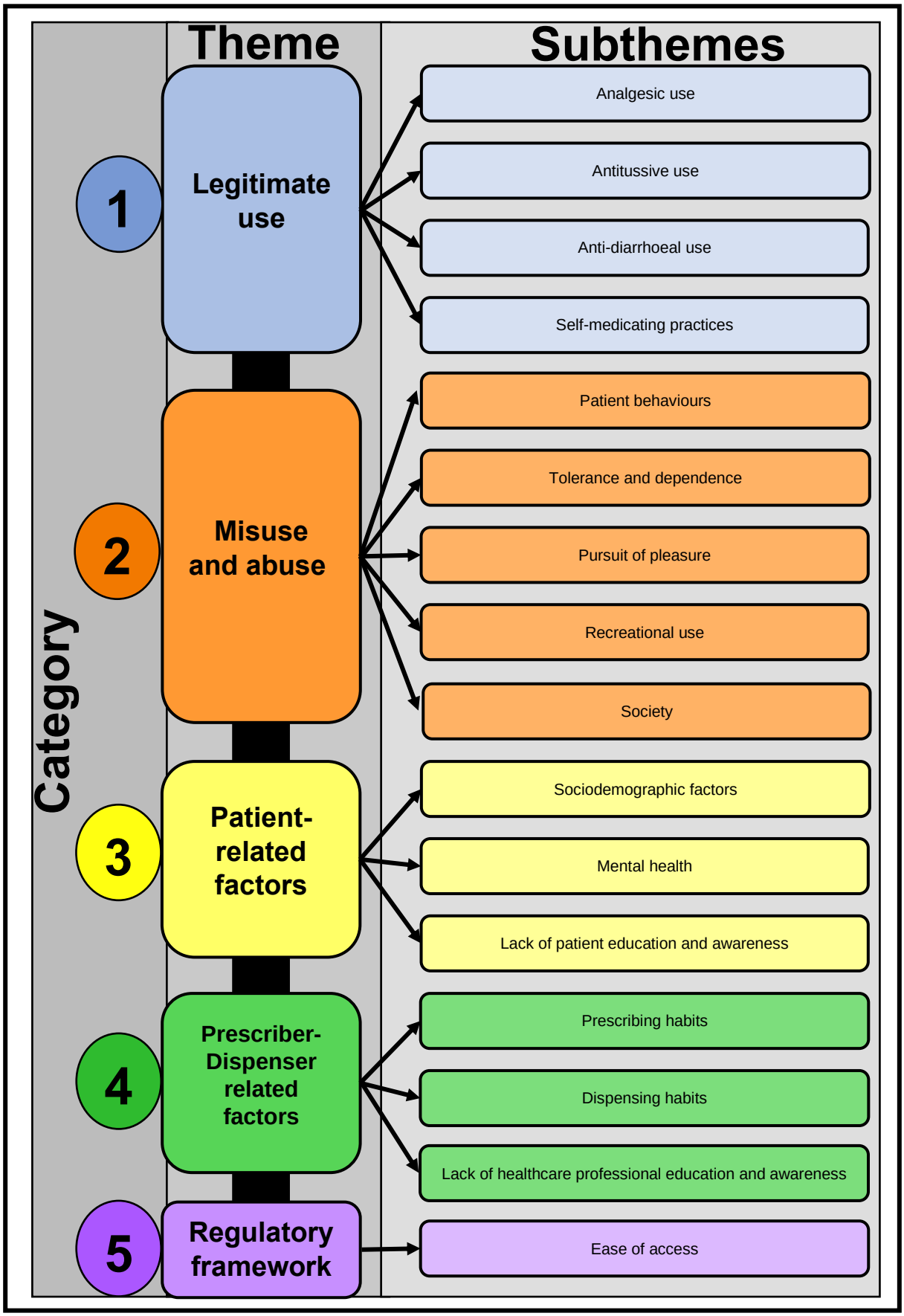


Figure 3.1: Categories and theme breakdown of this review.

3.2.1. Legitimate use

Many members of the public use codeine products for legitimate reasons (Van Hout *et al.*, 2014). Rational uses of codeine are present when patients utilise codeine for its intended therapeutic effects, not realising its potential for harmful effects. As some CCMs are available as OTC medicines in countries like SA, this accessibility leads to increased self-medicating practices, with correct usage of codeine commonly used for its analgesic, antitussive and anti-diarrhoeal properties (Van Hout *et al.*, 2014). However, minimal studies are available that suggest a preferred clinical indication for codeine.

Over-the-counter CCM products are most beneficial to individuals who take the onus of their health and utilise these products for rightful reasons, in accordance with the product's information leaflet guidelines or HCPs' advice regarding the use of such products. There is a risk that the extended legitimate use of CCMs may result in the misuse and abuse of codeine products (Nielsen *et al.,* 2013; O'Neill, 2016). At the point of prescribing or dispensing, increased rates of the patient's lack of understanding and knowledge of codeine have been shown (Kinnaird *et al.*, 2019). Healthcare professionals are concerned that the public does not always understand how codeine acts within the body, and hence, whilst patients use codeine for legitimate reasons, they reported that they "didn't know what [they were] taking, and [they] didn't know what the risks of [using codeine were], so [they] felt that [they] should really start understanding what [they're] being prescribed" (Kinnaird *et al.*, 2019).

3.2.1.1. Analgesic use

Codeine's analgesic properties are the result of the biotransformation of codeine to morphine (Singu and Verbeeck, 2021). Mediated via the μ-receptors in the central nervous system, codeine's analgesic effect occurs by inhibiting the transmission of nociceptive impulses triggered by tissue damage and is commonly used in the management of postoperative pain (Van Hout *et al.*, 2014). Compared to morphine, codeine has a lower sedative effect and is associated with a lower potential for respiratory depression (Van Hout *et al.*, 2014). Kimergard *et al.* (2017) reported in a study, that 91% of non-codeine-dependent respondents chose to use codeine as an

analgesic (95% CI [0.16 to 0.76]) (Kimergard *et al.*, 2017). Globally, codeine is known to be present in a wide range of pharmaceutical products that are indicated for the management of mild to moderate pain.

Although codeine is classified as a 'weak' opioid, a seven-country study proved that weak opioids were used more than strong opioids and that four of the seven countries reported results that codeine was the most used weak opioid (Fredheim *et al.*, 2009). A Norwegian study proved that codeine comprised of 82% of all weak opioid sales and 60% of all total opioid sales in DDDs, culminating in 12.9 DDDs/1 000 inhabitants/day (Fredheim *et al.*, 2009). Therefore, as suggested by literature, despite being classified as a 'weak' opioid, attention to using codeine as an opioid should not be disregarded for its addictive and habit-forming properties.

3.2.1.2. Antitussive use

Codeine is often present as a cough suppressant (an antitussive agent) in cough syrups (Morice and Kardos, 2016). However, literature has shown that there is minimal evidence proving codeine's antitussive intrinsic activity. As a prodrug, the conversion of codeine to morphine has demonstrated that morphine can only be effective in chronic cough treatments, as reported by a third to half of patients in a randomised control trial study (Morice and Kardos, 2016). In 2007, placebo-controlled studies showed that as an antitussive, codeine proved to be equally ineffective as a placebo in reducing cough symptoms (Bolser and Davenport, 2007). Therefore, with minimal clinical evidence supporting codeine's antitussive activity, codeine cough syrups should be avoided as a first-line suppressive cough agent (Van Hout *et al.*, 2014; Singu and Verbeeck, 2021). Although it is advised to avoid using codeine as an antitussive, codeine may be demonstrated to be an effective antitussive, since codeine's multifaceted effects, namely analgesic, sedative and antitussive properties, are all advantageous when experiencing a painful cough (Vora and Nadkar, 2015).

3.2.1.3. Anti-diarrhoeal use

Various opioids, including codeine, can be used for anti-diarrhoeal purposes (Singu and Verbeeck, 2021). Acting locally in the gastrointestinal tract, opioids reduce stool

volume by disrupting the neurotransmission pathways between smooth muscle cells and epithelial cells (Singu and Verbeeck, 2021). Codeine should be avoided as a first-line product in the treatment of diarrhoea due to the minimal research available on its anti-diarrhoeal properties. However, a study by Schiller *et al.* (1982), proved that codeine leads to the retention of luminal contents in the proximal gastrointestinal tract (Schiller *et al.*, 1982). As a result, this slows down the movement of fluid from the proximal to the distal regions in the intestine (Schiller *et al.*, 1982). While Schiller *et al.*'s (1982) study identifies codeine as an anti-diarrhoeal agent, their study is over three decades old. Yet, no recent and newer studies corroborate Schiller *et al.*'s (1982) findings. Additionally, many countries have not registered codeine as an anti-diarrhoeal product (Schiller *et al.*, 1982; Singu and Verbeeck, 2021).

3.2.1.4. Self-medicating practices

Self-medicating can be defined as the autonomous practice of independently obtaining and consuming non-prescription drugs, without the guidance and advice of a HCP for diagnosis, prescription, or management of an ailment (Builders, 2016; Padayachee, 2020). Pharmacist-initiated therapy (PIT) occurs when patients seek advice and recommendations from a pharmacist to help treat and or manage minor ailments of which the patient may present (Dooley *et al.*, 2004). The pharmacist will resort to suggesting the use of an OTC product, based on the pharmacist's professional medical knowledge and judgement (Dooley *et al.*, 2004). Although OTC medicines promote self-administration of medication for the treatment of minor ailments, they alleviate strain on healthcare services and enhance the availability of medicinal supplies, increasing the risk of overuse, misuse and abuse (Ino and Nakazawa, 2022). In 2005, one in ten adults in Norway was dispensed an OTC CCM product, increasing the overall rate of consumption, and purchasing of OTC CCMs (Van Hout *et al.*, 2014). The initial usage of PIT may sometimes result, over time, in the patient resorting to self-medicating practices (Dooley *et al.*, 2004; Ino and Nakazawa, 2022).

Correct self-medicating practices, including PIT, contribute to codeine use. Self-medicating practices are common in developing countries and are often linked to a lower-quality healthcare system (Padayachee, 2020). However, this has contributed to

public perceptions of the safety of codeine and a lack of awareness of the potential risks of overuse, misuse and abuse (Van Hout and Norman, 2016).

Seeking advice from a pharmacist during the self-medicating process will warrant PIT, which leads to the correct mechanism of using self-medicating practices (Dooley *et al.*, 2004). However, it is important to note that not all self-medicating practices warrant potential misuse, it may just be that based on circumstances, one will need to rely on a legitimate rationale for self-medicating.

As mentioned by Roussin *et al.* (2013), Cooper (2013) and Padayachee (2020), patients who purchase CCMs for genuine self-medicating practices, often purchase such products for legitimate reasons and often resort to using PIT (Cooper, 2013a; Roussin *et al.*, 2013; Padayachee, 2020). However, there is a risk that repetitive and long-term self-medicating practices with initial legitimate intention of codeine products may result in dependence which can lead to misuse, overuse and abuse of codeine products. Whether intentional or not, such risks may occur (Cooper, 2013a; Roussin *et al.*, 2013).

3.2.2. Misuse and abuse

Sales alone do not necessarily indicate the misuse and abuse of codeine. While misuse and abuse of CCMs significantly impacts sales, the direct link between CCM sales and misuse and abuse is not always apparent. At times, and becoming more evident, the practice of incorrect self-medicating occurs. This may refer to the consumption of medicines stored in home cupboards, including OTC products and leftover prescription medicines from previous ailments (Builders, 2016). Using this stock, users self-medicate and consume these medicines without seeking advice or guidance from a HCP (Builders, 2016). The practice of incorrect self-medicating will potentially contribute to codeine sales; however, it will lead to the misuse of codeine products.

The purchase of self-medicating products is increasingly being bought in copious quantities from online pharmacies and black-market sources (Cooper, 2018; Richards

et al., 2021). This shows the avoidance of pharmacist intervention at the point of sale (Cooper, 2018; Richards *et al.*, 2021). Kimergard *et al*. (2017), proved that individuals who were codeine dependent exhibited a higher tendency to seek assistance from online platforms in managing their codeine dependence, compared to those who were non-codeine-dependent, who sought advice from HCPs (Kimergard *et al.*, 2017). The lack of advice, surveillance and monitoring regarding codeine, from a HCP, encourages patients to disengage from available healthcare services. These patients will resort to using and self-medicating with codeine for all suspected treatment regimens, knowing that codeine would most probably be the first-line prescribed medicine should they visit a healthcare facility that disregards the risks of codeine (Kinnaird *et al.*, 2019).

Misuse and abuse of codeine contributes to certain patient behaviours that suggest the probable development of tolerance and dependence of codeine. Codeine is often then used for the pursuit of pleasure based on societal pressures, suggesting its use in recreational practices. Misuse and abuse of codeine is increasing among the youth (Peters *et al.*, 2007). Younger generations are becoming increasingly aware of codeine and therefore, various exercises of experimentation with this substance are being explored and developed (Cherian *et al.*, 2018).

3.2.2.1. Patient behaviours

Certain behaviours exhibited by individuals and patients promote codeine use, which often strongly leads to codeine misuse. These behaviours facilitate easier access to codeine while avoiding scrutiny of suspicious use. These inappropriate behaviours are often displayed by individuals aware of codeine's addictive nature and who are typically already addicted, resorting to such behaviours to satisfy their addiction. Table 3.2 lists and defines some of the behaviours that individuals may adopt to obtain codeine products.

3.2.2.2. Tolerance and dependence

Repeated utilisation of codeine products without experiencing pain results in the development of tolerance which may lead to codeine dependence (Van Hout *et al.*, 2014). 'Tolerance' may be defined as a reduced physiological response to the effect

of a drug/medicine, due to repeated and prolonged exposure, leading to the need for higher doses of the drug/medicine to achieve the same effect(s) (Pietrzykowski and Treistman, 2008). 'Dependence' may be defined as the excessive and continuous consumption of a psychoactive substance (such as codeine) with no surveillance from a HCP (Cooper, 2013a).

Evidence has shown that of a particular Canadian study sample size, over half of the sample, used OTC CCMs with an average of 179 mg per day (Van Hout *et al.*, 2014). Of this sample, 80% of users consume codeine for five or more days a week (Van Hout *et al.*, 2014). A French study highlighted that 17.8% (p<0.01) of study participants who had used codeine in the past month of the study period, were dependent on codeine (Roussin *et al.*, 2013).

3.2.2.3. Pursuit of pleasure

The 21st century contains various surrounding environmental variables that contribute to numerous emotions and feelings of individuals living within an environment. Table 3.1 highlights, but is not limited to, various emotions and feelings that codeine may emit (Kimergard *et al.*, 2017). Research has shown that CCM users begin utilising these products to treat legitimate physical pain (Kimergard *et al.*, 2017; Van Hout *et al.*, 2018). They then soon realise that such products subside emotional distress feelings and are, therefore, continued to be used for the pleasurable effects and life coping mechanism, that codeine products may portray (Van Hout *et al.*, 2018).

Table 3.1: Feelings of the pursuit of pleasure that codeine-use emits (Kimergard *et al.*, 2017).

The reason for codeine use	OR*	95% CI [lower limit to upper limit]
To enhance relaxation	3.94	2.13 to 7.29
To feel euphoric/elated	3.65	1.77 to 7.52
To prevent worrisome feelings	6.78	3.23 to 14.22

*OR = odds ratio

Sproule *et al*. (1999), reported that CCM misusers reported chronic pain to their HCP to obtain a CCM product, however, these patients are more likely to use these CCM

Table 3.2: Patient behaviours to obtain codeine.

Behaviour	Definition	References
Dress code	Individuals may dress in **smart business wear** when purchasing codeine products, to create a false impression, deceiving the pharmacist, that visually this individual is at minimal risk of codeine misuse. This may result in minimal pharmacist intervention and the codeine product is easily dispensed.	Nielsen *et al.,* 2013
Request of CCM by name	Individuals may repeatedly **request and often insist, by name, a specific codeine product** to either the doctor writing the prescription, or to the pharmacist performing PIT.	Chou *et al.*, 2009 Norman *et al.*, 2016
Out-of-proportion pain	During a doctor's consultation, an individual may present with **out-of-proportion pain, exaggerating the pain**, knowing that the doctor will possibly prescribe an opioid, such as codeine, to relieve the pain.	Norman *et al.*, 2016
Early opioid refills	Individuals may often tend to **request their early opioid prescription refills**, either from their prescribing doctor or from their pharmacist.	Foley *et al.*, 2018
Rehearsed answers	Over time, codeine misusers learn the proposed questions that they know their prescriber/dispenser may ask them during a consultation when deciding on what to prescribe/dispense to the individual. Therefore, over time, misusers tend to **rehearse answers** that they know will correctly answer the questions to lead the prescriber/dispenser into prescribing/dispensing codeine products.	Cooper, 2011 O'Neill, 2016
Agitated refusal of non-codeine products	Prescribers and or dispensers may suggest to an individual the usage of a non-codeine product. The individual will **refuse the suggestion of a non-codeine product**, as they rely on the codeine product to feed their addiction. This results in the individual becoming **agitated** with the prescriber and or dispenser when confronted with an alternative non-codeine product.	Chou *et al.*, 2009 Van Hout, 2014a Norman *et al.*, 2016
Largest pack size	Pertaining to individuals who frequently purchase OTC CCMs in a pharmacy, individuals learn to get to know the various pack sizes available for the various OTC codeine products. Often, these individuals will request to **purchase the largest OTC CCM pack size** available.	Chou *et al.*, 2009 Van Hout, 2014a Norman *et al.*, 2016
Doctor shopping	This may be defined as the practice of individuals **visiting multiple doctors over a brief period**, to obtain multiple codeine prescriptions, without disclosing previous visits or prescriptions.	Chou *et al.*, 2009 Van Hout, 2014a Norman *et al.*, 2016
Pharmacy hopping	This may be defined as the action of an individual **visiting multiple pharmacies**, often within close proximity, **to obtain OTC CCMs**, with the knowledge that no records will be recorded of these sales, as there is no central database detecting such recurring purchases. This phenomenon avoids suspicion among pharmacists.	Van Hout and Norman, 2016 Cooper, 2018
Paying cash for OTC CCMs	Individuals with medical aid may opt to **purchase codeine products using cash**, since they may want to purchase such products "secretively" and not have a record of such purchases on their medical aid profile, which may potentially track the codeine purchases.	Van Hout *et al.*, 2018
Friends and family	Codeine misusers may resort to **asking family members and or friends to purchase codeine products on their behalf**, therefore, creating a barrier to pharmacist intervention for the codeine user.	Nielsen *et al.,* 2013

products to reduce stress and achieve codeine's pleasurable relaxing effect (Ćelić *et al.*, 2020). This phenomenon is referred to as "chemical coping", whereby the user achieves a coping mechanism with the use of a chemical drug, like codeine (Van Hout *et al.*, 2014). Misusers of CCMs adapted to the "chemical coping" phenomenon as "[n]othing stressed [them] when it worked, codeine filled a void" to avoid the emotional and mental consequences of reality (Van Hout *et al.*, 2018). Others argue that codeine portrays a "buzz" feeling that no other substance portrays (Cooper, 2011). This causes misuse of CCMs, by ensuring codeine's pleasurable and euphoric effect is maintained throughout the day, for daily functioning (Van Hout *et al.*, 2018).

Wells *et al*. (2019) highlighted in a three-country study, that 0.5% of English respondents, 2% of Irish respondents and 6% of South African respondents, utilised CCMs for relaxation purposes (Wells *et al.*, 2019). In addition, Singu and Verbeeck (2021), reported that 6% of Irish, 13% of South African and 16% of English CCM users, purchased OTC CCM products weekly (Singu and Verbeeck, 2021). Other reasons for CCM purchase and usage included relief from emotional stress and codeine's ability to enhance motivation and confidence during normal daily activities (Van Hout *et al.*, 2018). Codeine created a 'liking' effect on users, which contributed to user misuse habits of codeine, continuously utilising codeine as a reward by "[looking] forward to [codeine] throughout the week … to treat [themselves] on Friday" (Van Hout *et al.*, 2018).

3.2.2.4. Recreational use

Various patient-reported rationales contribute to the recreational use of CCMs. Patient-reported factors include physiological dependency on codeine utilising the substitution phenomenon and alcohol/codeine co-use as well as the co-use of OTC and prescription CCMs (Cooper, 2011; Cooper, 2018; Kinnaird *et al.*, 2019). Experimentation contributes to the recreational usage of codeine, including experimenting with 'Purple Drank,' 'Krokodil', and 'Kratom Cocktails' concoctions (Van Hout, 2014b). Societal influences of increased CCM sales encompass the Hip-hop culture and social media influences.

3.2.2.4.1. Patient-reported contributions

Various patient-reported factors contribute to CCM misuse. Such contributions include using codeine as a substitute product in the event of addiction to an illegal drug (Kinnaird *et al.*, 2019). This also includes using alcohol and codeine together (Kinnaird *et al.*, 2019). Patients have also reported using OTC and prescription CCM products together (Cooper, 2011).

Substitution phenomenon and alcohol/codeine co-use

Codeine-containing products are often used by misusers as a replacement for other illicit drugs or products. The CCM 'Substitution phenomenon' may be defined as the use of OTC CCMs when illicit drugs or medicines cannot be acquired (Cooper, 2018). This phenomenon is intentional and inappropriate. Illicit drugs, such as heroin, are relatively expensive and not readily available (Escribano *et al.,* 2017). Instead, codeine is easily accessible and affordable, therefore users of CCMs substitute codeine for heroin to feed their illicit drug addiction (Kinnaird *et al.*, 2019). The substitution phenomenon acts as a gateway opportunity for the misuse and addiction of stronger opioids, purchasing codeine products to serve their "silent addiction" (Hockenhull *et al.*, 2022).

Frequent use of a drug/medicine leads the human body to be dependent on a certain drug/medicine and unpleasant symptoms will persist when the drug/medicine is ceased, therefore experiencing withdrawal symptoms. Continuous use over a long period of time on a certain substance will warrant tolerance and dependency (O'Neill, 2016). This will create a withdrawal phenomenon when the substance is stopped, as the body believes it cannot function without this substance, or the user claims that codeine provides a sense of companionship and security (O'Neill, 2016).

Opioids and illegal drugs, such as heroin, are common substances that create withdrawal symptoms once ceased. Codeine-containing medicines are often used to ease the withdrawal symptoms of such substances (Van Hout *et al.*, 2014; Kimergard *et al.*, 2017). A study correlating to this motive indicates that users utilise codeine to ease withdrawal symptoms of other opioids (OR=6.36, 95% CI [2.05 to 19.75])

(Kimergard *et al.*, 2017). Codeine possesses addictive properties, which the body physiologically seeks as a substitute substance harbouring addictive attributes. This substitution aids in the cessation process from other substances, such as heroin. Instead of being used for its psychoactive effects, polydrug users use CCMs for opiate maintenance (Van Hout *et al.*, 2014).

Although the motive of CCM use is for the 'alleviation' of withdrawal symptoms from other substances, users tend to utilise CCMs in "binge" episodes, thinking that the withdrawal symptom will be alleviated quicker if codeine products are used more frequently and in larger quantities (Van Hout *et al.*, 2014). This is untrue and although misuse rates of stronger substances such as heroin may be decreased, this, in turn, increases the rates of CCM misuse globally, which potentially increases irrational codeine sales and addiction (Van Hout *et al.*, 2014). Fredheim *et al*. (2009) reported in a European study that 0.5% of 1 787 study participants who received a codeine-based prescription, received more than 730 codeine DDDs which equates to more than 2 DDDs/day, exceeding the upper therapeutic limit of 240 mg of codeine/day (Fredheim *et al.*, 2009). Half of these participants maintained a prescription level above 730 DDDs over three years and were therefore likely to have developed codeine addiction (Fredheim *et al.*, 2009).

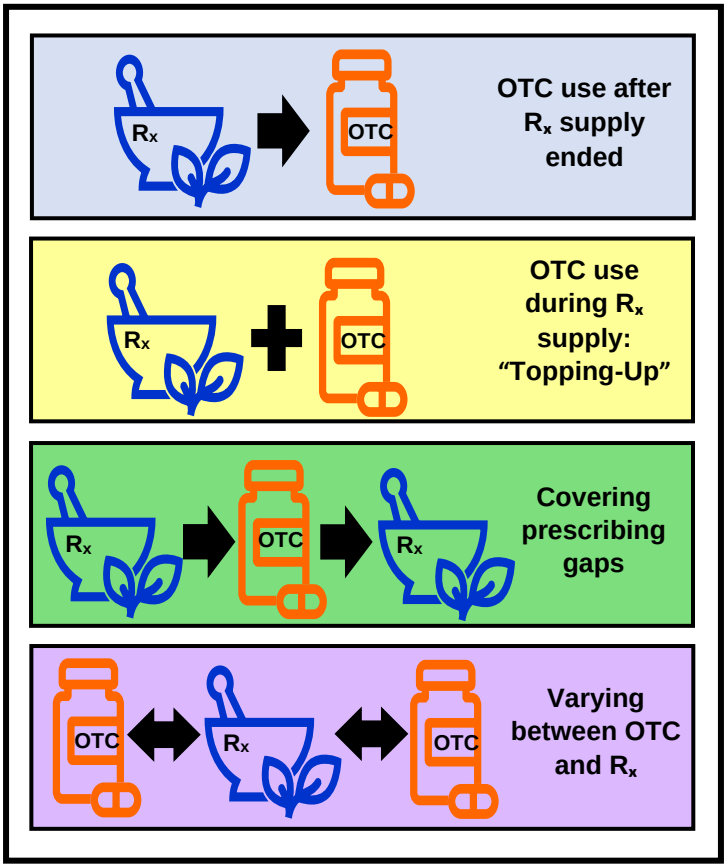
According to Nielsen *et al*. (2013), 55% of codeine-dependent study participants in Australia received previous treatment for alcohol or drug dependence, which included codeine drug dependence (Nielsen *et al.,* 2013). This statistic is concerning as the substitution phenomenon becomes more prevalent in global communities. Relating to this study, Van Hout *et al*. (2014) indicated that the use of polysubstance medicines is commonly used to achieve substitution effects of other drugs and therefore, reduce the negative outcomes associated with the use of illicit drugs (Van Hout *et al.*, 2014).

Prescription and OTC CCM co-use

Studies have shown that individuals tend to perceive OTC codeine-combination products as safe and therefore dependency and overuse risks are common (Kimergard *et al.*, 2017; Hockenhull *et al.*, 2022). This does not exclude the fact that

overuse of co-formulation ingredients such as paracetamol and or ibuprofen may present harmful effects such as gastric, cardiovascular and hepatotoxicity harm, of which the public is unaware (Roberts and Nielsen, 2018).

A three-country survey on pharmacist perspectives of codeine products sold reported that codeine-combination products were most popular in SA (72.1%), Ireland (98.2%) and the UK (99.2%) (Carney *et al.*, 2018). Contributing to these results, evidence has proven that often, codeine-combination products are initially used for genuine medical reasons, and over time, tolerance and dependency prevail and continued excessive and frequent daily use of codeine is prominent (Cooper, 2013a). As depicted in Figure 3.2, there are various associations that individuals practise when purchasing and consuming OTC and prescription-only codeine products (Cooper, 2011).



Rx = prescription medicine; OTC = over-the-counter

Figure 3.2: Various associations between prescribed and OTC codeine medicine use (Adapted: Cooper, 2011).

Note: Permission granted from author to use figure (Appendix B).

An association between prescribed and OTC CCMs presents when individuals finish a course of prescribed medication, often painkillers, and the individual feels that their body craves the painkiller once the prescribed dose has run out (Cooper, 2011). However, as prescribed, only a certain number of tablets are dispensed, and thus, the individual replicates the prescribed painkiller's effect with an OTC CCM (Cooper, 2011).

Another occurrence emerges as "Topping-up" when individuals use OTC CCMs to "top-up" the total amount taken of the prescribed medicine, increasing its strength and effect (Cooper, 2018). Often, practitioners prescribe repeated prescriptions of painkillers, and an individual is aware that the pharmacy will only dispense the next repeat after 30 days of supply of the first repeat. Thus, individuals apply the "gap phenomenon" by consuming OTC CCMs to cover the gap time of obtaining the next repeat of medicines (Cooper, 2013a). Lastly, a common association occurs whereby individuals make their prescribed medicines last longer by alternating between OTC and the prescribed product, therefore experimenting together with various OTC and prescription products (Cooper, 2011).

Experimentation

Home manufacture and experimentation with prescribed or OTC codeine products are becoming increasingly popular among global youth and recreational drug users (Van Hout, 2014b). The in-home-produced drugs in Table 3.3 allow users to think of the ideology that "no one can stop me" from producing these drugs in their own, personal capacity and homes, as minimal peer awareness is involved (Van Hout, 2014b). This contributes to the production of new, accessible and affordable recreational and illegal drug products (Van Hout, 2014b).

Home-manufactured codeine drugs and home experimentation of such products are driven by market factors such as ease of access, ease of tampering and extracting of formulations resulting in higher active ingredient dose consumption and a beneficial cost-benefit ratio (Van Hout, 2014b). Such actions are taken to ensure the elimination

of unwanted excipients and undesirable active ingredients, all to reach a heightened "sense of euphoria" addictive effect (Tettey *et al.*, 2020).

Table 3.3: Common home-manufactured codeine recreational drugs (Hart *et al.*, 2014; Van Hout, 2014a; Richards *et al.*, 2021).

	'Purple Drank'	**'Krokodil'**	**'Kratom Cocktails'**
Street names	Lean Sizzurp Dirty Sprite Syrup Purple Lean	Russian Magic Russian Heroin Crocodile	-
Origins	USA	Russia	Thailand
Typical constituents	Codeine cough syrup Sprite® Skittles® Alcohol Fruit juice	Codeine cough syrup Hydrochloric acid Red phosphorous Iodine	Codeine cough syrup Kratom leaves Coca-Cola® Alprazolam
Popularity*	1	2	3

***Popularity range:** 1 = the most popular; 3 = the least popular
USA = United States of America

Purple Drank

'Purple Drank' is a homemade codeine concoction that contains an OTC cough syrup, comprising of codeine and promethazine hydrochloride (an antihistamine and antiemetic with sedative effects) (Agnich *et al.*, 2013; Richards *et al.*, 2021). The purple hue results from the dye in the codeine cough syrup (Van Hout, 2014b). Together, the codeine and promethazine effects develop intensified euphoric effects and substance tolerance and dependence, leading to high rates of addiction to 'Purple Drank' (Cornell, 2023).

As depicted in Table 3.3, 'Purple Drank' contains a cold drink, namely Sprite®. The idea of cough syrup mixed with a cold drink often creates a false perception to users, that codeine is meant for recreational use. Users easily lose track of the amount of 'Purple Drank' consumed as the unpleasant cough syrup flavour is masked by the familiar Sprite® cold drink and candy flavour (Van Hout *et al.*, 2014). When consumed in copious quantities, a risk of harmful effects can occur (Cornell, 2023). Such effects may include dissociation, troubled breathing, irregular heart rate, sedation, altered levels of consciousness and life-threatening events such as serious brain damage

(Peters *et al.*, 2007; Agnich *et al.*, 2013; Van Hout, 2014b; Van Hout *et al.*, 2014; Cornell, 2023).

The appeal among adolescent users seems to be rooted in social norm beliefs that revolve around the notion that trying codeine products involves minimal risk, low potential for abuse and a low likelihood of adverse consequences (Van Hout, 2014b). A Texan study surveyed 61 college students, whereby the respondents were informed by HCPs about the dangers of codeine-abuse potential (Agnich *et al.*, 2013). However, the students ignored such information and were "peer pressured" into believing that codeine cough syrup misuse is perceived as "cool" (Agnich *et al.*, 2013). Codeine cough syrup use and experimentation are largely evident among unemployed young males (average age of 20±5 years old) in urban black ethnic groups and homosexuals, often associated with polysubstance use (such as marijuana and alcohol), use of novel psychoactives and an increased rate in sexual activity (Peters *et al.*, 2007; Van Hout, 2014b). Agnich *et al*. (2013) reported that 100% of American college 'Purple Drank' users, consumed alcohol within the past month of using 'Purple Drank' and that marijuana users were more likely to report 'Purple Drank' use (10.7%) than non-marijuana users (0.7%) (Agnich *et al.*, 2013).

Krokodil

Another illegal homemade codeine concoction is 'Krokodil' which is five times cheaper than heroin (Florez *et al.*, 2017). It is an injectable that contains addictive, low-cost desomorphine, which is synthesised by reacting codeine and thionyl chloride together, thereby producing alpha(α)-chlorocodide, a substrate of desomorphine (Escribano *et al.,* 2017). This novel injectable was reported to be a new phenomenon of estimates between 20 000 and 100 000 injectors in 2011, as well as being the homemade opiate of choice used as heroin substitution therapy in users in Georgia, USA (Van Hout, 2014b; Richards *et al.*, 2021).

Desomorphine's sedative and analgesic effect is ten times greater than that of morphine and its toxicity exceeds morphine by three-fold, making this concoction highly craved, wanted and used (Van Hout, 2014a; Escribano *et al.,* 2017). 'Krokodil' possesses a much faster and shorter half-life than morphine, resulting in the user

injecting larger amounts of the concoction to ensure its continuous effects (Florez *et al.*, 2017). Of note is the name given to this product, 'Krokodil', mimicking users' skin which becomes scale-like, green and or black discoloured and ulcerated (imitating the appearance of a crocodile's skin) (Florez *et al.*, 2017). When used in large quantities, 'Krokodil' reacts with the skin and causes necrosis of the blood vessels, necrosis of the jaw, skin infections, inflammation and damage to the liver and kidneys, deterioration of cognitive functioning, multiorgan failure, amputation of the limbs and may ultimately lead to death (Van Hout, 2014a; Richards *et al.*, 2021).

Kratom Cocktails

Originating from, yet banned in Thailand, a similar form of 'Purple Drank' and 'Krokodil' was discovered. The cough syrup in 'Kratom Cocktails', typically contains caffeine and three main active ingredients, namely chlorpheniramine (an antihistamine), codeine and phenylephrine (a decongestant) (Van Hout *et al.*, 2014). The Kratom leaves contain over 25 alkaloids, with mitragynine being its major psychoactive constituent (Van Hout *et al.*, 2014). Becoming increasingly popular amongst American and European youth, 'Kratom Cocktails' are often recreationally served with ice, coffee, or yoghurt (Van Hout *et al.*, 2014).

3.2.2.5. Society

The social surroundings of an individual's environment can generate both negative and positive outcomes relating to codeine-related use. Social settings and related factors influence the public's decisions for utilising CCMs recreationally and for non-therapeutic reasons. However, with minimal available quantitative findings to support this societal literature, these factors may be nuances that are not necessarily purported to be contributing factors to increased CCM sales. Not only limited to, but technology and social media encourage today's youth to adopt the 'media model' idea, affecting many of the youth's decisions which are influenced by what is seen and heard through social media and various music genres (Hart *et al.*, 2014).

3.2.2.5.1. Hip-hop culture

In the 1990s in Houston, Texas, USA, a Rap artist, DJ Screw, pioneered a genre of music (called "Screw music") dedicated to the feelings portrayed when consuming 'Purple Drank' (Van Hout *et al.*, 2014). The music featured "chopped and screwed" beats that were characterised by slower and relaxed beats, mimicking the effects of codeine contained in 'Purple Drank' (Van Hout *et al.*, 2014). "Chopped" refers to the "copy-cut-paste sampling technique and stutter effect" that is used to "chop up" the original song, thereby creating lyrics of repetition and delays (Cherian *et al.*, 2018). "Screwed" refers to the "decreased tempo and … pitched-down nature", which portrays the style of the physiological effects of consuming codeine products recreationally (Cherian *et al.*, 2018). Thereafter, other Rap and Hip-hop artists followed the lead and began producing influential music with lyrics portraying the perceived 'accepted' idea of recreationally drinking codeine cough syrups (Agnich *et al.*, 2013). Listeners became increasingly aware of these mixtures and started making and consuming them, thereby accelerating the rate of misuse of CCMs. Tettey *et al*. (2020), reported a study that analysed lyrics of "40 of The Best Hip Hop Songs That Mention Lean [codeine-containing products/Purple Drank reference]", whereby various themes were described, and the lyrics promoted codeine use (Tettey *et al.*, 2020). Table 3.4 highlights three examples of such lyrics and their related themes.

Table 3.4: Hip-hop song lyrics promoting the use of codeine (Tettey *et al.*, 2020).

Theme	Lyrics	Song name	Artist
'Lean' used in combination with another drug(s)	"Yeah, I'm on that gas / And yeah, I'm on that lean / We mix it all together and we call it gasolean"	Gasolean	2 Chainz
'Lean' used in combination with a cold drink	"You put the codeine in the Sprite / And then you mix it all up / Then you sip it slow…We call it Lean"	Lean	Jarren Benton
General mention of 'Lean'	"Money taller than mountains / Drinking lean out of damn water fountains"	Ounces	Migos

The majority of Hip-hop music listeners, are the younger generation, appealing to more idolising rappers and celebrities (Van Hout *et al.*, 2014). In support, is a study that reported that "drug-related messages in music predicted substance misuse in young adults aged 16-25 years and that drug-related slang was 19 times more common in

2017 than in 2007" (Richards *et al.*, 2021). Studies have shown that listeners who prefer Jazz, Country, Western and other genres of music rarely know about or use recreational codeine-containing products (Hart *et al.*, 2014; Tettey *et al.*, 2020). However, the prevalence and preference of the use of codeine-containing products are comparatively higher in listeners who prefer Rock, Alternative and most prevailing, Rap and Hip-hop genres of music (Hart *et al.*, 2014; Van Hout *et al.*, 2014; Tettey *et al.*, 2020). This indicates that there is a strong relationship between Rap and Hip-hop genres and recreationally using codeine-containing products (Hart *et al.*, 2014).

3.2.2.5.2. Social media influences

Social media influences individuals' choices to use certain pharmaceutical CCM products not necessarily for their chosen indication, but rather for situations of 'medicinal needs' (Builders, 2016). Unknowingly, CCM purchasers do not realise that the intended advertising is misleading and not factual, therefore demonstrating a great level of trust and attentiveness towards social media, as opposed to the professional opinion provided by HCPs (Wells *et al.*, 2019).

The youth of the 21st century spend countless hours browsing the internet and surfing social media platforms. Advertising and marketing schemes offer platforms, targeted to the youth, for constructing and disseminating narratives related to the misuse and probable addiction of codeine-containing products (Cherian *et al.*, 2018). The internet and social media are immediately available at the click of a button and are free to all. This poses a risk that users will ultimately be persuaded using social media, to use codeine products recreationally and experimentally, therefore increasing the rates of young, codeine-dependent individuals and addictive misuse (Kimergard *et al.*, 2017). The influence of media modelling on youth behaviour, regarding the specific consumption and purchase of codeine products, can be attributed to the presence of traits such as "curiosity" (15%) and "peer pressure" (72%) (Peters *et al.*, 2007).

Instagram®, the second most popular social media platform, is frequently described as an influential tool for the misuse of codeine (Cherian *et al.*, 2018). Public posts containing videos and pictures, are captioned by Instagram® users and are often

posted with accompanying hashtags. These hashtags contribute to and create an impromptu public forum to discuss a certain event or topic, thereby aggregating posts with the same hashtags. Cherian *et al.* (2018) conducted a study to determine the relationship between CCMs and Instagram®. The result showed that some of the most common Instagram® hashtag phrases related to CCM misuse were “weed”, “hiphop”, “luxury”, “yunglean” and “rap” (Cherian *et al.*, 2018). Many of these hashtag phrases revealed a congruent relationship between the misuse of codeine and polysubstance use, specifically marijuana (Van Hout *et al.*, 2014; Cherian *et al.*, 2018). Such influential Instagram® posts encourage followers and viewers to normalise CCM misuse behaviour and encourage the usage and purchase of CCMs (Van Hout *et al.*, 2014; Cherian *et al.*, 2018; Tettey *et al.*, 2020). These posts serve as instructional tools that both educate and establish a sense of normalcy around the misuse of CCMs, openly defying social and legal prohibitions (Cherian *et al.*, 2018).

However, social media and internet platforms may offer a space for CCM misusers to seek genuine help and support to overcome their addiction (Lee and Cooper, 2019). Online codeine support forums are readily available on the internet and may be utilised anonymously, thus creating comfort for the user, to prevent feeling any associated guilt or stigma (Lee and Cooper, 2019). Although social media and internet platforms may initially be stigmatised as negative platforms to curtail CCM misuse, social media can also offer support and advice to CCM misusers who desperately seek help to overcome their addiction. Subsequently, these platforms, depending on their posting aim, may contribute positively and or negatively to the opioid and codeine-use crisis.

3.2.3. Patient-related factors

Besides misuse and abuse, various other factors contribute to the increased sales of CCMs. Contributing patient-related factors include sociodemographic factors such as age, gender and geographical location. Mental health and the usage of CCMs are also explored. Another contributing factor is the lack of education and awareness that patients have regarding CCMs (Soumya *et al.*, 2016; Carney *et al.*, 2018).

3.2.3.1. Sociodemographic factors

In the remote and rural areas of high-income countries, such as Sweden and Australia, the highest utilisation patterns of CCMs were observed in regions characterised by low-income, low-education and high-unemployment areas (Henricson *et al.*, 1999; Gisev *et al.*, 2016). Most clinical profiles utilising and purchasing CCMs, predominantly consist of adolescent to middle-aged females (Nyoni *et al.*, 2022).

3.2.3.1.1. Age

Numerous studies have indicated that OTC CCMs are regularly bought by consumers in both the adolescent and middle-aged categories (Nyoni *et al.*, 2022). The adolescent age category can be defined as members of the public between the ages of 15-25 years old (Cooper, 2011; Nyoni *et al.*, 2022). Codeine-containing syrups are often bought by adolescents. In 2006, Cooper (2011), reported on the National Survey on Drug Use and Health, that 3.1 million individuals aged 12-25 years old, stated that they had used or tried an OTC syrup-form CCM to 'get high' for recreational purposes (Cooper, 2011). Individuals in the 12–25-year-old age bracket are in a transitionary stage of life whereby, through social pressures, experimentation with certain drugs, like codeine, is often encouraged (Ino and Nakazawa, 2022). Encouragement of such behaviour often stems from societal and peer-pressure influences (Ino and Nakazawa, 2022). As a result, increased crime rates, increased youth mortality and increased codeine misuse treatment admissions within the community often prevail (Dada *et al.*, 2015; Parry *et al.*, 2017; Harker *et al.*, 2020).

The middle-aged category can be defined as members of the public between the ages of 25-40 years old (Nielsen *et al*., 2013; Kimergard *et al.*, 2017). Various studies indicated that the mean age of CCM purchasers were individuals of the age 35±12.3 years old (Nielsen *et al*., 2013; Gisev *et al.*, 2016; Kimergard *et al.*, 2017; Nyoni *et al.*, 2022). A qualitative study on codeine-consumer's perspectives indicated that various middle-aged women were scrutinised during a purchase of a CCM, since their age regarded them as "some raving drug addict" of which they also purchased something else with the CCM, so not to raise suspicion (Nielsen *et al.,* 2013). A further study also revealed that 47% of non-codeine-dependent respondents and 28% of codeine-

dependent respondents were below the age of 30 years old (OR=0.44, 95% CI [0.23 to 0.84]) (Kimergard *et al.*, 2017). The same study proved that only 3% of non-codeine-dependent respondents were aged 61 years and over (Kimergard *et al.*, 2017). Additionally, only 4% of codeine-dependent respondents were older than 61 years (Kimergard *et al.*, 2017). Recent and older studies have collectively agreed that middle-aged persons are more likely to use CCMs (Nielsen *et al.,* 2013; Gisev *et al.*, 2016; Kimergard *et al.*, 2017; Nyoni *et al.*, 2022).

3.2.3.1.2. Gender

The findings are unanimous that the use of prescription and non-prescription CCMs are more prevalent in the female gender (Henricson *et al.*, 1999; Myers *et al.,* 2003; Nielsen *et al.*, 2015). Myers *et al*. (2003) reported that women, being more susceptible to mood disorders, and as such, may be more socially accepted to purchase OTC and prescription medicines, inclusive of codeine products (Myers *et al*., 2003). This acceptance is reinforced by the hormonal mechanisms unique to females. The prevalence of mood disorders, particularly evident in menopausal women, further normalises the purchase of such medicines (Pearlstein *et al.,* 1997; Soares, 2014). A novel case series study comparing codeine users and strong opioid users found that the codeine users' group were three times more likely to be female (OR=3.37, 95% CI [1.63 to 6.96]) (Nielsen *et al.*, 2015).

Worldwide, men from both working-class and professional backgrounds often exhibit a reluctance to seek healthcare, influenced by cultural perceptions that viewing health concerns is a weakness that contradicts traditional masculine behaviour (Fardell and Kate, 2005; Galdas *et al.,* 2005). It is thus evident that over the duration of three decades, the female gender purchases codeine products, as compared to male patients.

3.2.3.1.3. Geographical location

Geographical location often contributes to various populations' codeine-product sale trends. Urban pharmacies are associated with increased purchase patterns of CCMs (Cooper, 2011). In addition, urban locations house pharmacies that contain a larger

selection of CCMs to accommodate the general public's needs within the area (Henricson *et al.*, 1999). In contrast, rural pharmacies lack access to and supply of CCM products (Gisev *et al.*, 2016). Rural pharmacies prioritise essential medicines, such as paracetamol and ibuprofen, due to limited national funding (Derry *et al*., 2013; Gisev *et al.*, 2016). Codeine products, being costlier than paracetamol and ibuprofen, therefore receive less attention (Derry *et al.,* 2013). However, utilisation patterns and increased suspected abuse rates of codeine are often highest in remote and rural locations (Almarsdóttir and Grímsson, 2000). Furthermore, Gisev *et al.* (2016) reported in their Australian study, that the rates of prescription and OTC CCMs were largely used in rural and remote environments (Gisev *et al.*, 2016).

In rural areas, there is limited access to healthcare and support systems. This results in patients self-medicating, which may result in the incorrect and potential misuse of codeine products (Parry *et al.*, 2017). Misusers in rural locations frequently seek alternative avenues to alleviate all forms of pain, and to achieve this, they will make use of the limited supply of OTC CCMs available (Gisev *et al.*, 2016). While rural pharmacies may exhibit lower sales of codeine products compared to urban pharmacies, the rural population demonstrates a higher incidence of codeine abuse comparable to urban areas (Gisev *et al.*, 2016; Parry *et al.*, 2017; Nyoni *et al.*, 2022). Limited literature exists to explain this trend, but it is notable that rural residents often acquire OTC CCMs in urban areas, where work and or school is situated, and subsequently use or abuse these products in their rural communities (Nyoni *et al.*, 2022). These individuals tend to then bring back these products to their rural home area to use, misuse and or abuse (Nyoni *et al.*, 2022). Gisev *et al*. (2016), reported that 0.8 packs/person of CCMs were used by CCM users located in remote areas of Australia (95% CI [0.79 to 0.80]) (Gisev *et al.*, 2016).

A study published in the UK highlighted that areas with greater social deprivation may be more prone to a higher prevalence of opioid use (Mordecai *et al.*, 2018). A factor relating to this may suggest that individuals living in areas with lower socioeconomic status may experience a higher prevalence of chronic pain, which could lead to a greater need for opioid medication to manage their pain (Mordecai *et al.*, 2018).

A South African geospatial codeine-use study highlighted that three provinces in SA were considered “codeine hotspots,” indicating that such provinces may be prone to high codeine use (Figure 3.3) (Nyoni *et al.*, 2022). These provinces included Gauteng, Mpumalanga and the North-West (Nyoni *et al.*, 2022). Although Gauteng is the smallest province, it is the most urbanised province in SA, and hence, CCMs are easily and widely available, with a relative risk of 1.6 for CCM exposure (Nyoni *et al.*, 2022). However, North-West, a rural province, is the greatest “codeine hotspot” province in SA, with two distinct clusters of codeine use within this province, represented by two relative risk results for CCM exposure of 2.4 and 1.6 respectively (Nyoni *et al.*, 2022). This increases the risk of codeine prevalence with its limited supply, as there is minimal point-of-care to educate CCM purchasers on the dangers of misuse and abuse of such products (Nyoni *et al.*, 2022). Mpumalanga, another rural province in SA is also considered a “codeine hotspot” province with a relative risk of 1.8 for CCM exposure (Nyoni *et al.*, 2022).

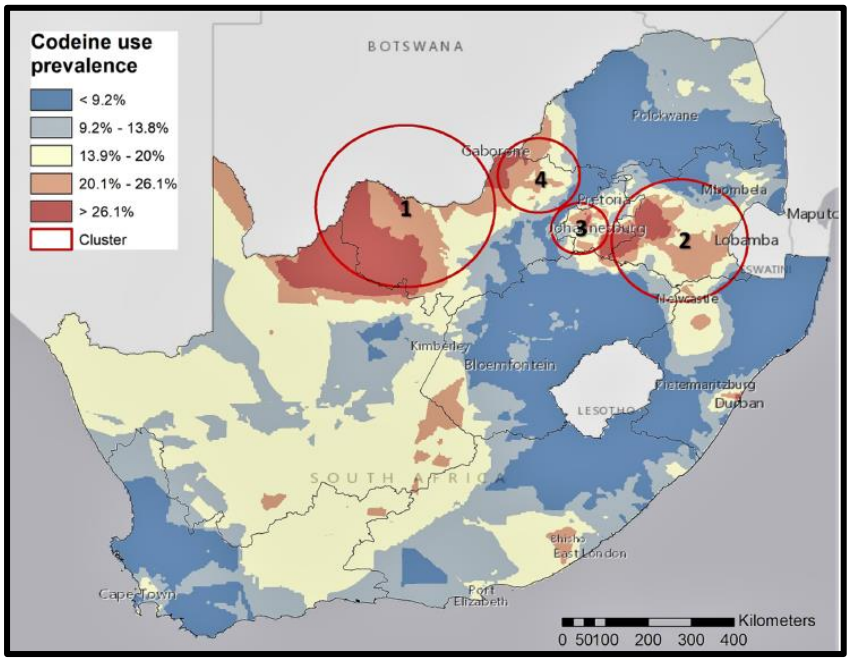


Figure 3.3: South African “codeine hotspots” (Nyoni *et al.*, 2022).

Note: Permission granted from authors to use figure (Appendix E).

These notable findings could indicate that SA, a developing country, and Australia and the UK, first-world countries, depict diversity in economic statuses but may still lead to similar research outcomes. Various geographical locations with differing

characteristics may contribute to the usage of codeine, with both urban and rural areas potentially influencing sales and usage patterns, influenced by different community factors.

3.2.3.2. Mental health

Various mental health conditions have been identified with the increased use of codeine products. However, due to limited literature available, further analyses are required to prove whether these disorders cause the use of codeine or if codeine use causes symptoms of mental health disorders.

3.2.3.2.1. Depression

Depression is a mental health disorder characterised by persistent feelings of sadness, hopelessness and a loss of interest or pleasure in activities (Romach *et al.*, 1999; Cooper, 2018). Romach *et al.* (1999) conducted a Canadian survey proving that long-term codeine-use participants are at risk for the onset of depression (Romach *et al.*, 1999). Of the study participants, 64% sought mental health assistance, and 70% of this group were diagnosed with depression (Romach *et al.*, 1999). Reasons for the use of codeine were described as to manage chronic pain, which was reported to be strongly associated with depression (Romach *et al.*, 1999). This study, however, did not indicate whether the depressive symptoms preceded the long-term codeine use (Romach *et al.*, 1999).

A study by Nyoni *et al*. (2022), found that 60.7% of study participants were unemployed and 65.8% held a matric (Grade 12) certificate (Nyoni *et al.*, 2022). This underlines the association between CCM use and socioeconomic factors such as unemployment and lower educational attainment, which in turn can contribute to the development of mental health disorders like depression (Cooper, 2018). Unemployment factors often exacerbate depressive feelings, leading individuals to seek relief through substance abuse, such as cocaine, alcohol and opioids (Dada *et al.*, 2015; Nyoni *et al.*, 2022). However, due to the affordability of codeine compared to cocaine and alcohol, individuals may opt for CCMs as a means of finding solace and temporary happiness, hoping to alleviate the negative emotions associated with unemployment (Dada *et al.*,

2015). Studies from as early as 1999 (Romach *et al.*, 1999), and as recent as 2022 (Nyoni *et al.*, 2022), consistently show that depressive symptoms are closely linked to the long-term use of codeine.

3.2.3.2.2. Fibromyalgia

Fibromyalgia is a complex chronic pain disorder which primarily affects the musculoskeletal system (Goldenberg *et al.*, 2016). While not classified as a mental health disorder, fibromyalgia significantly contributes to mental health disorders such as depression, stress and anxiety, thereby impacting daily functioning (Goldenberg *et al.*, 2016). With body pain being the principal symptom and no “gold standard” guidelines available for this disorder, individuals often acquire pain relief medications, such as opioids to aid in its management (Fitzcharles *et al.*, 2011).

A Canadian study evaluated the reported use of opioids in patients diagnosed with fibromyalgia (Fitzcharles *et al.*, 2011). The study found that patients using opioids, like codeine (16%), in the management of fibromyalgia were significantly more likely to be unemployed ($p<0.0001$) and to have a current unstable mental disorder ($p=0.0007$) (Fitzcharles *et al.*, 2011). These individuals were also characterised as ‘drug-seekers’, citing their fibromyalgia diagnosis as justification for previous substance abuse and seeking opioids ($p=0.0005$) (Fitzcharles *et al.*, 2011). Another study reported that no evidence from clinical trials was shown for the effectiveness of the usage of opioids in the treatment of fibromyalgia (Goldenberg *et al.*, 2016). The study also found that patients who were using opioids for fibromyalgia pain relief, had poorer health outcomes than those who did not use opioids in the management of fibromyalgia (Goldenberg *et al.*, 2016).

The use of opioids is strongly discouraged in fibromyalgia management and is not recommended by any guideline (Fitzcharles *et al.*, 2011; Goldenberg *et al.*, 2016). While mood disorders are commonly associated with fibromyalgia, it is important to recognise that other significant mental health conditions may present similarly to pain syndromes (Fitzcharles *et al.*, 2011).

3.2.3.3. Lack of patient education and awareness

Greater public exploration is required to increase knowledge, education and awareness of the risks associated with dependency and safe use of codeine products (Foley *et al.*, 2017). Foley *et al*. (2018) highlighted in a study that patients (89.2%) do not fully understand the harmful effects of OTC CCMs, and only understand that because a certain codeine-containing product is OTC, all OTC products are thus considered safe to use (Foley *et al.*, 2018). There is significant concern about the insufficient awareness among patients regarding the utilisation of OTC CCMs. Such concern should be corrected by practitioners providing detailed advice to patients, particularly concerning CCMs prescribed and non-prescribed products (Foley *et al.*, 2017).

Patients feel that doctors do not provide sufficiently detailed advice during the consultation, posing a risk of long-term misuse or addiction to certain prescribed medicines (Cooper, 2013a). Once addiction has occurred, patients may become receptive to warning and preventative information, whereby "[in] the beginning information about risks of opioid dependence would have been valuable … but when [they were] addicted [they] would not have been interested" (Nielsen *et al.,* 2013). Patients' emotions towards CCM products have previously been analysed and patterns have indicated that "[the] majority of participants commented on the need for greater information provision around use, and risks of misuse from prescribing doctors relating to codeine-containing medicines" (Van Hout *et al.*, 2018). Medical jargon also affects patients' understanding of harmful drug effects, side effects, and correct dosing regimens (Cooper, 2013a). Thus, HCPs should use simplified language when counselling patients on CCMs, as this could potentially increase public awareness and understanding of CCM's harmful and addictive effects (Foley *et al.*, 2017).

In conclusion, patient-related factors play a significant role in the sale of OTC CCMs. Various individual factors contribute to the purchase of these products. However, it is often the accumulation of multiple factors that are observed in individuals who purchase codeine with the intent to misuse these products. One prevalent combination of factors is observed in middle-aged females dressed in smart business wear, who may be unemployed, possess only a matric certificate and have been diagnosed with

a mental health condition such as depression. Additionally, socioeconomic factors such as low educational attainment and unemployment, which can be influenced by geographical location and community dynamics, contribute to increased codeine use.

3.2.4. Prescriber-Dispenser related factors

A culmination of various prescriber-related factors influences the decisions and actions undertaken by patients to purchase CCMs. Many of these factors relate to irrational prescribing habits, such as the lack of consideration for codeine's addictive properties, the lack of advice and communication regarding codeine, and private versus public sector prescribing habits. Lack of patient medical reviews during a doctor's consultation is another prescriber-related factor. From a public health perspective, it is crucial to prioritise rational prescribing, to closely monitor the usage of prescribed OTC CCMs, as well as to implement screening, support and treatment interventions within the medical and pharmacy sectors (Van Hout, 2014a). Extensive and relevant literature was analysed and discussed regarding general practitioners. However, a significant lack of relevant literature relating to other prescribers (e.g. dentists, specialists etc.) was noted, and thus the prescriber factors described below are specific to general practitioners.

Dispensers, particularly pharmacists, play a pivotal role in healthcare, particularly in self-medicating with products like OTC CCMs. Patients often rely on pharmacists for advice when purchasing OTC products (Lalagkas *et al.*, 2022). However, worrisome dispensing practices, particularly with analgesics such as CCMs, have been identified, posing a risk of misuse (Ravichandran and Basavareddy, 2016; Soumya *et al.*, 2016). Instances of irrational dispensing, including dispensing without a necessary prescription or dispensing larger, more expensive products unnecessarily, contradict pharmacy guidelines and may compromise patient health, increasing the risk of misuse and abuse of such products (Ravichandran and Basavareddy, 2016; Lalagkas *et al.*, 2022).

3.2.4.1. Prescribing habits

Whether intentional or not, prescribing habits influence numerous patients' decisions regarding the usage of opioid medicines, particularly CCMs (Gisev *et al.*, 2016). Global regulatory guidelines are continuously updated to support the safe and rational prescribing of opioid analgesics (Van Hout, 2014a). However, large percentages of practitioners do not remain abreast of such guidelines, and hence, such lack of adherence results in a significant increase of irrational analgesic prescriptions (Builders, 2016).

Concerns are being noted regarding the possible lack of a thorough medical review performed by prescribers during a consultation, and the typical period of a consultation limiting the opportunity to discuss personal concerns or fully discuss the various options, in particular, for pain therapy (Kinnaird *et al.*, 2019). Prescriber appointments are often limited in duration due to the largely influenced low prescriber-to-population ratio, which places substantial pressure on healthcare providers to serve a high volume of patients (Foley *et al.*, 2017; Foley *et al.*, 2018). Therefore, appointment lengths are often restricted in order to accommodate the demand (Kinnaird *et al.*, 2019). Prescribers and HCPs must perform thorough medical and history-taking reviews at the time of prescribing medicines as well as at the supply and sale of the medicines (Gisev *et al.*, 2016). If done correctly and thoroughly, addiction habits and misuse of CCMs can often be reduced. Many prescribers remain unaware of patients' self-medication habits and may be unable to identify potential CCM misuse or dependence, if not informed by the patient themselves, which rarely occurs (Foley *et al.*, 2018). An Irish study reported that only 50% of practitioners document their patients' OTC use in medical records, during a medical review (Foley *et al.*, 2017). Practitioners should, by law, always assess their patients regarding any OTC self-medicating habits, as well as provide detailed advice about the correct short-term use of both prescribed and OTC products (O'Neill, 2016).

During the patient history-taking process, prescribers should assess and question their patients regarding any current or past family history of opioid addiction (Kinnaird *et al.*, 2019). Healthcare professionals should remain abreast of the potential portrayal of misuse behaviours that the individuals may portray, in order to obtain codeine. Open-

ended questions relating to opioid side effects should also be assessed and noted, as these types of questions allow the patient to answer freely and in detail (Cooper, 2018). Time should be taken to examine past medical review notes and should a pattern of themes occur whereby the patient only finds a therapeutic response to opioid classes effective, further questions should follow to determine if the patient is at risk of irrational CCM use (Norman *et al.*, 2016).

3.2.4.1.1. Poor practice in lack of consideration for codeine's addictive properties

Its short half-life and strong euphoric-inducing effects contribute to codeine's addictive properties (Lo *et al.*, 2015; Van Hout and Norman, 2016). In situations where there are potential risks involved, having extended access to codeine without proper guidance from a HCP, may make it easier for patients to purchase codeine irrationally and this warrants potentially harmful risks (Nielsen *et al.,* 2013). Patients who have previously used prescribed codeine products, mentioned that before leaving the consultation they were given codeine as the initial choice for pain management, even when the patient was inclined to explore alternative methods and options for pain treatment (Kinnaird *et al.*, 2019). Furthermore, genetic polymorphisms may result in codeine's biotransformation to arise in toxic or ineffective levels of morphine (Benini and Barbi, 2014). This further increases the effect of codeine addiction, suggesting that the user may not always be aware of codeine's addictive effects (Benini and Barbi, 2014). Prescribers at times nonchalantly turn away patients and may at times prescribe codeine products to "quickly get rid of [patients]", rather than taking the time to explore alternative treatment regimens for the patients (Cooper, 2013a).

Globally, a large number of patients express concerns that their general practitioners regard addiction to OTC CCMs as less severe compared to other addictions, leading to a lack of concern or the belief that it could be easily managed without professional intervention; "I have mentioned it to the doctor and he sort of said 'well it's something you handle yourself'" (Cooper, 2013a). Cooper (2013) and Kinnaird *et al*. (2019) have expressed concerns that prescribers may disregard codeine as an addictive substance (Cooper, 2013a; Kinnaird *et al.*, 2019). Furthermore, many prescribers believe that codeine should often be prescribed as a first-line treatment since many CCM products

are on a country's Essential Medicines List (EML). Due to the risk of addiction associated with codeine, treatment regimens that include codeine should always be monitored by a HCP, throughout the regimen (Cooper, 2013a). Not all physicians prescribe according to updated pain management guidelines, and thus, inadvertently, this exposes patients to long-term codeine use which may potentially lead to the addiction of codeine. Considering the above arguments, it is thus suggested that alternative treatment regimens should be explored before prescribing a codeine product.

Repeat codeine prescriptions

Irrational prescribing habits are enhanced when prescribers repeat a prescription, often for six months (Van Hout *et al.*, 2018). This may decrease monitoring and surveillance of the treatment regimen and development of CCM misuse, whereby pharmacist intervention is minimised due to the products being on a repeat prescription (Cooper, 2013b). Parry *et al*. (2017) reported that 65% of study participants were admitted to a treatment centre because of intentional misuse for intoxication and dependence in response to excessive and long-term use of CCMs (Parry *et al.*, 2017). This misuse may have been triggered by long-term repeat prescriptions of CCMs (Parry *et al.*, 2017). Patients, therefore, feel entitled to purchase CCM products, as their misuse was heightened by the sense of having "a repeat prescription and [codeine products] were on tap" (Kinnaird *et al.*, 2019).

Prescribing habits of CCMs should be restricted to month-to-month obtainment, thereby increasing surveillance and monitoring. At the time of this study, it was reported in an Irish and English study that there is no universal tracking system to prevent patients from visiting and receiving prescriptions from three or more prescribers or pharmacies within a six-month period (14% of study participants achieved this) (Kimergard *et al.*, 2017). Repeated CCM prescriptions increase the risk of long-term use of CCMs, comparable to an English study that reported on average, codeine users have been using CCMs daily for 9.1±7.6 years (Kinnaird *et al.*, 2019).

3.2.4.1.2. Lack of advice and communication

Patients tend to feel overwhelmed and hesitant about treatment regimens if prescribers do not provide detailed advice about what medicines the patients were prescribed (Van Hout *et al.*, 2018). Thus, before leaving a doctor's consultation, the prescriber must ensure that the patient understands exactly what they are being prescribed, particularly when prescribing codeine, to avoid uncertainty about the treatment regimen (Kinnaird *et al.*, 2019). A lack of effective communication and trust between prescriber and patient results in a poor understanding of codeine risks, increasing the risk for irrational usage of CCMs (Van Hout *et al.*, 2018).

Challenging patients' perceptions regarding the improper utilisation and exploitation of codeine-containing products depicts a crucial role in managing the unwanted consumption of such products (Kimergard *et al.*, 2017). With a strong relationship between prescriber and patient, a correct diagnosis can be achieved, thereby prescribing only necessary medicines, and decreasing the risk of experimentation and long-term use of CCMs (Van Hout, 2014a). The patient then understands their health autonomy and importance of compliance for improved health outcomes (Cooper, 2013b; Builders, 2016).

3.2.4.1.3. Private versus public sector prescribing habits

Private and public practice prescribing habits may vary (Henricson *et al.*, 1999). A Swedish study reported that private-sector practitioners prescribed 60% more DDDs of codeine per number of visits compared to public-sector practitioners (Henricson *et al.*, 1999). Literature has shown that private practitioners tend to have a more lenient listening ear than public practitioners (Henricson *et al.*, 1999; Cooper, 2018). This results in private practitioners simply prescribing exactly what the patient requests (Henricson *et al.*, 1999; Cooper, 2018). Once a practitioner has established a precedent by issuing a patient-requested codeine prescription, the subsequent refusal of the patient's request on successive consultations becomes progressively challenging (Grzybowski, 2004).

3.2.4.2. Dispensing habits

Dispensers play a crucial role in the healthcare community, especially in the role of self-medicating with OTC medicines, such as CCMs (Soumya *et al.*, 2016). Studies have shown that patients rely on the advice from either a dispenser or a physician when purchasing an OTC product (Ravichandran and Basavareddy, 2016; Lalagkas *et al.*, 2022). A Greek study found that 84% of patients sought advice from HCPs, such as pharmacists, before purchasing OTC products in the pharmacy (Lalagkas *et al.*, 2022). This suggests that while some OTC medicines are available outside of pharmacy settings such as in retail stores, the guidance provided by pharmacists during OTC dispensing, reinforces the preference to purchase these products in a pharmacy (Lalagkas *et al.*, 2022).

Many of these studies have reported that analgesics, such as OTC CCMs were the most purchased OTC product (Ravichandran and Basavareddy, 2016; Soumya *et al.*, 2016; Lalagkas *et al.*, 2022). Due to their misuse potential, dispensing analgesics such as CCMs, need to be rationally dispensed with good pharmacy practice, so to avoid the potential risk of misuse with these products (Ravichandran and Basavareddy, 2016). Certain dispensing habits which may undermine the value of pharmacists' advice and expertise, are increasingly becoming apparent (Soumya *et al.*, 2016). These habits intend to indicate that dispensers are dispensing higher-cost medicines, without explicit consideration of the financial burden on patients, seemingly in pursuit of maximising profitability within the pharmacy setting (Soumya *et al.*, 2016; Padayachee *et al.*, 2019).

In SA, Padayachee *et al.* (2019) reported that when comparing identical OTC products prescribed and dispensed by physicians and pharmacists, pharmacists dispensed the larger pack size and the more expensive product to the patient (Padayachee *et al.*, 2019). Physicians, on the other hand, opted to prescribe the smaller and inexpensive product for the patient (Padayachee *et al.*, 2019).

An Indian study found that 45% of dispensing encounters, were dispensed without a prescription, when the product (most often being an analgesic and or an antibiotic) required a prescription to be dispensed (Soumya *et al.*, 2016). The same behaviours

were seen in Egypt (72%), Tanzania (77%) and Vietnam (99%) (Soumya *et al.*, 2016). Such behaviours counteract the good pharmacy practice guidelines that require dispensers to maintain and uphold when rationally dispensing all medicines (Soumya *et al.*, 2016; Lalagkas *et al.*, 2022).

Irrational dispensing habits may compromise the health of patients and potentially increase rates of misuse and abuse of certain products like CCMs. It is therefore imperative that pharmacists counsel patients at the point of dispensing, thereby enhancing patient CCM knowledge and fostering safer medication use practices, specifically tailored towards OTC CCMs (Ravichandran and Basavareddy, 2016; Soumya *et al.*, 2016).

3.2.4.3. Lack of healthcare professional education and awareness

Although highly qualified, attention to HCPs' knowledge and understanding of CCM products is concerning, and urgent interventions are required to prevent further CCM harm to the public (Nielsen *et al.,* 2013). Healthcare professionals, specifically general practitioners and pharmacists are at the forefront of prescribing and dispensing codeine products. Codeine-product use is influenced by physician advice (33.1%) and pharmacist advice (33.1%), indicating that HCPs play a vital role in patients' decisions regarding CCM use (Roussin *et al.*, 2013). A lack of awareness and education from HCPs creates a lack of awareness and education about CCMs to patients, therefore potentially increasing habit-forming CCM patterns (Roussin *et al.*, 2013).

A South African study detected that only 10% of practitioners received specialist training in codeine misuse and or dependence (Parry *et al.*, 2017). Another study, comparing three countries, analysed pharmacist perspectives on codeine use and misuse, and such are in agreement with Parry *et al*. (2017), reporting that Irish (61.5%), British (62.8%) and South African (71.3%) pharmacists described an urgent need for intervention to enhance confidence in training and education on codeine-product dispensing to prevent irrational codeine-sales (Parry *et al.*, 2017; Carney *et al.*, 2018; Ino and Nakazawa, 2022). Extensive scientific literature was available regarding the training and education of codeine to HCPs in SA, Ireland and

Britain. Limited literature with relevance, was available on other countries discussing the same themes as that of the South African, Irish and British studies reported.

At the point of prescribing, the practitioner must determine if codeine-product prescribing is appropriate. However, the prescriber's lack of education and awareness of CCMs may increase irrational prescribing, thus posing potential risks to patient CCM misuse (Builders, 2016). Foley *et al*. (2017) indicated in a study, that only 21% of practitioners specified confidence in identifying codeine dependence (Foley *et al.*, 2017). This is supported by 76% of practitioners indicating the urgent need for training on rationally prescribing addictive medicines, such as CCMs (Foley *et al.*, 2017). When dispensing or selling OTC CCMs, the pharmacist must determine the appropriate dispensing and supply of CCMs so that the trusting engagement between pharmacists and patients at the point of an OTC CCM sale, realigns such sales with environmental factors to reduce potential harm (Kinnaird *et al.*, 2019; Ino and Nakazawa, 2022).

3.2.5. Regulatory framework

Access to codeine products is a global concern. Various regulatory frameworks are considering several options to help mitigate the ease of access to many codeine products. These may include international pharmaceutical regulations, controlled substance frameworks and global drug control guidelines from organisations such as the WHO and the UNODC (UNODC, 2019; WHO, 2022). However, it is imperative to maintain a balance between regulations and avoid the increased burden of illicit sales due to strict regulations. Ease of access and the phenomenon of ‘pharmacy hopping’ contribute to codeine’s regulatory framework and how such contributing factors portray increased usage and sales of CCMs.

A pharmacy, a point of sale for medicines, is categorised as a primary model of care. This describes a pharmacy as being the most accessible healthcare facility, a continuous service, and a highly patient-focused environment (WHO, 2022). Pharmacists should ensure that care is patient-centered to allow patients to feel empowered in their own medical decisions (Norman *et al.*, 2016). There are numerous instances when patients cannot afford to see a doctor, and hence the pharmacy is

their first point of call (Foley *et al.*, 2017; Kinnaird *et al.*, 2019). This integrated service delivery by pharmacists is fundamental in the healthcare chain, to ensure that patients are treated correctly, in the right place, with the right medicines and at the right time (WHO, 2022). This allows for the building of vital and trusting therapeutic relationships between the patient and their pharmacist (WHO, 2022).

3.2.5.1. Ease of access

Many countries have various codeine medicines that are available to patients OTC (Voigt, 2022). Over-the-counter products cannot be strictly controlled by a HCP, and therefore, these medicines are readily available, promoting irrational codeine use (Padayachee *et al.*, 2019). Being easily accessible, a Norwegian study proved that 400 000 Norwegians received an average of 49.1 DDDs of codeine in a single year (Fredheim *et al.*, 2009). Although a strong healthcare system is structured to ensure ease of access, quality and care, considerations related to legitimate versus irrational use of OTC products should not be ignored (Padayachee *et al.*, 2019). In 2013, an Australian study recorded a total of 55.8% of OTC codeine-combination products sold, amounting to over 15 million packs (Gisev *et al.*, 2016). Studies argue that the wide availability of OTC CCMs is associated with a greater risk of non-medical usage of CCMs (Richards *et al.*, 2021; Hockenhull *et al.*, 2022; Nyoni *et al.*, 2022).

Codeine is formulated in many painkillers, and patients in Western countries are beginning to justify that their general lifestyle and daily functioning, heavily rely on the consumption of codeine products (Almarsdóttir and Grímsson, 2000). In Ireland and the UK, Kimergard *et al*. (2017) reported that opioid analgesics, containing codeine, are extensively used leading to risks of misuse (Kimergard *et al.*, 2017). The use of such analgesics surged from 35.9 million DDDs between 2001-2003 to 117.9 million DDDs in 2011-2013 in the UK and from 3.1 million DDDs to 9.3 million DDDs in Ireland, during the same period (Kimergard *et al.*, 2017).

Although lacking in scientific relevancy, an Australian study concluded that in 2013, 33% of respondents had misused OTC codeine analgesics, which dramatically increased to 75% in just three years (Roberts and Nielsen, 2018). Overall, ease of

access to OTC CCMs does encourage self-medication and reduces the burden on the healthcare system. Global concern though, is tailored towards the wide availability of OTC CCMs, promoting drug use among young adults (Ino and Nakazawa, 2022). Efforts to deter and address the irrational global use of codeine are obstructed by the convenient accessibility of both prescription-only and OTC CCMs (Van Hout, 2014a).

3.3. Conclusion

Sales of codeine-containing products are increasingly becoming a global public health concern. Varying contributing factors to the sale of CCMs largely encompass misuse and abuse of CCMs. However, legitimate rationale for the sale of CCMs also contributes to increased codeine product sales. Contributing factors possess the potential to exert dual influences wherein they can prompt as well as mitigate detriments linked to codeine usage (Kinnaird *et al.*, 2019). Better care and the identification of irrational prescribing and dispensing habits are required to ensure the safe and rational use of CCMs, both OTC and prescription based (Nielsen *et al.,* 2013; Kinnaird *et al*., 2019). It is important to create environments that promote alternative treatment options, thereby enhancing the rational purchase of CCMs (Kinnaird *et al.*, 2019). Identifying strategies to reduce the use of CCMs should mitigate unnecessary risks to patients (Shi *et al.*, 2021). Pharmacies are easier to access and are quicker to approach than scheduling a doctor's appointment, and therefore, enhanced pharmacist intervention at the point of sale of OTC codeine products is warranted (Kinnaird *et al.*, 2019).

Researchers have indicated that guidance from policymakers, regulators, governments and public health strategists should be adhered to, to encourage the admissible and best-use practice of codeine products (Foley *et al.*, 2017). The need for greater public health awareness and education on the harmful uses of codeine is required (Pottegård *et al.*, 2023). Regulatory policy reform decisions are needed to globally present a healthcare plan to achieve rational and admissible usage of all codeine products (Van Hout, 2014a). By combatting various contributing factors that encourage codeine-product sales, the global public health challenge to decline irrational codeine sales, may be achieved.

In conclusion to this review, fulfilling **objective I** of this study, **objective II**, in **Chapter 4** of this study will provide a descriptive overview of the sales trends analysed and identified on the OTC CCM sales in SA. The next objective (**objective IIb**) will also determine if there were any differences found because of the Covid-19 pandemic on the sales trends of OTC CCMs within SA.

CHAPTER 4: RESULTS AND DISCUSSION OF OBJECTIVE II

4.1. Introduction

This chapter, reports and discusses the descriptive results of **objective IIa** and **IIb**. **Objective II** was divided into two parts viz. **objective IIa** and **objective IIb**, as follows:

IIa. To describe the sales trends of OTC CCMs across all provinces in SA.
IIb. To assess any difference between the effect of the Covid-19 pandemic on the sales trends of OTC CCMs across all provinces in SA.

These objectives reported on descriptive statistics that were used to describe trends within the dataset, offering an overview of the South African OTC CCM sales over the study's period.

The following variables were analysed in **objective II**.

- Method of payment
- Month
- OTC CCM product
- Pack size
- Pharmacy classification
- SEP (Single exit price)
- The nine South African provinces

For purposes of this study, 'Sale counts' / 'Sales' is indicative of the number of packs or bottles of a product sold. All sales refer to the sale of OTC CCM products in SA. Where 'Unknown/Not Specified' is mentioned, this is indicative of findings from the dataset, whereby some pharmacies preferred not to disclose any relevant information about the pharmacy pertaining to its data. For purposes of this study, where 'Covid-19' is mentioned, this is referring to the Covid-19 pandemic in SA. For this study,

1 January 2019 to 29 February 2020 is classified as the ‘Pre-Covid-19’ period. Since the study’s trends are analysed monthly, the ‘During Covid-19’ period is classified from 1 March 2020 to 31 December 2020.

4.2. Objective IIa

Objective IIa was to describe the sales trends of OTC CCMs across all provinces of SA. Table 4.1 and Table 4.2 provide an overview of the OTC CCM sales across SA. Thereafter, various sales trend analyses line graphs have been created to further explore the specific variables relating to the sales of OTC CCMs.

4.2.1. Descriptive statistics

Table 4.1 provides an overview of the frequency and percentage distribution of the national South African sales of OTC CCMs categorised into variables within the period of the study.

The total number of sales counts of OTC CCMs in SA between 2019 and 2020 was 34 607 555. During this period, just under half, 40.95%, of the total percentage of OTC CCM sales, were sold in Gauteng. Following Gauteng, Western Cape (16.18%) and KwaZulu-Natal (12.05%) concluded the top three provinces with the greatest sales of OTC CCMs. Limpopo (3.06%) and the Northern Cape (2.35%) provinces sold the least amount of OTC CCMs. The majority (46.71%) of sales were purchased through private/cash methods of payment. Purchasing such products through this method of payment maintains anonymity and privacy, prolongs medical aid savings, and offers convenience by bypassing electronic transactions and the need for credit or debit cards (Discovery, 2018). Only 21.13% were purchased through a medical aid. Payment details were not specified for 32.08% of the sales. During this period, just over half of the sales (59.37%) were through chain pharmacy groups, followed by 29.03% from independent pharmacies. In Gauteng and the Western Cape, there is a higher proportion of chain pharmacy groups compared to independent pharmacies, and this is supported by the findings in Table 4.1 (Nyamuzihwa *et al.*, 2023; SAPC, 2024). These findings suggest that Gauteng and the Western Cape were the top two provinces in terms of sales, with two-thirds of these sales happening in chain pharmacy

groups (Nyamuzihwa *et al.*, 2023). Conversely, in the remaining seven South African provinces, the ratio of independent pharmacies exceeds that of chain pharmacy groups (Nyamuzihwa *et al.*, 2023).

Table 4.1: The sales of OTC CCMs in SA between 1 January 2019 to 31 December 2020, categorised into variables.

Variable	Category	Frequency of sales	Distribution (%)
Province	Gauteng	14 171 029	**40.95**
	Western Cape	5 600 988	**16.18**
	KwaZulu-Natal	4 169 685	**12.05**
	Eastern Cape	2 780 078	8.03
	Mpumalanga	2 358 152	6.81
	North-West	1 948 081	5.63
	Free State	1 704 437	4.93
	Limpopo	1 060 536	**3.06**
	Northern Cape	814 569	**2.35**
Method of payment	Private/Cash	16 165 644	**46.71**
	Unknown/Not Specified	11 102 534	**32.08**
	Medical Aid	7 313 030	**21.13**
Pharmacy classification	Chain	20 545 847	**59.37**
	Independent Pharmacy	10 045 308	**29.03**
	Independent Pharmacy Groups	3 972 743	11.48
	Unknown/Not Specified	17 823	0.06
Month	**2019**		
	January	1 390 238	4.02
	February	1 316 708	**3.80**
	March	1 474 297	4.26
	April	1 475 439	4.26
	May	1 556 444	**4.50**
	June	1 546 289	**4.47**
	July	1 522 268	4.40
	August	1 502 260	4.34
	September	1 367 140	3.95
	October	1 364 266	3.94
	November	1 371 221	3.96
	December	1 540 880	4.45

Variable	Category	Frequency of sales	Distribution (%)
Month	**2020**		
	January	1 495 810	4.32
	February	1 356 914	**3.92**
	March	1 724 744	**4.98**
	April	1 272 673	**3.68**
	May	1 389 722	4.02
	June	1 364 189	3.94
	July	1 532 796	**4.43**
	August	1 429 329	**4.13**
	September	1 328 904	**3.84**
	October	1 412 542	4.08
	November	1 319 569	3.81
	December	1 552 913	4.49

Note: Frequency of sales is indicative of the number of packs or bottles of a product sold.
Bold and highlighted values represent noteworthy data, which are further discussed in the text.

The monthly trends show that in 2019, February accounted for a decrease in sales with only 3.80% of sales, whilst with the start of the South African winter months, May and June, sales increased and contributed to 4.50% and 4.47% respectively. The winter months posed a risk of increased bacterial and viral infections (Insight Survey, 2017). Thus, commonly, OTC cold, flu and cough remedies rise in sales during the winter months (Liu *et al.*, 2013). Many of the OTC CCM products analysed in this study, are often first-line purchase products for cold, flu and cough remedies. In SA, a shift in cultural attitude has prevailed, indicating that the general public is leaning more towards self-medicating practices. Globally, access to OTC products is high, leading to an increase in self-medicating practices (Padayachee, 2020). This trend reflects patients' desire for autonomy in managing their health, as they feel empowered and take responsibility for their well-being (Cooper, 2013b). As supported by Pfizer, 81% of adults are increasing the practice of purchasing OTC products, in times of illness, especially during the winter months (Insight Survey, 2017).

In 2020, March contributed to the highest percentage distribution of OTC CCM sales, amounting to nearly 5% of sales for the year. In SA, the Covid-19 pandemic was confirmed in the country on the 15th of March 2020, indicating the start of the pandemic. The first Covid-19 lockdown in SA began on the 27th of March 2020. Therefore, April

2020 was the first official month of lockdown with level five restrictions (the highest level of Covid-19 spread within SA and only few individuals were able to leave their homes during this time (South African Government, 2020)). Reflecting this, April 2020 showed the lowest percentage (3.68%) of sales. Due to the announcement of the Covid-19 virus and the likelihood of a strict lockdown occurring in April 2020, citizens of SA resorted to panic buying, and to stock up on essential daily supplies. Panic buying can be defined as the act of purchasing substantial amounts of a product(s) out of sudden concern about an impending shortage, or a restriction to access the shops/pharmacies (such as in the case of a national lockdown) (Neumann and Temple, 2023). The above arguments contribute to the findings that resulted in the most OTC CCM sales sold throughout the two-year study period, occurring in March 2020 (4.98%) (the first month of the Covid-19 pandemic in SA and increased acts of panic buying) and the sudden low plummet of OTC CCM sales occurring in the subsequent month, April 2020 (3.68%), the first month of South African lockdown. Thereafter, there was a gradual decrease in sales shown between July to September 2020 (from 4.43% to 3.84% respectively).

Table 4.2 shows the top 20 OTC CCM product sales in SA between 2019 and 2020. The table also highlights the SEP of each product, depicted in South African Rands (R). The SEP is the regulated price at which pharmacies purchase medicines from wholesalers (Moodley and Suleman, 2019). The government sets and enforces these prices, ensuring that wholesalers do not sell medicine below the specified SEP (Moodley and Suleman, 2019). Appendix F highlights the remaining 21-55 OTC CCM products ranked in this study. The results in Appendix F were negligible as the remaining products each contributed less than 1% of the total percentage distribution analysed.

Nationally, the top five most common products purchased were Adco-Dol® Tab (40s), Mybulen® Tab (30s), Gen-Payne® Cap (30s), Adco-Dol® Tab (20s) and Acurate® Tab (40s). Adco-Dol® Tab in pack size 40 contributed to just over a fifth, 21.34%, of the total percentage of sales. Investigating OTC codeine products for misuse and dependence potential, a South African study highlighted Adco-Dol® as the foremost contributor, comprising nearly 25% of purchases (Dada *et al.*, 2015). Note, in this

study, the larger pack size of 40 tablets of Adco-Dol® was ranked first, with a larger percentage (21.34%), as compared to a smaller pack size of 20 tablets (10.02%), contributing only approximately half of the percentage distribution of the 40 tablet pack size. The recommended daily dosage for Adco-Dol® is one to two tablets every four hours, as necessary, not exceeding eight tablets in a 24-hour period (Adcock Ingram, 2021). Therefore, this suggests that with the recommended dosage regimen, a pack of 40 tablets would last for a minimum of five days. Furthermore, opting for the pack of 40 tablets is preferable due to its convenience and meeting the maximum dosage requirement. However, both pack sizes of this product fell within the top four of ranked OTC CCM products sold. To note, the price per tablet (R 1.02) is equal when comparing the pack size 20 tablets versus the pack size 40 tablets SEP of Adco-Dol®, therefore, not indicating any price discrepancies.

Within the top five of most products sold, Mybulen® Tab (30s) (12.80%), Gen-Payne® Cap (30s) (10.78%) and Adco-Dol® Tab (20s) (10.02%) each accounted for approximately a tenth of the total percentage distribution. Cumulatively, the top five products alone contributed to just over 60% of all the 55 OTC CCM products analysed. Mybulen® Tab (30s) costs R 75.91 per pack and ranked second (12.80%) versus Gen-Payne® Cap (30s) costing R 66.30 per pack and ranked third (10.78%). A possible reasoning could be that although both products contain 200 mg of ibuprofen and 10 mg of codeine, Mybulen® contains 100 mg more of paracetamol (350 mg), than that of Gen-Payne® (250 mg) (Otorkpa, 2020). Combination analgesics, which include active ingredients like codeine, doxylamine, paracetamol and ibuprofen, are increasingly becoming popular as OTC products. According to a South African study, of the OTC CCM products purchased, 59% of these medicines were codeine-combination analgesics with the most popular product containing codeine, paracetamol, doxylamine and caffeine (Padayachee *et al.*, 2023). This finding supports the results of this study indicating that the purchase and potential misuse of codeine-combination analgesics are on the rise in SA (Dada *et al.*, 2015; Padayachee *et al.*, 2023).

Table 4.2: The top 20 national OTC CCM product sales between 1 January 2019 to 31 December 2020.

Ranking position	Product	Dosage form	Pack size	SEP per product	Frequency of sales	Distribution (%)
1st	Adco-Dol®	Tab	40	R 40.68	7 385 261	**21.34**
2nd	Mybulen®	Tab	30	**R 75.91**	4 429 391	**12.80**
3rd	Gen-Payne®	Cap	30	**R 66.30**	3 729 462	**10.78**
4th	Adco-Dol®	Tab	20	R 20.34	3 466 632	**10.02**
5th	Acurate®	Tab	40	R 29.17	2 742 725	**7.93**
6th	Sinutab Sinus Pain ES®	Tab	24	R 70.58	1 572 749	4.54
7th	Broncleer & Codeine®	Syr	100 mL	**R 15.24**	1 301 674	**3.76**
8th	Benylin & Codeine®	Syr	100 mL	**R 56.60**	1 144 118	**3.31**
9th	Stilpane®	Syr	100 mL	**R 20.58**	875 873	**2.53**
10th	Betapyn®	Tab	18	R 38.68	711 651	2.06
11th	Acurate®	Tab	20	R 14.58	677 470	1.96
12th	Betapyn®	Tab	40	R 86.06	561 830	1.62
13th	Tensodol®	Tab	40	R 29.14	531 666	1.54
14th	Lenapain®	Tab	36	R 44.00	518 553	1.50
15th	Adco-Napacod®	Tab	1 000	R 494.74	497 975	1.44
16th	Pynstop®	Tab	40	R 72.01	471 148	1.36
17th	Syndol®	Tab	40	R 77.45	404 293	1.17
18th	Nurofen Plus®	Tab	24	R 77.27	374 674	1.08
19th	Syndol®	Tab	18	R 34.76	373 882	1.08
20th	Mybulen®	Susp	100 mL	R 78.56	344 635	1.00

Tab = tablets; Cap = capsules; ES = extra strength; Syr = syrup; Susp = suspension; SEP = Single exit price
Note: Frequency of sales is indicative of the number of packs or bottles of a product sold.
Bold and highlighted values represent noteworthy data, which are further discussed in the text.

Larger and varying product pack sizes may lead to codeine misuse (Norman *et al.*, 2016). As such, limiting OTC codeine sales involves reducing the quantity of tablets, capsules, or mililitres within each pack size. Furthermore, to mitigate potential misuse, dispensers may request a valid explanation for the purpose of purchasing the OTC CCM and ensure that all OTC CCMs are stored on shelves within the dispensary (Norman *et al.*, 2016; Harker *et al.*, 2020; Ino and Nakazawa, 2022). Visible warning labels highlighting the potentially harmful risks associated with codeine should be affixed to all OTC CCM products (Norman *et al.*, 2016; Harker *et al.*, 2020; Ino and Nakazawa, 2022). However, such labels are typically only effective for those who purchase codeine for legitimate reasons, as these individuals are more likely to heed the warnings, being not yet dependent on codeine (Cooper, 2011).

Within the top ten highest sold products, there are three different 100 mL syrup products, namely Broncleer & Codeine®, Benylin & Codeine® and Stilpane®, contributing 3.76%, 3.31% and 2.53% respectively. Cumulatively, these three syrups contribute almost 10% of the total percentage distribution of all analysed products.

The prevalence of codeine OTC cough syrup use is increasing, particularly among today's youth, driven by social peer pressures to experiment with various concoctions that include these syrups (Hockenhull *et al.*, 2022). The recreational use of these syrups, particularly among adolescents, is increasing, and homemade mixtures like 'Kratom Cocktails' and 'Krokodil' are becoming more prevalent (Escribano *et al*., 2017). The result of this study correlates with literature that indicates that the past decade has shown an overall increase in codeine cough syrup consumption with a 2 065 kg annual increase in consumption and sale of such syrups during 2014 (Lo *et al.*, 2015). In addition, the World Health Organisation Expert Committee on Drug Dependence reported a global concern related to the increased consumption and purchase of OTC codeine-containing cough syrups, particularly due to ease of access, availability, and social acceptance of these formulations (Hockenhull *et al.*, 2022).

Listed in Table 4.2, it is evident that the SEP of Benylin & Codeine® Syrup (ranked 8th) is almost four times more expensive (R 56.60) than Broncleer & Codeine® Syrup (ranked 7th and costing R 15.24). Benylin & Codeine® Syrup is also almost three times

more expensive than its successor, Stilpane® Syrup (ranked 9th) costing R 20.58 per bottle. Broncleer & Codeine® Syrup and Stilpane® Syrup, cost almost the same price per bottle. An explanation could be that Stilpane® Syrup contains 5 mg of codeine per 5 mL of the syrup, compared to Broncleer & Codeine® Syrup and Benylin & Codeine® Syrup, both containing 10 mg of codeine per 5 mL of syrup (double that of Stilpane® Syrup). Being very affordable for young individuals, syrups like Broncleer & Codeine® and Stilpane® are widely favoured as codeine cough syrups among the youth. According to a South African study, high school students interviewed in rural Free State and Mpumalanga, specifically mentioned purchasing Stilpane® cough syrup for recreational use in homemade concoctions (Essack *et al*., 2020). As one participant noted, "'They buy a medicine called Stillpain at pharmacies and they mix it with Sprite. That medicine is strong, so they get drunk after that!'" (Essack *et al*., 2020). Scholars are also aware that these relatively inexpensive cough syrups can be used to produce large quantities of recreational mixtures;

"*Interviewer:* 'How much is [the codeine]?*'*

Participant: 'R25, if I remember.'

Interviewer: 'So, that small bottle of R25, how much codeine can you make?'

Participant: 'Two litre'" (Essack *et al*., 2020).

As depicted in Table 4.2, the top 20 ranked OTC CCM products sold, cumulatively contributed to 92.82% of all the 55 OTC CCM products analysed in this study. Interestingly, there are four products in the top 20 that represent two of their different pack sizes. These products include Adco-Dol® (pack size 40 and 20 tablets), Acurate® (pack size 40 and 20 tablets), Betapyn® (pack size 18 and 40 tablets) and Syndol® (pack size 40 and 18 tablets). Of these products and accompanying pack sizes ranked in the top 20, all of them had their larger pack size ranked before the smaller pack size, except for Betapyn®. Pack size choice may subtly contribute to the impact and duration of CCM use (McGuire, 2019). Potential motives for choosing larger pack sizes could encompass the anticipation of prolonged availability and the potential for communal usage among individuals (Marti and Sindelar, 2015). Subtly, purchasing larger pack sizes may also indicate a potential misuser, as this implies daily consumption from the same pack (Marti and Sindelar, 2015).

4.2.2. Variable related sales trends

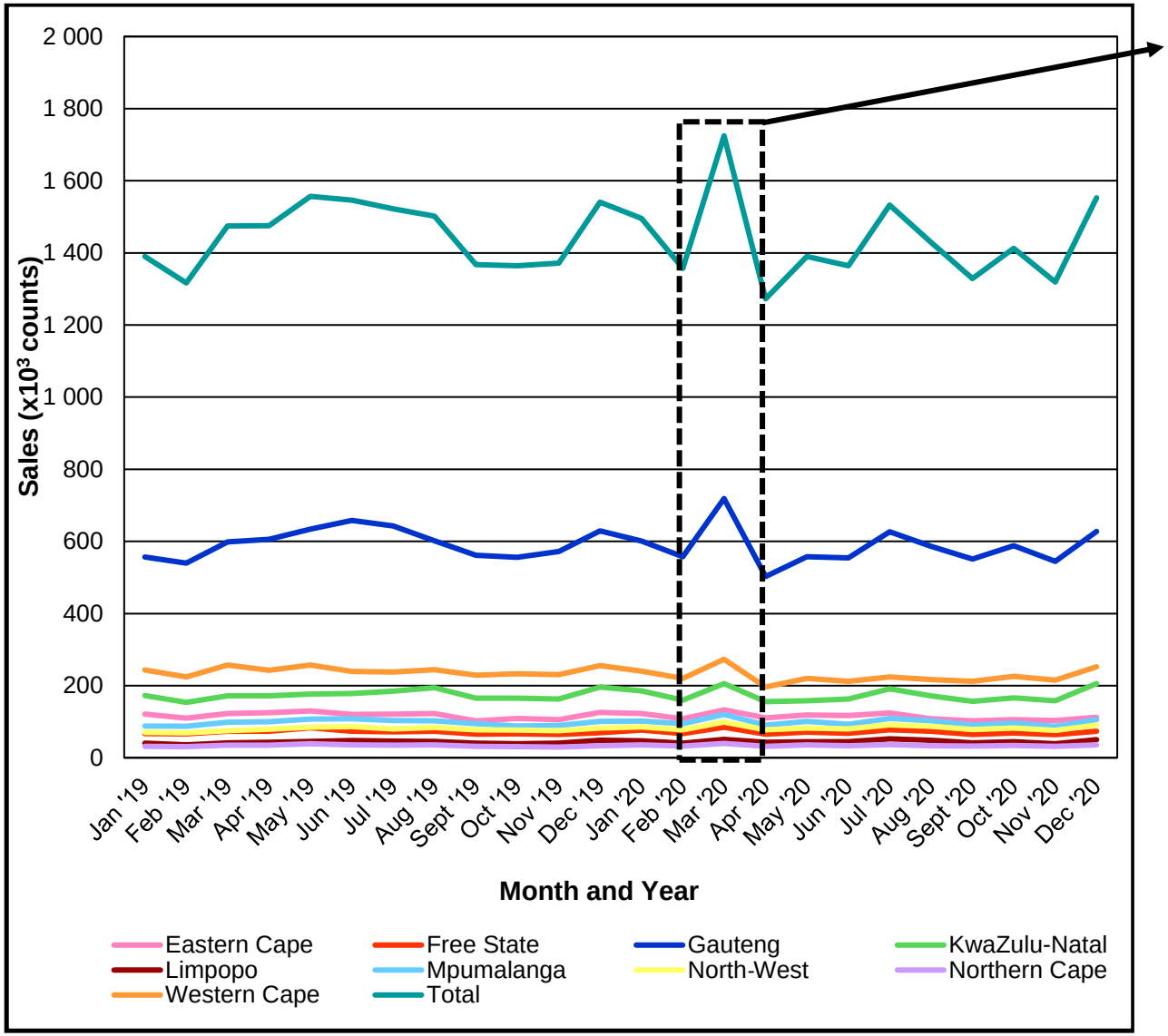
Monthly sales trends were analysed using various related variables. Each graph depicted below, contains an accompanying numerical table within the appendices, to illustrate the detailed statistical findings of each graphical representation.

Sales trends as per province

Figure 4.1 shows the monthly OTC CCM sales trends per province in SA (Appendix G provides detailed statistics). The ***total*** sales trendline distributed across all provinces mirrors the national findings found in the monthly analysis of Table 4.1.

Most provinces followed a similar monthly trend throughout the study period. The sales were the highest in Gauteng over time, followed by the Western Cape and KwaZulu-Natal. Although Gauteng is the smallest province in SA, it is highly urbanised and populated (Harker *et al.*, 2020). Over the years, *Stats SA* has named Gauteng the economic hub of the country, with a 71% growth rate of the province's gross domestic product (GDP) from 2013 to 2022 (StaffWriter, 2023b). *Stats SA* also observed that within trends of semigration patterns, Gauteng is anticipated to experience the largest influx of migrations between 2021 and 2026, attracting an estimated 1.4 million individuals to the province (StaffWriter, 2023b). This increases the sale of medicines thus, posing a risk for the increase in drug use and potential misuse of products, like OTC CCMs (Nyoni *et al.*, 2022). The second and third economic hubs of SA are KwaZulu-Natal and Western Cape, respectively (StaffWriter, 2023b). Both provinces are populous and urbanised, imitating the increased sales trends of OTC CCMs in Figure 4.1 within these provinces (Harker *et al.*, 2020).

The increased OTC CCM sales within these top three provinces shown in Figure 4.1, also mirrors the number of community pharmacies found within each province, contributing to the increased sale of OTC CCMs. Gauteng houses the most community pharmacies within SA (35.10%), followed by KwaZulu-Natal (15.94%) and the Western Cape (14.01%) (Nyamuzihwa *et al.*, 2023; SAPC, 2024). The overall sales were the lowest in the Northern Cape. Despite being the largest and least densely populated



Province	Month and Year		
	February 2020	*March 2020*	*April 2020*
Total OTC CCM sales	**1 356 914**	**1 724 744**	**1 272 673**
Gauteng	557 247	718 760	502 560
Western Cape	220 166	273 067	196 159
KwaZulu-Natal	159 661	205 488	155 990
Eastern Cape	108 333	132 835	110 178
Mpumalanga	94 179	120 020	90 206
North-West	77 452	98 983	77 288
Free State	67 431	84 554	65 737
Limpopo	40 317	51 345	42 545
Northern Cape	32 128	39 692	32 010

Snapshot of the numerical findings of the highlighted trend.

Figure 4.1: The number of OTC CCM sales over time per province.

province in SA, the Northern Cape contributes the least to the country's GDP (Harker *et al.*, 2020; Nyamuzihwa *et al.*, 2023; StaffWriter, 2023b). The Northern Cape also houses the least number of community pharmacies, at only 1.85% of the total of SA's community pharmacy contribution (SAPC, 2024).

From September to November 2019, there was a moderately consistent and stable trend of OTC CCM sales, followed by a peak in sales in December 2019. As shown in the accompanied snapshot table of Figure 4.1, February 2020 showed a national decrease in OTC CCM sales (to approximately 1.3 million ***total*** sale counts). This was followed by an overwhelming spike of sales in March 2020 (to just under 1.8 million ***total*** sale counts), before plummeting in April 2020 (sales decreasing by half a million sale counts to just above 1.2 million ***total*** sale counts). This trend was probably caused by the Covid-19 virus in SA in March 2020, leading to the public panic buying consumables, especially medicines such as OTC CCMs, before the arrival of the total lockdown in April 2020 (Neumann and Temple, 2023). Thereafter, a national gradual and fluctuating rise in sales occurred until December 2020, the last month of the study period.

Sales trends as per pharmacy classification

Figure 4.2 shows the monthly OTC CCM sales trends in SA per pharmacy classification (Appendix H provides detailed statistics). The "Unknown/Not Specified" trend line constitutes negligible results.

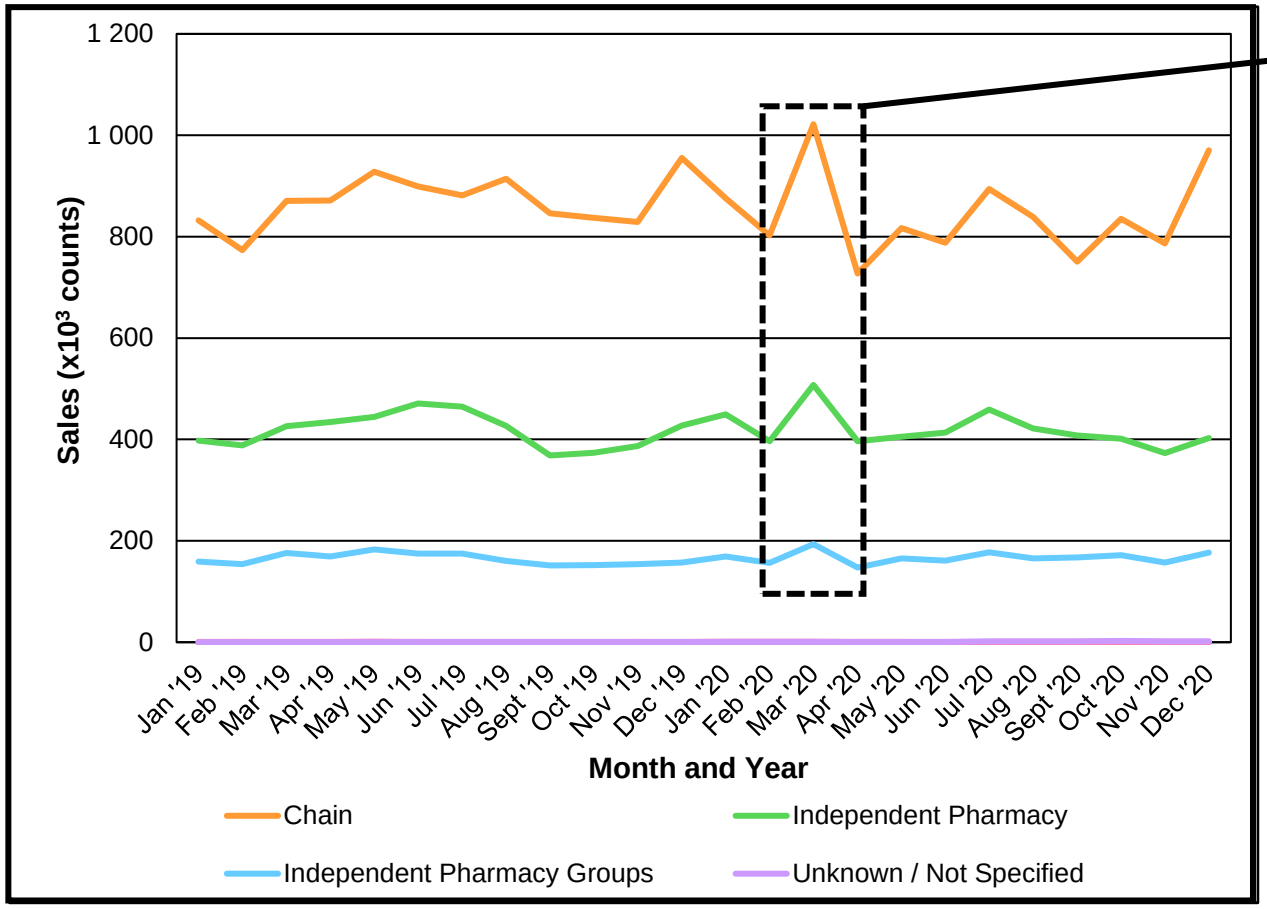
All the pharmacy classifications in this study, are retail/community pharmacies. Accessibility to a pharmacy is crucial for most of the country's population (Hernandez *et al.*, 2023). Community pharmacies retail prescription and OTC products as well as provide health advice to patients (Nyamuzihwa *et al.*, 2023). A 'chain' pharmacy can be defined as a community/retail pharmacy that is part of a larger franchise, located in multiple locations under the same brand and having standardised policies and structure (Hernandez *et al.*, 2023). An 'independent' pharmacy is a retail/community pharmacy that is independently owned and not affiliated to larger chain pharmacies. 'Independent Pharmacy Groups' refer to a collection of independent pharmacies that

join for various reasons that still allow individual pharmacies to maintain their independence whilst still benefiting from the collective advantages of being part of a group (Hernandez *et al.*, 2023).

In 2019, the top three sale trends slightly declined from January 2019 to February 2019. In 2019, chain pharmacies had a sudden rise in sales in May (927 857 sale counts), thereafter, followed by a gradual plummet in sales for the next two months (898 908 and 881 475 sale counts). Independent pharmacy groups remained moderately consistent with sales in 2019. As depicted in the accompanied snapshot beside the figure, the top three sale trends mirrored each other with a steep peak in the highest number of sales for the period occurring in March 2020. This was then followed by a rapid decline in sales in April 2020. A gradual rise in sales of OTC CCMs increased from December 2020 for all pharmacy classifications.

Throughout the period, Figure 4.2 shows that the sales were consistently highest at chain pharmacies followed by independent and independent group pharmacies. As suggested by literature, chain pharmacies contribute the largest (31%) percentage of community pharmacy distribution in SA (Nyamuzihwa et al., 2023). The proportion of chain to independent pharmacies is greatest in Gauteng (40% vs 33%) and the Western Cape (21% vs 11%) (Nyamuzihwa et al., 2023). Many independent pharmacies are often located in rural areas and locations that are underserved (such as Mpumalanga and the North-West), in comparison to large chain pharmacies that are situated in the more populous areas (such as Gauteng and the Western Cape) (Mercer et al., 2022). This is evident in a South African study proving that over 40% of independent pharmacies, are in rural communities (Nyamuzihwa et al., 2023).

However, not all countries contain a higher percentage of chain pharmacies versus independent pharmacies. Poland, a first world country, houses 57% of independent pharmacies, versus 43% of chain pharmacies (Bratkowska *et al.*, 2020). However, like SA, the Polish public frequently use more chain pharmacies, than independent pharmacies (52.15% vs 47.85%) (Bratkowska *et al.*, 2020). Medical Schemes (also referred to as Medical Aids) are changing their conditions, such that they list certain



Pharmacy classification	Month and Year		
	February 2020	***March 2020***	***April 2020***
Chain	802 450	1 021 771	727 268
Independent Pharmacy	396 597	507 613	396 478
Independent Pharmacy Groups	156 532	193 470	147 269

Snapshot of the numerical findings of the highlighted trend.

Figure 4.2: The number of OTC CCM sales over time per pharmacy classification.

‘designated service providers (DSPs)’ that members may frequent to purchase their medicines at certain DSP pharmacies (Hernandez *et al.*, 2023). A DSP can be defined as a healthcare provider designated by the scheme to provide services to its members (Bratkowska *et al.*, 2020). Should the member voluntarily decide not to frequent the DSP, the member may be liable for a pharmacy co-payment or deductible which is outlined in the rules of their particular scheme (Hernandez *et al.*, 2023). Many of the chosen DSPs, exclude South African independent pharmacies and groups and are favouring chain pharmacy groups, therefore possible increased OTC CCM sales may be higher in chain pharmacy groups than any other pharmacy classification (Hernandez *et al.*, 2023) as depicted in Figure 4.2.

Literature has suggested that in many countries, independent pharmacies provide a more personal approach to its patients, allowing for enhanced pharmacist-patient relationships (Bratkowska *et al.*, 2020). Although chain pharmacies may have a wider range of products, such as OTC CCMs, sufficient healthcare advice is often omitted when dispensing products like codeine, that are purchased from chain pharmacy groups (Bratkowska *et al.*, 2020). Hence, independent pharmacies and independent pharmacy groups are increasingly becoming more popular amongst the public and are slowly attracting chain pharmacy customers to switch to using independent pharmacies which can offer a more personal and dedicated approach to its customers (Bratkowska *et al.*, 2020; Hernandez *et al.*, 2023). The increasing popularity of independent pharmacies, known for their personalised approach and enhanced pharmacist-patient relationships, is linked to rising codeine sales, as they are likely to provide more comprehensive healthcare advice compared to chain pharmacy groups. In addition, there is a rise in purchase of products like CCMs within a more welcoming environment, such as an independent pharmacy, where individuals feel comfortable in making such purchases, thereby, fostering a sense of trust and ease.

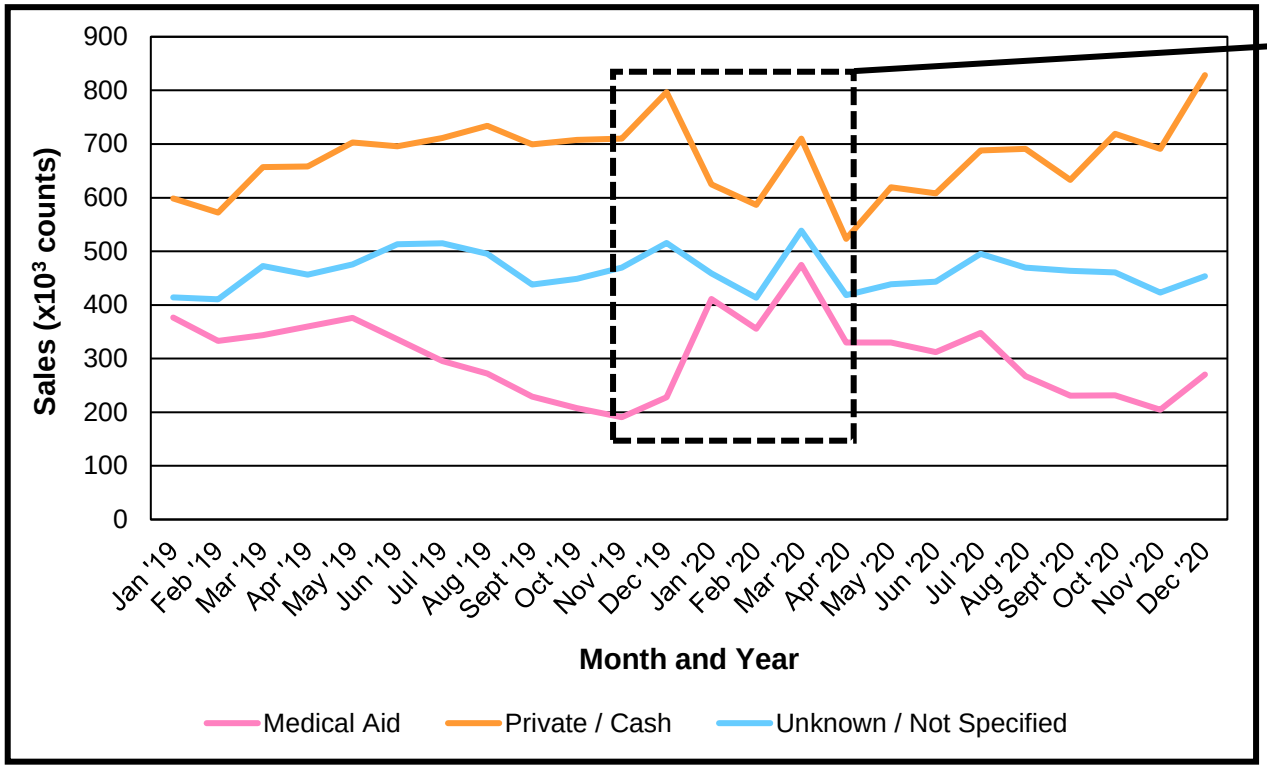
Sales trends as per method of payment

Figure 4.3 represents the monthly OTC CCM sales trends in SA per method of payment (Appendix I provides detailed statistics). A comprehensive list of all the

medical scheme (medical aid) names classified under “Medical Aid” in the figure, is available in Appendix D.

Over time, sales were highest through private/cash payments, followed by unknown/not specified and medical aids respectively. Only 17% of the South African population relies on healthcare services provided by the private sector (Padayachee *et al.*, 2020). This private sector is managed by medical schemes/medical aids. Within the medical aid, it is advisable to undertake all measures to prolong the savings account for the year (Discovery, 2018). Therefore, purchasing OTC products, including those listed in this study, through a medical aid, reduces the balance of the medical savings account (Discovery, 2018). Since OTC claims do not accumulate toward the annual threshold, this increases the out-of-pocket expenses for the year (Discovery, 2018). Such knowledge may be an accountable manner as to why the reason when purchasing products using private funds in the form of cash payments are highest and medical aid is lowest in Figure 4.3. Nevertheless, some schemes contain an “acute medicines” component that included medicines for non-chronic treatments, with a sub-category that covers PIT, allowing a pharmacist to advise on the benefit of an OTC product (Padayachee *et al.*, 2020). The goal of this medical scheme benefit is to allow for patients to accept responsibility of their health and apply this benefit to claim OTC products accordingly (such as the OTC CCM products of this study) (Padayachee *et al.*, 2020).

However, not all patients have access to medical aid and hence, paying out-of-pocket/paying cash for OTC products could possibly result in the highest trend line in Figure 4.3. Although codeine has a lower potency compared to other opioids, addiction risks are high, and many users may use it for misuse and possible abuse. Some patients may be aware of their addiction, and therefore feel embarrassed, so they therefore consume codeine “secretively” and privately in their home (Van Hout *et al.*, 2018). This may suggest that such users could potentially not want to have a record of their codeine purchase on their medical aid, and thus opt to pay for such products privately/with cash or prefer to not answer and leave this response as unknown/not specified, contributing to Figure 4.3’s results.



Month and Year	Method of payment		
	Private/Cash	*Unknown/Not Specified*	*Medical Aid*
November 2019	710 042	469 760	190 709
December 2019	796 464	515 597	227 986
January 2020	624 653	458 884	410 914
February 2020	586 512	413 443	355 785
March 2020	709 919	538 563	474 678
April 2020	523 242	418 302	329 769

Snapshot of the numerical findings of the highlighted trend.

Figure 4.3: The number of OTC CCM sales over time per method of payment.

Evident in the accompanied snapshot, the top two trend lines (private/cash and unknown/not specified) showed a sudden incline in sales in December 2019 (to 796 464 and 515 597 sale counts respectively), and then decreased in January 2020 (to 624 653 and 458 884 sale counts respectively). Medical aid represented a gradual decline in sales from May 2019 to November 2019 (from 376 199 to 190 709 sale counts). A possible reason for this could be such that most medical aid members are usually in their self-payment gap during these later months of the year (Discovery, 2018). All the trend lines plummeted in February 2020 and rose in March 2020 before plummeting again in April 2020, likely due to the Covid-19 virus and the South African lockdown restrictions. The private/cash sales steadily increased until December 2020 with fluctuations, possibly contributing to depleted medical aid funds in the later months of the year (Discovery, 2018). All types of methods of payment sales increased from December 2020. Possible explanations for this trend may include patients attempting to utilise remaining medical aid funds towards the end of the year (Padayachee, 2020; News24, 2022). Others may find themselves depleting their medical aid funds early in the year, necessitating cash payments for medicines later in the year, and thus awaiting the replenishment of their medical aid funds in January of the new year to help stock up on monthly medicines (Padayachee *et al.*, 2020).

4.2.3. Monthly product sales trends

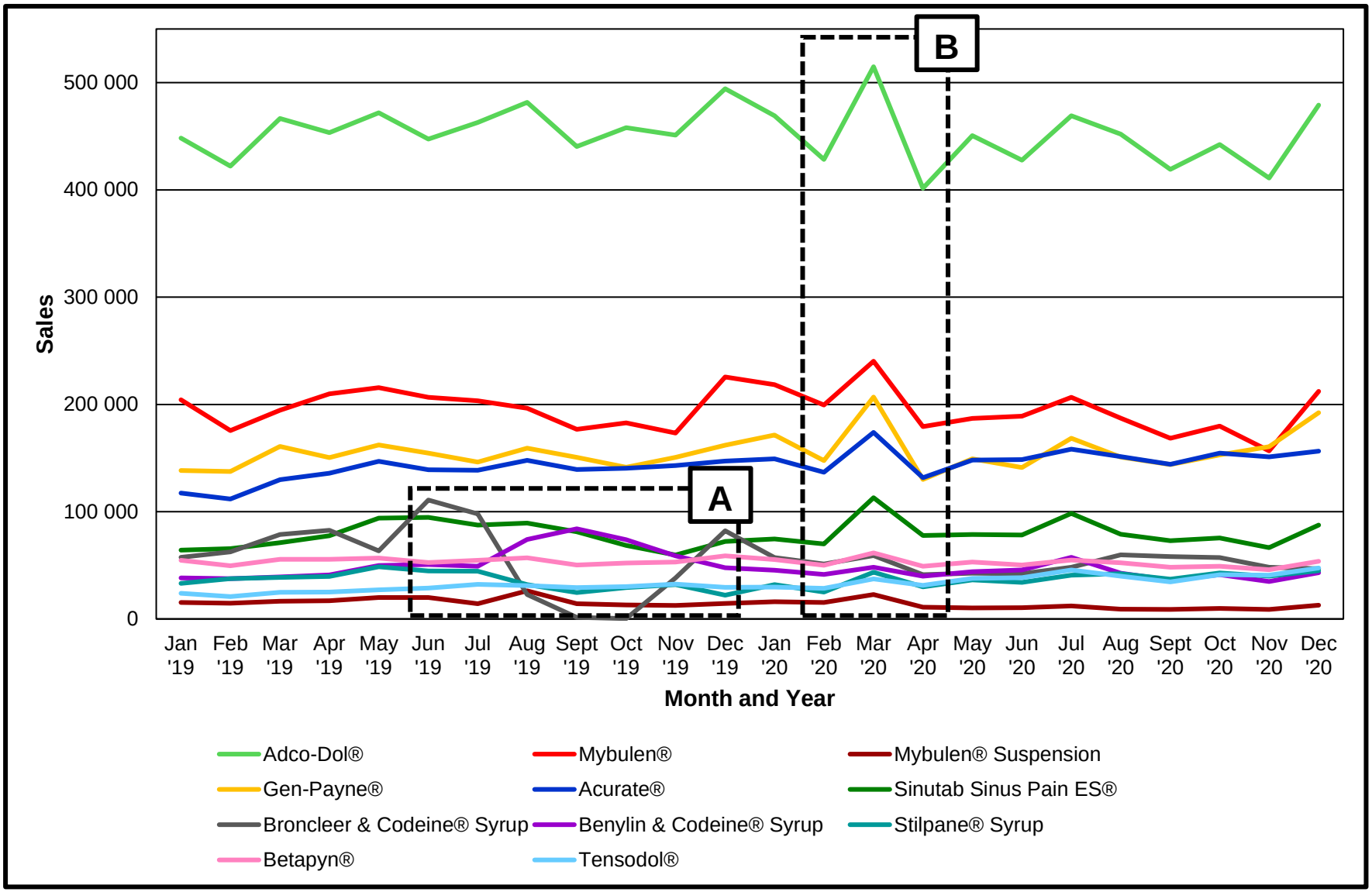
The following line graphs show the monthly sale trend analyses of all OTC CCM products investigated in this study. The various pack sizes of products have been amalgamated so that each trend line represents an individual OTC CCM product. However, liquid dosage forms of certain products have been represented separately, and not accumulated together with the solid dosage form of the same product.

Figure 4.4 represents the national monthly sales of the top 11 (Group 1) OTC CCM products investigated in this study. Appendix J corresponds to the numerical results of Figure 4.4. Table 4.3 and Table 4.4 provide the numerical results of blocks ‘A’ and ‘B’ in Figure 4.4.

Over-the-counter CCMs are more commonly purchased than many prescription-only products (Roberts and Nielsen, 2018). In support of this statement, a global study proved that South Africans accounted for almost a third of OTC CCM sales, contributing to the high purchase of OTC codeine products in South African pharmacies (Richards *et al.*, 2021).

As clearly seen in Figure 4.4, Adco-Dol® showed an overwhelmingly high number of sales before and during Covid-19. Of this product, 481 654 sales were sold in August 2019, and December 2019 (494 384 sales) (before Covid-19) and reached its peak of approximately 515 000 sales in March 2020 (during Covid-19). Continuous fluctuations of sales followed for Adco-Dol® throughout the remaining months. As suggested by the trend line, Adco-Dol® is the most popular OTC CCM product bought in South African pharmacies. Carney *et al.* (2018) also proved it in their study, that Adco-Dol® was the most popular-mentioned codeine product purchased as OTC (53.2% of study participants stipulated this) (Carney *et al.*, 2018). Possible reasons that Adco-Dol® is so largely favoured, may be likely due to its broad spectrum of pharmacological therapeutic uses, such as antipyretic, antihistamine, sedative and analgesic properties (Adcock Ingram, 2021). Adcock Ingram, the manufacturer of Adco-Dol®, reported in 2019, that this product was its leading product in the OTC pain category in pharmacies (Adcock Ingram, 2019b). This product also has a comparatively low SEP and is available in varying pack sizes, as depicted in Table 4.2. As represented in Table 4.4, April 2020 represented Adco-Dol®'s lowest month of sales, to just above 400 000 sales.

Mybulen® was the second highest product sold with just under 240 000 sale counts sold in December 2019 and March 2020. Mybulen® sales were lower during Covid-19 than before Covid-19. Contrasting this, Mybulen® Suspension was the product contributing to the lowest number of sales throughout the national monthly sales trends for Group 1. Gen-Payne®, Acurate® and Sinutab Sinus Pain ES® completed the top five most-sold OTC CCM products per month, as depicted in Figure 4.4. Another popular OTC CCM product in SA, is Acurate®, proven in a South African study, to be the ninth most popular OTC codeine product purchased with the intent to misuse or



ES = extra strength

Figure 4.4: The national monthly sales over time per OTC CCM product (Group 1).

Table 4.3: Snapshot numerical results from block 'A' in Figure 4.4.

	Month and Year						
Product	**June 2019**	**July 2019**	**August 2019**	**September 2019**	**October 2019**	**November 2019**	**December 2019**
Broncleer & Codeine® Syrup	110 837	97 876	22 788	1 453*	326*	38 347	82 116

***Note:** This drastic drop in sales is related to Adcock Ingram's temporary suspension of this product.

Table 4.4: Snapshot numerical results from block 'B' in Figure 4.4.

	Month and Year		
Product	**February 2020**	**March 2020**	**April 2020**
Adco-Dol®	428 396	514 817	401 518
Mybulen®	199 468	240 251	179 365
Mybulen® Suspension	15 239	22 732	10 876
Gen-Payne®	147 559	206 844	130 064
Acurate®	136 798	173 901	131 709
Sinutab Sinus Pain ES®	69 831	113 023	77 781
Broncleer & Codeine® Syrup	51 239	59 104	41 242
Benylin & Codeine® Syrup	41 510	48 166	39 866
Stilpane® Syrup	25 109	43 637	29 929
Betapyn®	50 127	61 569	49 180
Tensodol®	28 559	37 407	31 287

ES = extra strength

target dependence effects (Dada *et al.*, 2015). The sales trend of Acurate® depicts moderately consistent sales throughout the period, increasing month-on-month. Most products in Figure 4.4, display similar monthly sale trends over the study period.

As displayed in Figure 4.4 and Table 4.3, Broncleer & Codeine® Syrup, reached its peak sales in June 2019 (approximately 110 000 sales), and then suddenly plummeted to a minimum between September 2019 (just under 1 500 sales) to

October 2019, showing a minimal amount of 326 national sales, before starting to increase again. Broncleer & Codeine® Syrup's manufacturer, Adcock Ingram, temporarily voluntarily suspended the sales of this product between July to December 2019 (Adcock Ingram, 2019a). Adcock Ingram manufactures and distributes a wide range of CCMs, and has been aware of the ongoing opioid crisis, which has led to many South Africans purchasing and thus misusing numerous OTC codeine products (Buthelezi, 2020). To facilitate the mitigation of abuse, Adcock Ingram implemented the suspension of sales for this product, for six months, which is evident in the results of the trend line (Figure 4.4) and the numerical findings in Table 4.3.

Codeine cough syrups are becoming the latest "trend", especially amongst the South African youth (Tettey *et al.*, 2020). Users are purchasing codeine cough syrups, such as Broncleer & Codeine® Syrup, Benylin & Codeine® Syrup and Stilpane® Syrup, to concoct homemade mixtures like 'Purple Drank' (Van Hout, 2014b). As displayed in Figure 4.4, three codeine cough syrups constitute the top ten of Group 1 products. A study done to analyse pharmacist's perspectives on codeine use and misuse in three countries, reported that Benylin & Codeine® Syrup and Broncleer & Codeine® Syrup, contributed 21.8% and 16.9% respectively, to the most popular mentioned codeine products purchased as OTC in SA (Carney *et al.*, 2018). Another South African study investigated adolescents' views on OTC CCM misuse, whereby many high school scholars agreed that Stilpane® Syrup and Benylin & Codeine® Syrup were frequently purchased to concoct and consume products like 'Purple Drank', to get "high" (Essack *et al*., 2020). Participants from this study, described the ease of access to such products as being affordable, widely accessible and the appeal of consuming cough mixture with cold drink, was perceived as "cool" in social settings (Essack *et al*., 2020). These three mentioned syrups, showed more sales of each product before Covid-19 and then plummeted in April 2020, thereafter, slowly increasing in sales until December 2020.

As depicted in Table 4.4, reflecting the numerical findings of Figure 4.4, all products in Group 1, showed a plummet in sales in February 2020, then increased rapidly in March 2020 (of which most products reached their peak), and then subsequently plummeted to a low in April 2020.

Figure 4.5 represents the national monthly sales of the last eleven (Group 2) OTC CCM products investigated in this study. Appendix K corresponds to the numerical results of Figure 4.5. Table 4.5 and Table 4.6 provide the numerical results of blocks ‘C’ and ‘D’ in Figure 4.5.

As depicted in Figure 4.5, Syndol®, Lenapain® and Pynstop® are the top three products sold in Group 2. Most of Group 2’s products showed higher sales before Covid-19, compared to during Covid-19. Syndol® sales had the highest number of sales before Covid-19 in Group 2. However, overall, Tensopyn® sales were higher during Covid-19, than before Covid-19.

Table 4.6 shows the results of all products findings between February 2020 and April 2020. This was the start of the Covid-19 virus in SA, and the beginning of the Covid-19 national lockdown. As seen, all product sales greatly increased from February 2020 to March 2020 and then plummeted to below February 2020’s sales, in April 2020. All products except for Tensopyn®, showed lower sales in April 2020 than in February 2020. Tensopyn®, reflected the most fluctuating sales trend in Figure 4.5, as seen in Table 4.5. Its sales are highest in January 2019 (26 710 sales), and then subsequently decreased in April 2019 (to just over 11 000 sales), with fluctuations between April 2019 and April 2020. Sales of Tensopyn® plummeted to their lowest in August 2019 (approximately 5 500 sales) and November 2019 (approximately 4 500 sales). No literature or media coverage is available to suggest potential reasons for such fluctuations in the sales over this 12-month period.

In 2015, a South African study reported that Syndol®, was ranked the fifth most frequently purchased OTC CCM product to be misused or for cause of dependence (Dada *et al.*, 2015). Although this literature finding is not consistent with this study, Syndol® shows moderately higher sales for OTC CCMs compared to other products investigated in this study. In this study and in Figure 4.5, Syndol® reached its peak of just under 40 000 sales in March 2020, plummeting to its lowest monthly sales of 21 974 sales in May 2020.

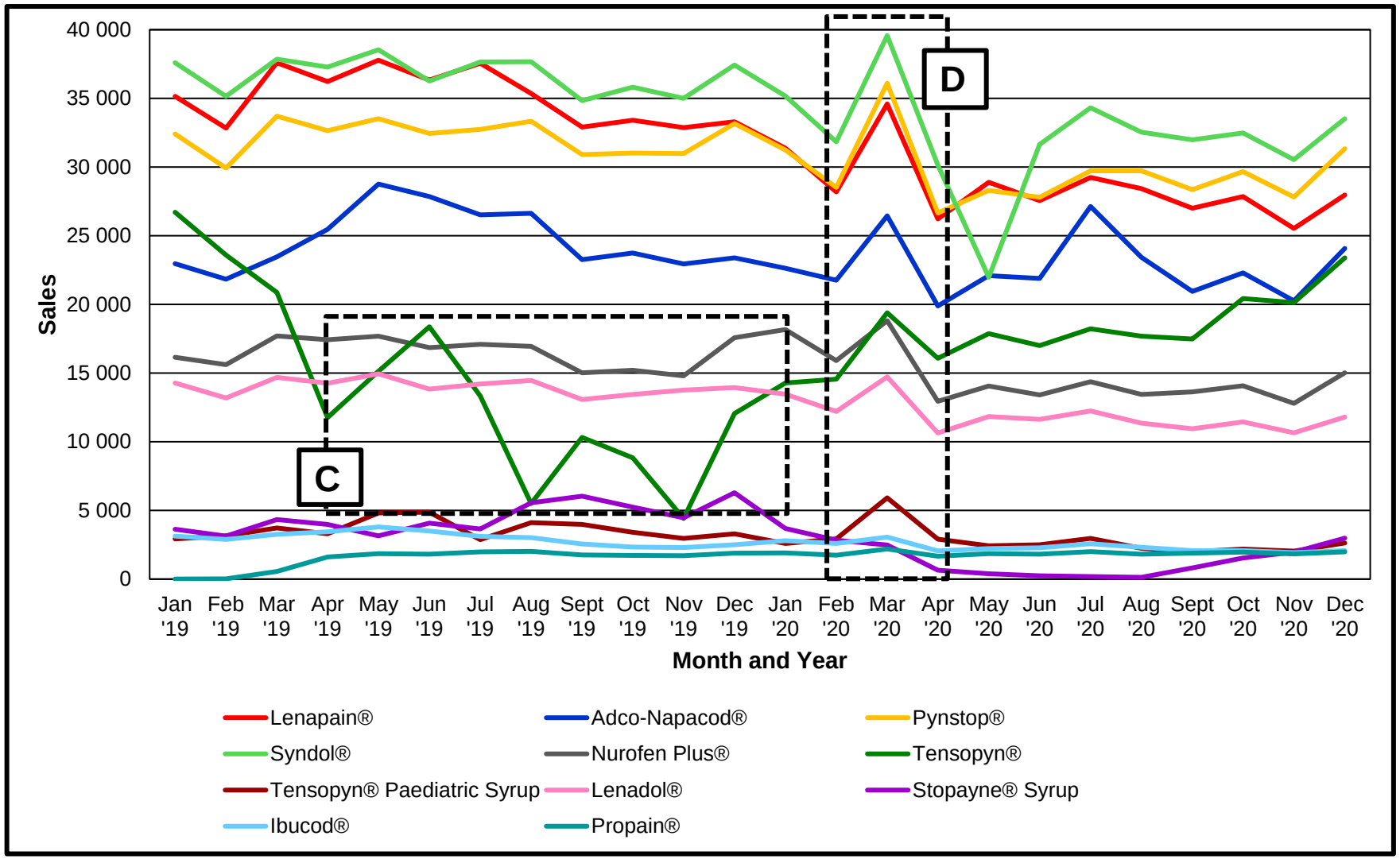


Figure 4.5: The national monthly sales over time per OTC CCM product (Group 2).

Table 4.5: Snapshot numerical results from block 'C' in Figure 4.5.

	Month and Year				
Product	**April 2019**	**May 2019**	**June 2019**	**July 2019**	**August 2019**
Tensopyn®	11 757	15 128	18 375	13 340	5 507
	September 2019	**October 2019**	**November 2019**	**December 2019**	**January 2020**
	10 309	8 828	4 413	12 048	14 279

Table 4.6: Snapshot numerical results from block 'D' in Figure 4.5.

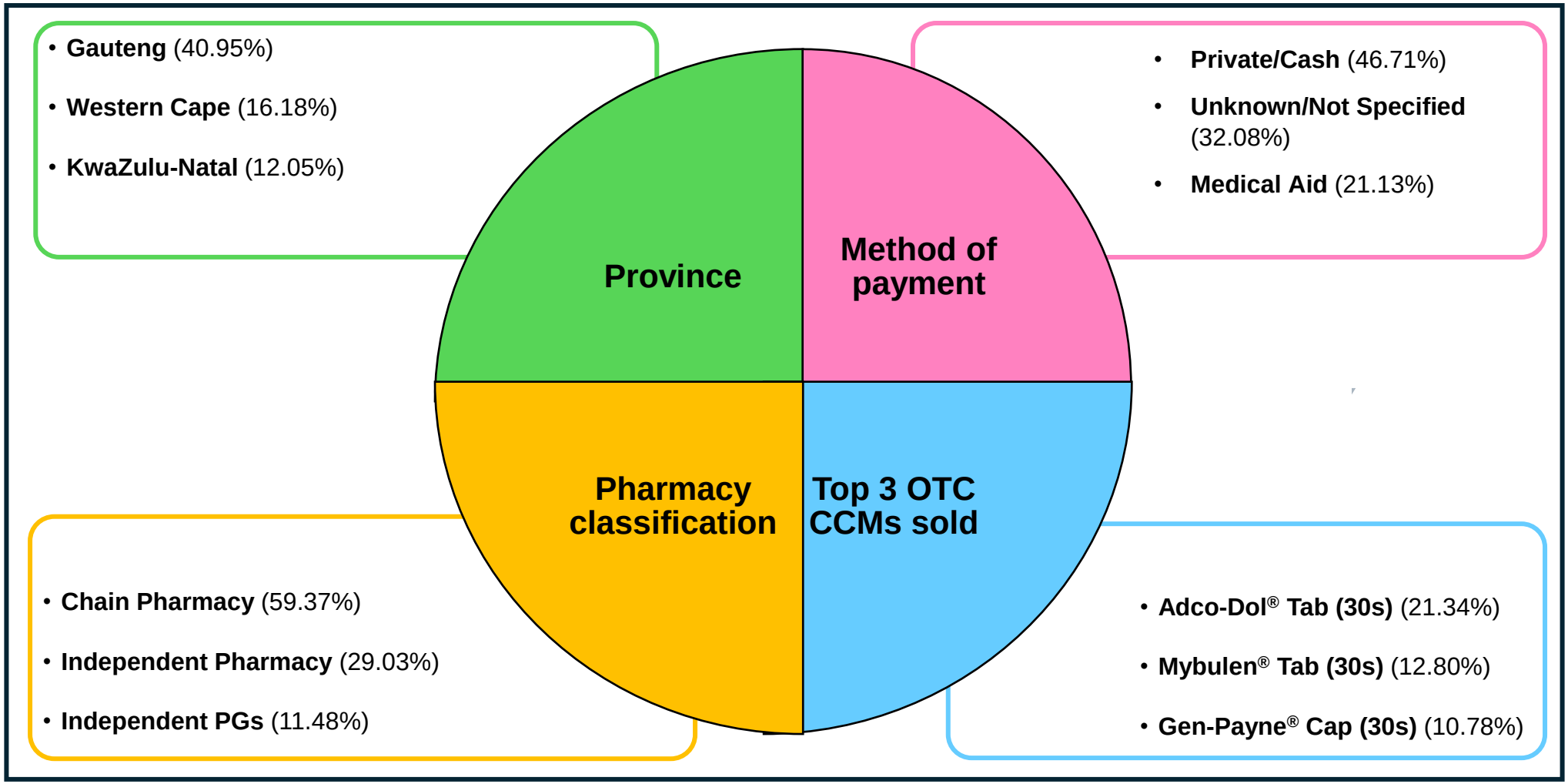
	Month and Year		
Product	**February 2020**	**March 2020**	**April 2020**
Syndol®	31 829	39 572	30 154
Lenapain®	28 185	34 591	26 226
Pynstop®	28 522	36 104	26 660
Tensopyn®	14 563	19 384	16 067
Adco-Napacod®	21 769	26 455	19 887
Nurofen Plus®	15 908	18 813	12 941
Lenadol®	12 211	14 730	10 641
Stopayne® Syrup	2 832	2 478	648
Ibucod®	2 593	3 056	2 048
Tensopyn® Paediatric Syrup	2 922	5 918	2 917
Propain®	1 745	2 192	1 667

Nurofen Plus® is another common OTC CCM product on the South African OTC market. Although this product shows moderately low and consistent sales in Figure 4.5 in SA, it is interesting to note that in various literature, this product is often mentioned and used in codeine misuse practices in other countries. In the UK (approximately 60%) and Ireland (approximately 75%), Nurofen Plus® was reported as one of the most popular codeine products purchased by users in a pharmacy (Carney *et al.*, 2018). One participant from this study, reported using between 24 to 115 tablets of Nurofen Plus® daily (the maximum pack size is 24 tablets, thus this patient purchased up to five boxes per day), to feed their addiction and to 'feel normal',

attributable to the product's codeine effect (Van Hout *et al.*, 2018). Another Irish study reported that 90% of study participants mentioned that a CCM product, such as Nurofen Plus®, was their primary drug for misuse purposes (Van Hout *et al.*, 2018). Products containing codeine are often chosen due to their psychoactive effects and their associations with abuse, dependence and misuse (Wright *et al.*, 2016).

Considering both Figure 4.4 and Figure 4.5, OTC CCM product sales in South African pharmacies reflect moderately high amounts of monthly sales throughout the years. Although this study only presents a two-year period, sales show the popularity of such products being bought, due to ease of access, a wide availability, being OTC products and are relatively affordable. Considerations and proposals in a developing country, namely SA, have been put in place to reclassify and up-schedule all OTC CCMs to prescription-only (Voigt, 2022). Vincent Tlala, Chief Executive Officer of the South African Pharmacy Council, argues that global countries that have made codeine medicines prescription-only, resulted in a reduction of legal codeine sales, but no statistics have proven a reduction in codeine medicine abuse (Voigt, 2022). He then states that "[the] only persons who seem to suffer from such bans are legitimate patients who must endure pain or fork [out] more money for stronger painkillers than those which are available over-the-counter" (Voigt, 2022). This argument emphasises that authentic patients rely on OTC CCMs for pain relief (de Villiers, 2020). Imposing new regulations to reclassify all OTC CCMs would necessitate these patients to bear the costs of physician consultations and prescription fees, which many cannot afford (de Villiers, 2020; Voigt, 2022). In turn, it could also increase irrational codeine use and illegal codeine sales (Karami *et al.*, 2023). Adcock Ingram, one of the largest CCM suppliers in SA, mentioned that OTC CCMs contribute to 10% of its sales, and should all OTC CCMs be up-scheduled to prescription-only, this too could affect the market shares of companies such as Adcock Ingram (de Villiers, 2020).

Concluding **objective IIa**, Figure 4.6 depicts a graphical summary of the main descriptive findings found within the top variables analysed in **objective IIa**.



OTC = over-the-counter; CCMs = codeine-containing medicines; PGs = Pharmacy Groups; Tab = tablets; Cap = capsules
Note: The percentages (%) represent the frequency of sales of the top three findings within each variable.

Figure 4.6: Graphical summary of the main results found in objective IIa.

4.3. Objective IIb

Objective IIb was to assess any difference between the effect of the Covid-19 pandemic on the sales trends of OTC CCMs across all provinces in SA. Since various categorical data has been analysed for this objective, the data is best represented in bar graphs and tables, suited to categorical data analyses.

Table 4.7 shows the top 20 OTC CCM product ranking sales before and during Covid-19. The sales of OTC CCMs before and during the Covid-19 pandemic, indicate that there were higher sales of approximately 60% of OTC CCMs sold before Covid-19, compared to just over 40% of the total sales that were sold during the study's Covid-19 period. The pre-Covid-19 period was four months longer than the stipulated during Covid-19 period of the study. Due to national lockdowns, regulations were put in place that only essential workers (such as pharmacists, doctors and shopkeepers etc.) during Covid-19 were allowed to leave their homes during such periods, therefore naturally decreasing normal daily stock sales (Chua *et al.*, 2021).

Adco-Dol® Tab (40s) was the most bought medication before and during Covid-19. It accounted for 21.05% of before Covid-19 sales and 21.76% of during Covid-19 sales. As depicted in **objective IIa** as well, Adco-Dol® is a very common OTC CCM product bought in SA and throughout the world. This also remained the case during the Covid-19 period in SA. The top nine most bought products were the same in the two time periods with minimal differences shown in the respective percentage distributions. However, the overall sale counts were lower during Covid-19. Together, the top five OTC CCM products in each period, respectively represented approximately 60% of each period's sales. Interestingly, the larger pack size (40 tablets) of both Adco-Dol® and Acurate® were favoured in the ranking of Table 4.7. This may suggest that users were taking OTC medicines for longer periods (and therefore a bigger pack size would last longer), or many household members shared the same OTC product (and hence a bigger pack size was favoured).

Table 4.7: A comparison ranking of the top 20 OTC CCM sales between pre-Covid-19 and during Covid-19 periods.

	Pre-Covid-19			During Covid-19		
Ranking position	**Product, dosage form and pack size**	**Frequency of sales**	**Distribution (%)**	**Product, dosage form and pack size**	**Frequency of sales**	**Distribution (%)**
1st	Adco-Dol® Tab (40s)	4 267 992	**21.05**	Adco-Dol® Tab (40s)	3 117 269	**21.76**
2nd	Mybulen® Tab (30s)	2 619 112	**12.91**	Mybulen® Tab (30s)	1 810 279	**12.64**
3rd	Gen-Payne® Cap (30s)	2 132 926	**10.52**	Gen-Payne® Cap (30s)	1 596 536	**11.14**
4th	Adco-Dol® Tab (20s)	2 120 991	**10.46**	Adco-Dol® Tab (20s)	1 345 641	**9.39**
5th	Acurate® Tab (40s)	1 518 057	**7.49**	Acurate® Tab (40s)	1 224 668	**8.55**
6th	Sinutab Sinus Pain ES® Tab (24s)	874 901	**4.31**	Sinutab Sinus Pain ES® Tab (24s)	697 848	**4.87**
7th	Broncleer & Codeine® Syr (100 mL)	802 302	**3.96**	Broncleer & Codeine® Syr (100 mL)	499 372	**3.49**
8th	Benylin & Codeine® Syr (200 mL)	718 962	**3.55**	Benylin & Codeine® Syr (200 mL)	425 156	**2.97**
9th	Stilpane® Syr (100 mL)	484 287	**2.39**	Stilpane® Syr (100 mL)	391 586	**2.73**
10th	Betapyn® Tab (18s)	437 590	2.16	Tensodol® Tab (40s)	291 907	2.04
11th	Acurate® Tab (20s)	391 173	1.93	Acurate® Tab (20s)	286 297	2.00
12th	Lenapain® Tab (36s)	319 344	1.57	Betapyn® Tab (18s)	274 061	1.91
13th	Betapyn® Tab (40s)	318 050	1.57	Betapyn® Tab (40s)	243 780	1.70
14th	Adco-Napacod® Tab (5 000s)	298 511	1.47	Adco-Napacod® Tab (5 000s)	199 464	1.39
15th	Pynstop® Tab (40s)	272 174	1.34	Lenapain® Tab (36s)	199 209	1.39
16th	Syndol® Tab (18s)	240 410	1.19	Pynstop® Tab (40s)	198 974	1.39
17th	Tensodol® Tab (40s)	239 759	1.18	Syndol® Tab (40s)	167 424	1.17
18th	Syndol® Tab (40s)	236 869	1.17	Nurofen Plus® Tab (24s)	142 547	0.99
19th	Nurofen Plus® Tab (24s)	232 127	1.14	Syndol® Tab (18s)	133 472	0.93
20th	Mybulen® Susp (100 mL)	228 767	1.13	Sinutab Sinus Pain ES® Tab (12s)	129 231	0.90

Tab = tablets; Cap = capsules; ES = extra strength; Syr = syrup; Susp = suspension
Note: Frequency of sales is indicative of the number of packs or bottles of a product sold.
Bold and highlighted values represent noteworthy data, which are further discussed in the text.

Within the top nine most bought products over the two periods, two codeine cough syrups, namely Broncleer & Codeine® (100 mL) and Benylin & Codeine® (200 mL) were reported. The Covid-19 virus may have initially presented as a fever, a dry cough, body pains and fatigue (Çalıca Utku *et al.*, 2020). Increasing self-medication practices, and to avoid entering a doctor's practice to mitigate the risk of contracting the virus, many individuals resorted to purchasing cough syrups, such as Broncleer & Codeine® (100 mL) and Benylin & Codeine® (200 mL) to alleviate the irritating cough symptom (Çalıca Utku *et al.*, 2020).

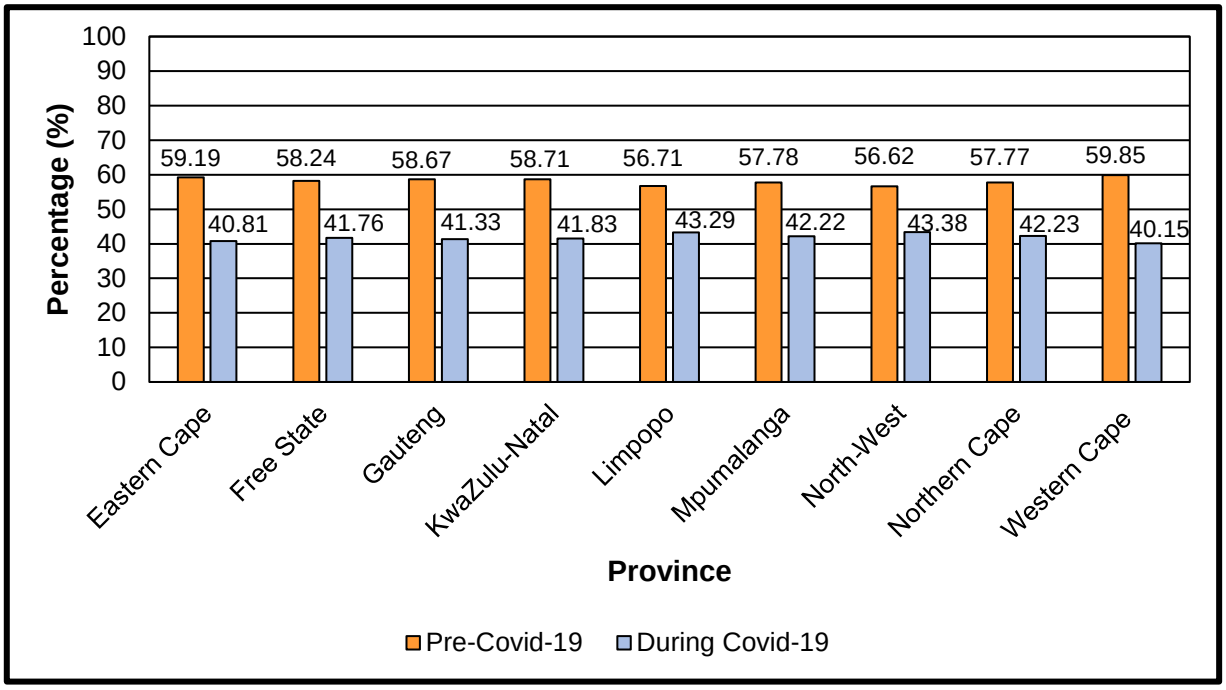
A Swedish study reported that there was a 96% increase in sales of OTC products during some periods of the Covid-19 pandemic (Eccles *et al.*, 2023). Individuals who experienced mild symptoms of Covid-19 were likely to resort to self-medicating with easily accessible OTC medicines to alleviate the symptoms (Eccles *et al.*, 2023). Such symptoms were commonly treated with analgesic opioids and antipyretic OTC products, many of which contained paracetamol and ibuprofen. All the OTC CCMs explored in this study contained codeine, ibuprofen and or paracetamol, and hence many of the bought OTC medicines (for self-management of the Covid-19 symptoms), included the products discussed in this study (Eccles *et al.*, 2023).

Figure 4.7, Figure 4.8 and Figure 4.9 graphically present the data with varying variables, and each figure has an accompanying table (Table 4.8, Table 4.9 and Table 4.10) indicating the average monthly consumption (rounded off to the nearest whole number) and its percentage change between the two periods, of the sales represented graphically.

Effect of Covid-19 on sales trends as per province

Figure 4.7 shows the percentage distribution of the OTC CCM sales by province before and during the Covid-19 pandemic. The sale patterns before and during Covid-19, corresponded similarly across all provinces during the two periods. Each province highlighted that all province's OTC CCM sales before Covid-19 were almost 20% greater than OTC CCM sales within each province recorded during the Covid-19 period. Analysed by province, the percentage distributions of OTC CCM sales before Covid-19 and during Covid-19, were significantly different (p<0.001).

Limpopo (13.42% difference) and the North-West (13.24% difference) were the two provinces with the least percentage difference between the two periods. Corresponding to these findings, Table 4.8 also showed that Limpopo (increased by 6.88%) and the North-West (increased by 7.27%) were the provinces with the greatest increase in average monthly consumption of OTC CCM sales before and during Covid-19.



Note: Each individual province represents 100% of its sales throughout the study's time period.

Figure 4.7: The comparison of percentage distribution of OTC CCM sales by province pre and during Covid-19.

The provinces showing the greatest percentage difference between the two periods were the Western Cape (19.70% difference) and the Eastern Cape (18.38% difference). Table 4.8 also suggested that the Western Cape's average monthly consumption of OTC CCMs moderately decreased by 6.09% over the two periods, viz. before and during the Covid-19 pandemic.

It is evident in Figure 4.7 and Table 4.8 that there were varying results in each province with regards to the effect of Covid-19 and OTC CCM sales. Various provinces may have received varying information regarding the Covid-19 pandemic, and hence different behaviours may have occurred within the different province communities. An

example of this is the perception of the pandemic as an unknown threat, with concerns that lockdowns could lead to medicine shortages (Kostev and Lauterbach, 2020). This fear stemmed from the temporary halt in medicine manufacturing in countries like India and China, major suppliers for SA, which experienced the pandemic earlier than SA (Kostev and Lauterbach, 2020).

Table 4.8: Average monthly consumption of OTC CCMs purchased pre and during Covid-19, corresponding to Figure 4.7.

	Average monthly consumption		
Province	**Pre-Covid-19**	**During Covid-19**	**Change (%)**
Eastern Cape	117 533	113 462	↓ by 3.46
Free State	70 900	71 184	↑ by 0.41
Gauteng	593 866	585 691	↓ by 1.38
KwaZulu-Natal	174 154	173 154	↓ by 0.57
Limpopo	42 958	45 913	↑ by 6.88
Mpumalanga	97 321	99 566	↑ by 2.31
North-West	78 785	84 510	↑ by 7.27
Northern Cape	33 614	34 398	↑ by 2.33
Western Cape	239 455	224 862	↓ by 6.09

↑: increase; ↓: decrease

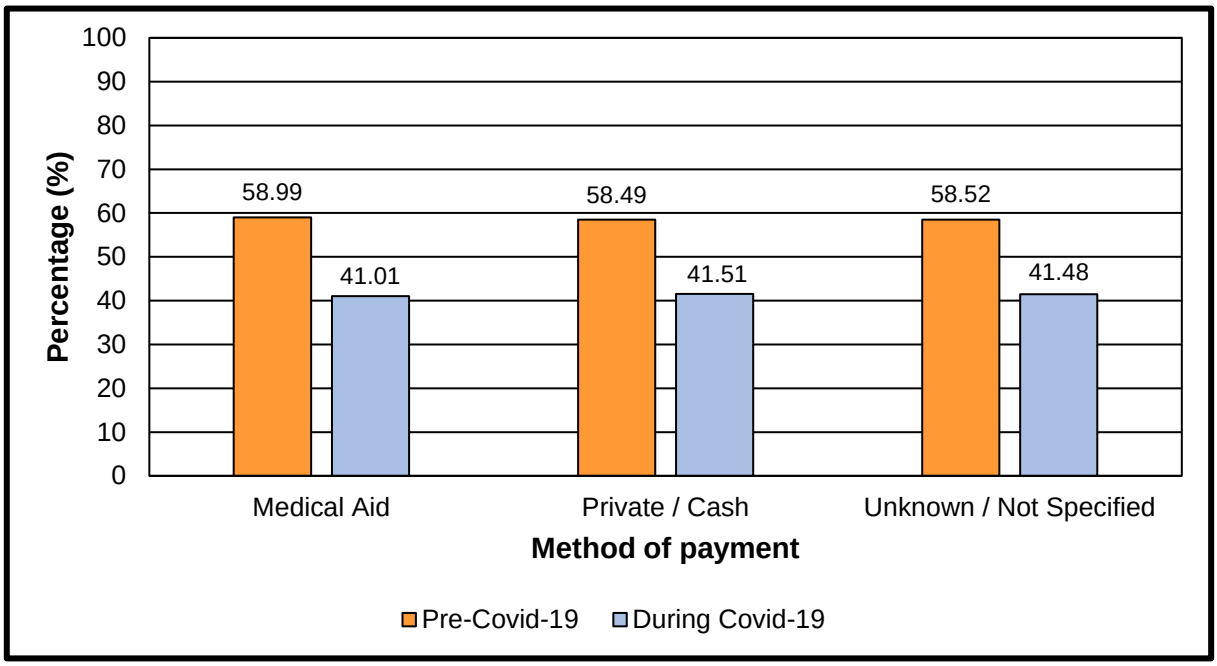
This suggests that various provinces may have exhibited different panic buying patterns, with individuals purchasing large quantities to shield themselves from potential virus exposure (Chua *et al.*, 2021). This reduced the frequency of shopping trips and the potential contact with viral environments, such as pharmacies (Chua *et al.*, 2021). These behaviours may have been human instincts that prompted panic buying as a means to alleviate anxiety and fear induced by the Covid-19 pandemic (Al Zoubi *et al.*, 2021).

The economic statuses of provinces, whether rural or urban, can affect the supply of medicines during periods like the pandemic. Consequently, provinces with varying economic conditions may receive limited medication supplies, considering the population's needs (Henricson *et al.*, 1999; Gisev *et al.*, 2016; Al Zoubi *et al.*, 2021).

Effect of Covid-19 on sales trends as per method of payment

Figure 4.8 shows the percentage distribution of the OTC CCM sales by method of payment before and during Covid-19. The sale patterns before and during Covid-19,

corresponded similarly across all methods of payment during the two periods. Each method of payment highlighted that all OTC CCM payments before Covid-19 were almost 20% greater than the purchases of the OTC CCM products within each method of payment recorded during the Covid-19 period. Appendix D provides a comprehensive list of all the medical scheme names classified under “Medical Aid”. Analysed by the method of payment, the percentage distributions of OTC CCM sales before Covid-19 and during Covid-19, were significantly different (p<0.001).



Note: Each individual method of payment represents 100% of its sales throughout the study’s time period.

Figure 4.8: The comparison of percentage distribution of OTC CCM sales by method of payment pre and during Covid-19.

Table 4.9 shows that purchasing products using private funds in the form of cash, method of payment, contributed the most to the average monthly sales of OTC CCMs both before and during the Covid-19 period. This indicates that individuals preferred to pay cash for their OTC CCM products. Contributing to this finding, an individual with medical aid, is advised not to claim OTC products through their medical aid, since this will decrease their medical aid savings account (Discovery, 2024). Another indicator is that individuals with medical aid who recognise the possibility of misusing opioid products, like OTC CCMs, might choose to conceal this behaviour from their medical aid (Foley et al., 2018). Consequently, these individuals may choose to pay in cash

for OTC CCMs to avoid having such transactions documented on their medical aid profile (Foley et al., 2018). Table 4.9 also indicates that all methods of payments per average monthly consumption decreased from before to during the Covid-19 period.

Table 4.9: Average monthly consumption of OTC CCMs purchased pre and during Covid-19, corresponding to Figure 4.8.

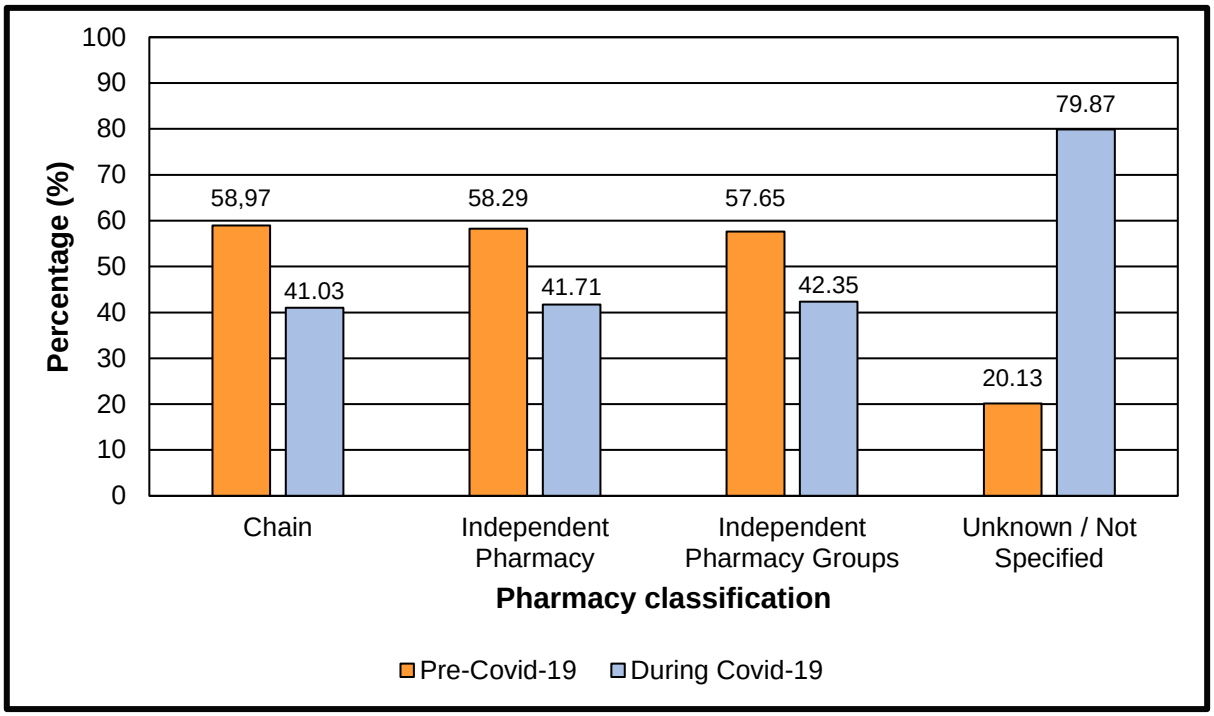
	Average monthly consumption		
Method of payment	**Pre-Covid-19**	**During Covid-19**	**Change (%)**
Medical Aid	308 140	299 908	↓ by 2.67
Private/Cash	675 329	671 104	↓ by 0.63
Unknown/Not Specified	464 071	460 554	↓ by 0.76

↑: increase; ↓: decrease

A Jordanian study reported that 81% of medicine purchasers during the Covid-19 period paid cash for their medicines even if they were members of a medical aid (Al Zoubi et al., 2021). This highlights that individuals were still willing to pay cash for such medicines, even during an economically challenging period, such as the pandemic. This translates into a coping mechanism during stressful periods, striving to still keep oneself and their family healthy and protected during the pandemic (Al Zoubi et al., 2021). This may be a possible factor that contributed to the findings in this South African study, stipulated in Figure 4.8 and Table 4.9.

Effect of Covid-19 on sales trends as per pharmacy classification

Figure 4.9 shows the percentage distribution of the OTC CCM sales by pharmacy classification before and during Covid-19. The sale patterns before and during Covid-19, corresponded similarly across all pharmacy classifications during the two periods. Each pharmacy classification highlighted that most of the pharmacy classifications selling OTC CCMs before Covid-19 were almost 18% greater than the purchases recorded during the Covid-19 period. Not necessarily useful to the results, but the unknown/not specified group greatly increased from before to during Covid-19, as is also evident in Table 4.10. Analysed by pharmacy classification, the percentage distributions of OTC CCM sales before Covid-19 and during Covid-19, were significantly different (p<0.001).



Note: Each individual pharmacy classification represents 100% of its sales throughout the study's time period.

Figure 4.9: The comparison of percentage distribution of OTC CCM sales by pharmacy classification pre and during Covid-19.

Table 4.10 indicates that the average monthly consumption of OTC CCMs in respect to pharmacy classification, mostly increased from before Covid-19 to during Covid-19, excluding chain pharmacies, which showed a slight decrease. However, chain pharmacies still represented the greatest monthly consumption of OTC CCM sales between both periods, followed by independent pharmacies.

Table 4.10: Average monthly consumption of OTC CCMs purchased pre and during Covid-19, corresponding to Figure 4.9.

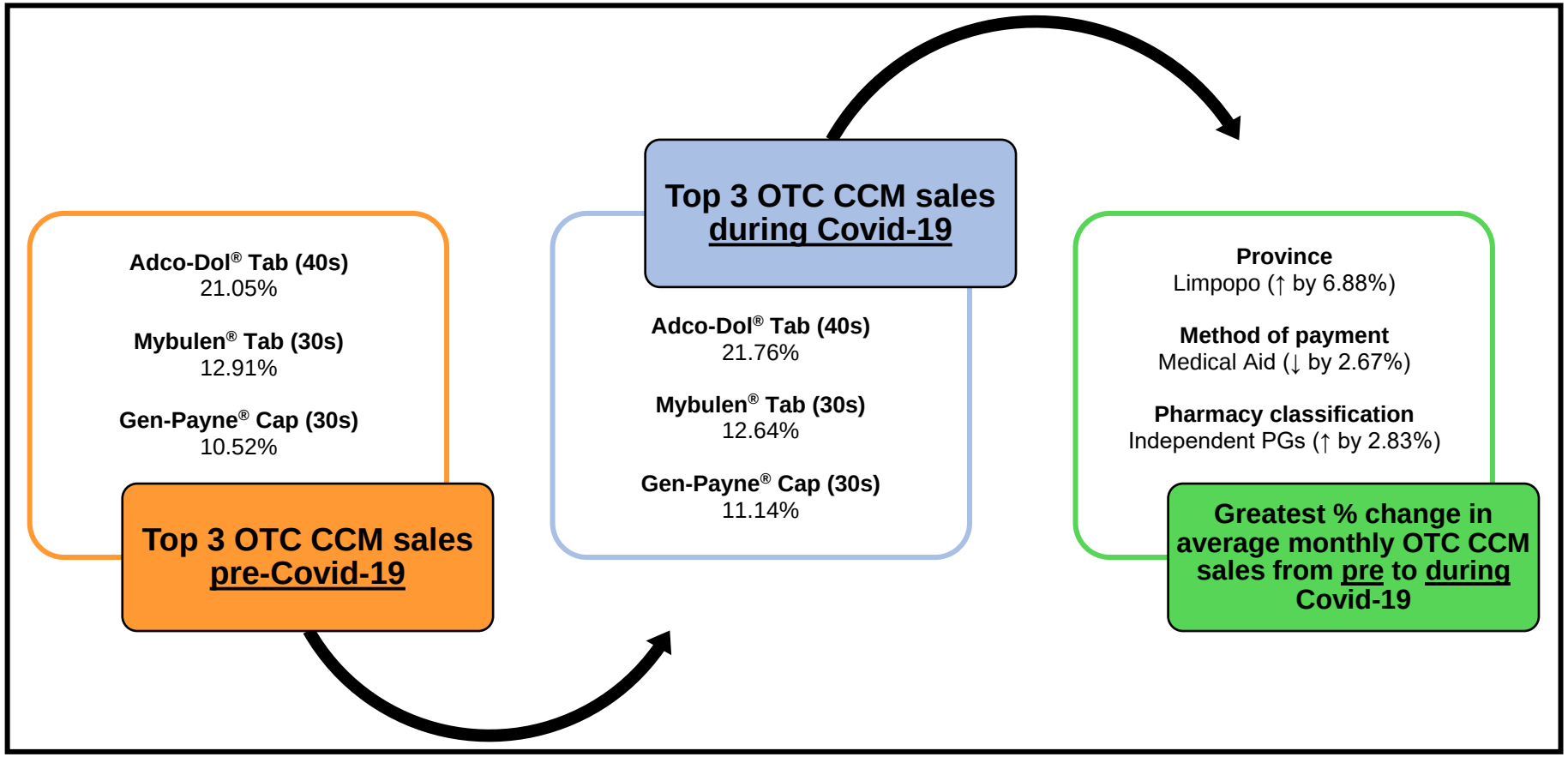
	Average monthly consumption		
Pharmacy classification	**Pre-Covid-19**	**During Covid-19**	**Change (%)**
Chain	865 434	842 977	↓ by 2.59
Independent Pharmacy	418 248	418 983	↑ by 0.18
Independent Pharmacy Groups	163 600	168 234	↑ by 2.83
Unknown/Not Specified	256	1 424	↑ by 456.25

↑: increase; ↓: decrease

As seen in Figure 4.9 and Table 4.10, the Covid-19 pandemic has revealed many instances where essential functions suggest that societies are hindered by excessive market concentration. This is intensified by the disappearance and avoidance of use of locally controlled businesses, such as independent pharmacies (Mitchell, 2021). Over the years, independent pharmacies have had to compete with larger chain pharmacy groups. Hence, efforts to maintain the business of an independent pharmacy, have had to these pharmacies having to lower their prices and create a more personal approach in the serving of customers (Mitchell, 2021). This has resulted in many customers preferring to purchase from an independent pharmacy, especially post the pandemic, since financially, inexpensive medicine prices are more appealing and shorter waiting times with a more personal pharmacist-patient relationship became more desirable. Many independent pharmacies also provide a free same-day delivery service, which many chain pharmacy groups do not offer, and thus, during a pandemic, this creates a convenient factor and the avoidance of entering a pharmacy and risking the possibility of contracting the Covid-19 virus in a pertinent healthcare facility (Mitchell, 2021).

Concluding **objective IIb**, Figure 4.10 depicts a graphical summary of the main descriptive findings found between the two periods of before Covid-19 to during Covid-19, with respect to the sale of OTC CCMs in SA, between 2019-2020.

In conclusion of **Chapter 4**, this chapter (**objectives IIa** and **IIb**), highlighted an overview of the descriptive trends of all OTC CCM sales found in all of SA, between 2019-2020. This chapter also highlighted any differences of OTC CCM sales before the Covid-19 pandemic, and during the first ten months of the pandemic. These summarised findings are graphically represented in Figure 4.6 and Figure 4.10. Some of the discussion points in this chapter, related to the factors explored in the overview of **Chapter 3** (**objective I**). The next chapter, **Chapter 5** (**objective III**), will inferentially report on the factors contributing to OTC CCM sales specifically found in the South African provinces of Gauteng, Mpumalanga and the North-West.



OTC = over-the-counter; CCM = codeine-containing medicine; PGs = Pharmacy Groups; Tab = tablets; Cap = capsules; % = percentage
↑ = increase; ↓ = decrease
Note: The percentages (%) represent the frequency of sales of the top findings within each variable.

Figure 4.10: Graphical summary of the main results found in objective IIb.

CHAPTER 5: RESULTS AND DISCUSSION OF OBJECTIVE III

5.1. Introduction

Chapter 5 reports and discusses the inferential findings of **objective III**. **Objective III** is as follows:

III. To determine the contributing factors associated with OTC CCM sales in the South African provinces of Gauteng, Mpumalanga and the North-West, identified as “codeine hotspots”.

The following variables were analysed in **objective III**.

- Annual sum amount of OTC CCM costs (in Rands)
- Annual time
- Bi-annual time
- Combinations (Medicine classification + method of payment)
- Dosage form
- Gauteng, Mpumalanga and North-West provinces
- Medicine classification
- Method of payment
- Pack size
- Single exit price (SEP)

In this study, ‘Dosage form’ refers to the class of dosage form, categorised as either an **oral solid** or an **oral liquid**. Table 5.1 presents the various dosage forms classed into each classification. Notably, oral solid dosage forms outnumber oral liquid products, as indicated in the IQVIA datasheet and as displayed in Table 5.2.

Table 5.1: Dosage form classifications.

Dosage form	
Oral solid	**Oral liquid**
Tablets	Syrups
Capsules	Suspensions
Effervescent tablets	

'Medicine classification' denotes whether a medicine was a **generic** or an **original** product as shown in Table 5.2. There is a larger proportion of generic medicines analysed, as compared to original OTC CCM products.

Table 5.2: Medicine classifications.

Medicine classification			
Original products	**Dosage form**	**Generic products**	**Dosage form**
Benylin & Codeine®	Syrups	Acurate®	Tablets
Ibucod®	Tablets	Adco-Dol®	Tablets
Mybulen®	Tablets	Adco-Napacod®	Tablets
Nurofen Plus®	Tablets	Betapyn®	Tablets
Sinutab Sinus Pain ES®	Tablets	Broncleer & Codeine®	Syrups
Syndol®	Tablets	Gen-Payne®	Capsules
		Lenadol®	Tablets
		Lenapain®	Tablets
		Mybulen®	Capsules
		Mybulen®	Suspensions
		Propain®	Tablets
		Pynstop®	Tablets
		Stilpane®	Syrups
		Tensodol®	Tablets
		Tensopyn®	Effervescent tablets
		Tensopyn®	Tablets
		Tensopyn®	Paediatric syrups

ES = extra strength

In reference to "bi-annual time", some of the data was analysed in bi-annual halves. This means that the '1st half of 2019' referred to the months January to June 2019, followed by the '2nd half of 2019' referring to the months of July to December 2019. The same motion applied for 2020.

Literature has shown that Gauteng, Mpumalanga and the North-West are three of the most prevalent "codeine hotspot" provinces within SA. In 2016, a South African Governmental Report highlighted that North-West (24.9%), Gauteng (23.1%) and Mpumalanga (12.2%) were the top three provinces to show evidence of percentage usage of CCMs within the past 12 months of the report (StatsSA, 2016). Six years

later, the same three provinces were highlighted in a geospatial study, indicating high codeine prevalence (p<0.005) in SA (Nyoni *et al.*, 2022). Despite their differing economic backgrounds, reviewing various variables within these provinces will provide valuable insights into the factors associated with OTC CCM sales.

Although Gauteng, Mpumalanga and the North-West all share the same title of being prevalent "codeine hotspot" provinces in SA (StatsSA, 2016; Nyoni *et al.*, 2022), there are numerous notable economic differences among the three provinces. Table 5.3 illustrates the estimated economic overview of each province. The information compiled in this table used averaged estimates between 2019 and 2020, covering this study period.

Table 5.3: Economic overview of the three provinces.

	Gauteng	**Mpumalanga**	**North-West**
Population	15 332 127	4 635 987	4 067 988
Approximate percentage of the South African population (%)	26	8	7
Area (km^2)	18 178	76 495	104 882
Province rank*	9th	8th	6th
Approximate density (per km^2)	843	61	39
Sparsely/Densely populated	Densely	Sparsely	Sparsely
Largely characterised by urban/rural areas	Urban	Rural	Rural
Key province sectors	Finance Manufacturing Trade	Coal mining Forestry Agriculture	Platinum mining Livestock farming Agriculture
National GDP contribution (%)	33.1	8	6.6
References	SAMI, 2020 Young, 2020 Nyoni *et al.*, 2022 StatsSA, 2022 StatsSA, 2023	SAMI, 2020 Nyoni *et al.*, 2022 StatsSA, 2022 StatsSA, 2023 MEGA, 2024	Harker *et al.*, 2020 SAMI, 2020 Nyoni *et al.*, 2022 StatsSA, 2022 StatsSA, 2023

***Province rank** refers to the land size rank amongst South African provinces; from largest to smallest
GDP = gross domestic product

As depicted in Table 5.3, urban Gauteng is largely densely populated home to a quarter of the country's total population, yet it has the smallest area coverage in SA. It is also the "economic hub" of the country (Young, 2020). In comparison, both Mpumalanga and North-West provinces are sparsely populated, characterised mainly

by rural settings and are considerably larger (in km^2) than Gauteng. These non-urban provinces have a lower proportion of the country's population residing within their borders. Nevertheless, all three provinces share the same characteristic of being "codeine-prevalent" provinces (StatsSA, 2016; Harker *et al.*, 2020; Nyoni *et al.*, 2022). A South African Report highlighted that CCM usage was greatest in urban areas at 16.6%, followed by non-urban areas, at 9.2% respectively (StatsSA, 2016).

5.2. Annual sum amount (in Rands)

Figure 5.1 displays the total cost (in Rands) of OTC CCM expenditure over two years across the three provinces. Gauteng had the most expenditure both in 2019 and 2020 while North-West province had the least costs in both years. In the three provinces, the total medication cost increased in 2020.

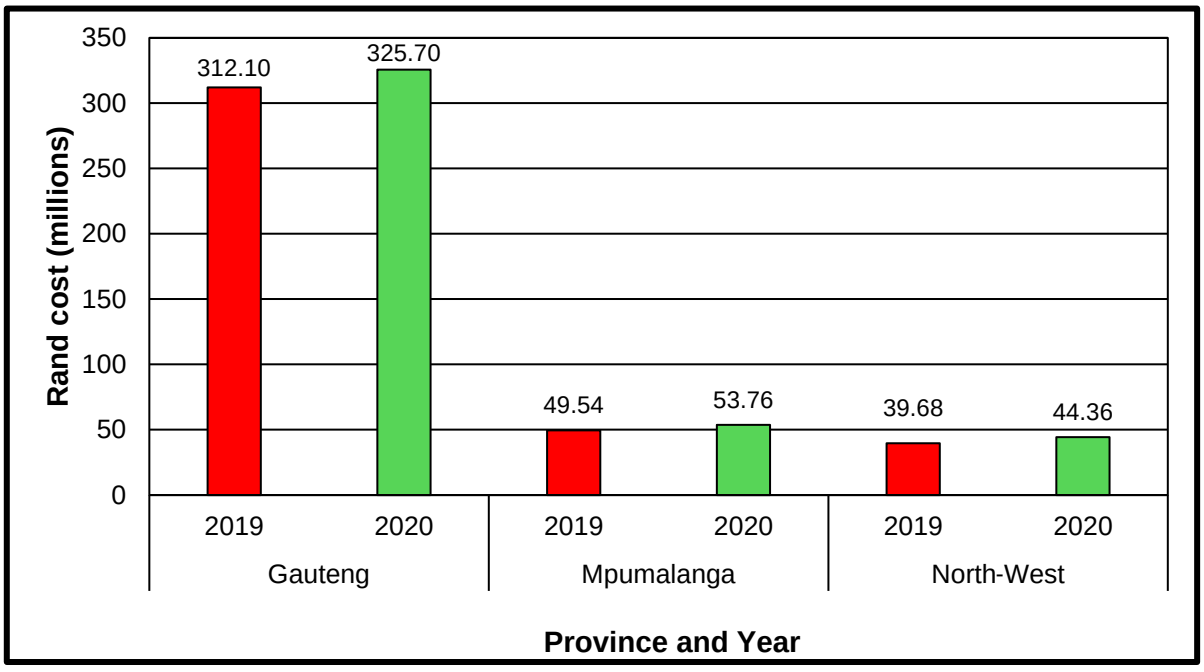


Figure 5.1: Annual sum amount (in Rands) of OTC CCM expenditure.

Table 5.4 provides an estimated mean expenditure of the money spent on OTC CCMs throughout the study's period. This table provides an inclination as to how much each person in each respective province annually spent on OTC CCMs in the stipulated years.

Table 5.4: Annual mean OTC CCM expenditure incurred per person per province.

	Province		
Year	**Gauteng**	**Mpumalanga**	**North-West**
2019	R 20.36	R 10.69	R 9.75
2020	R 21.24	R 11.60	R 10.90

In 2019, SA medicine price increases were capped at 3.78% (StaffWriter, 2019). In 2020, there was a general medicine price increase of 4.53% (StaffWriter, 2019). Annually, inflation rates also affect the pharmaceutical industry (Movahed *et al.*, 2021). As seen in Figure 5.1, 2020 displayed an increase in patient expenditure on OTC CCMs in all three provinces. Corresponding to these results, in Table 5.4, it is evident that annually, the South African population spends more money each year, per person, on OTC CCMs. This could relate to the effect of inflation and annual increases in costs. Considering this, a study conducted by Richards *et al.* (2021) in 31 countries showed that the public spent an estimated R 60.3 billion on OTC CCMs over six years (Richards *et al.*, 2021). Of this expenditure, SA exhibited the second largest mean expenditure of OTC CCMs at approximately R 30.00 per person (Richards *et al.*, 2021). In agreement with this, it is seen that through Table 5.4 and Richards *et al.*'s (2021) study, from 2019 to 2021, OTC CCM prices annually increased and each year residents had to increase expenditure on respective OTC CCMs. In 2015, SA reported that R 10.2 billion (which is 26% of all South African medicines) was spent on OTC products alone, of which OTC CCM products are included (Kohli and Buller, 2013; Padayachee *et al.*, 2019). From this finding, it is evident that these three provinces cumulatively spent over R 400 million on OTC CCM products in 2019, whilst in 2020, these same provinces and products spent just under R 425 million on the same products.

As reported by the South African Government, for the 2019/2020 fiscal year, R 206.6 billion was spent on healthcare, in SA (StatsSA, 2021). Gauteng spent more funds on healthcare services than Mpumalanga and the North-West, which both spent more funds on education rather than healthcare services. No South African literature is available to report on the precise amounts spent on OTC CCMs alone in the years 2019 and 2020, however, it was reported that Gauteng spent R 49.9 billion on healthcare for the 2019/2020 fiscal year (StatsSA, 2021). Instead, Mpumalanga and the North-West, respectively spent R 13.9 billion and R 12.1 billion on healthcare

during the same period (StatsSA, 2021). Figure 5.1 reflects these findings as well, in that Gauteng, the economic powerhouse of SA (Young, 2020), shows the most funds spent on OTC CCMs during the period, followed by Mpumalanga and then the North-West respectively.

5.3. Differences in sales between provinces

Table 5.5 summarises the sales per province and depicts any differences thereof. It is important to also consider the economic overviews of each province (from Table 5.3) when analysing the results of Table 5.5.

Table 5.5: Differences in sales between provinces.

Variable and categories	Province			Total (%)	*p*-value
	Gauteng (%)	Mpumalanga (%)	North-West (%)		
Dosage form					<0.001
Oral liquid	15.29	9.35	7.94	13.75	
Oral solid	**84.71**	**90.65**	**92.06**	**86.25**	
Method of payment					<0.001
Medical Aid	17.43	22.43	20.71	18.42	
Private/Cash	**46.16**	**44.80**	35.11	**44.81**	
Unknown/Not Specified	36.41	32.77	**44.18**	36.77	
Medicine classification					<0.001
Generic	**74.54**	**79.05**	**75.70**	**75.24**	
Original	25.46	20.95	24.30	24.76	
Bi-annual time					<0.001
1st half 2019	**25.34**	**25.03**	**23.91**	**25.15**	
2nd half 2019	25.14	24.57	24.32	24.98	
1st half 2020	24.64	25.49	25.78	24.87	
2nd half 2020	**24.89**	**24.91**	**26.00**	**25.01**	
Annual time					<0.001
2019	**50.48**	49.61	48.22	**50.13**	
2020	49.52	**50.39**	**51.78**	49.87	
Combinations (Medicine classification + Method of payment)					<0.001
Generic + Medical Aid	11.08	15.10	12.62	11.75	
Generic + Private/Cash	**36.00**	**37.44**	27.39	**35.27**	
Generic + Unknown/Not Specified	27.46	26.51	**35.68**	28.21	
Original + Medical Aid	6.36	7.33	8.09	6.67	
Original + Private/Cash	**10.15**	**7.37**	7.72	**9.54**	
Original + Unknown/Not Specified	8.95	6.25	**8.49**	8.56	

Bold and highlighted values represent noteworthy data, which are further discussed in the text.

The oral solid dosage form of sales was significantly higher across the provinces. The North-West had the highest oral solid dosage form of sales at 92.06%. This finding

can be supported by the fact that in the South African codeine pharmaceutical market, oral solid dosage forms dominate the oral liquid forms. While oral liquids primarily serve specific groups such as paediatrics and patients unable to swallow pills, their demand is smaller than the oral solid products (Glass and Haywood, 2006).

The private/cash scheme sales were significantly higher across these three provinces. However, the North-West had the highest unknown scheme medication sales at 44.18%. In total, the prevalence of the “Unknown/Not Specified” ‘Method of payment’ was 36.77% which was moderately high, and this limits the method of payment inferences since one cannot assume whether the “Unknown/Not Specified” category is private/cash or medical aid.

Generic medication sales were significantly higher across provinces, with Mpumalanga having the highest sales at 79.05%. The Food and Drug Administration (FDA), describes a ‘generic’ drug as “a medication created to be the same as an already marketed brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use” (FDA, 2021). Minor acceptable differences may occur between a ‘generic’ and ‘original (brand-name)’ medicine such as the difference in inactive ingredients that will not affect the therapeutic use of the product (FDA, 2021). When an ‘original’ (innovator drug) medicine is produced, the development and manufacturing process is lengthy and complex, affording it the ability to be developed with a protected patent, safeguarding the investment of this development (Haque, 2017).

In SA, the official guideline of ‘Parallel Importation of Medicines’ is advised to be applied when the development of an original medicine is proposed. This guideline is implemented with the specific aim of ensuring universal access to affordable healthcare and equitable availability of medicinal products for all individuals in the population (Du Plessis, 1999; Efuetlateh and Mullis, 2013). The South African Medicines and Related Substances Control Amendment Act 90 of 1997 (MRSCA) provides provision for this approach, indicating that Parallel Importation provides a more cost-effective alternative to the original medicine, often more expensive when registered and available in SA (MRSCA, 1997; MCC, 2003). This concept is unique to SA, as many other countries lack an inexpensive alternative when an original medicine

enters the pharmaceutical market and thus, equity and fair access are not always guaranteed in these instances (Du Plessis, 1999; Efuetlateh and Mullis, 2013). Once the patent has expired, other pharmaceutical companies can produce generic products that are bioequivalent to the innovator drug (Haque, 2017).

Overall, there was a significant change in medication sales over time. Gauteng and Mpumalanga provinces decreased in sales, between the 1st half of 2019 and the 2nd half of 2020 while the North-West increased sales in the same period (p<0.001). Generic and private/cash sales were most common in Gauteng and Mpumalanga while North-West province had the most generic sales purchased through an unknown/not specified scheme type. However, amongst all three provinces, in total at 35.27%, generic medicines purchased through private funds in the form of cash were significantly highest throughout the period (p<0.001).

Alluding to Figure 5.2 and Appendix L, statistically significant association results were shown for all variables (p<0.001). Greater sales were present with generic rather than original products, possibly contributing to the fact that there were more generic medicines analysed in this study, as compared to limited original medicines. In all the time periods of the figure, except for the 1st half of 2019, Mpumalanga first, followed by Gauteng and lastly the North-West, displayed the highest sales respectively when OTC CCMs were purchased using private funds in the form of cash and with a generic option. However, sales were higher in the second half compared to the first half of each year. North-West province displayed greater results when associated with the unknown/not specified method of payment. Following this category, private/cash generic sales were the second greatest in the North-West, imitating the trends seen in Gauteng and Mpumalanga.

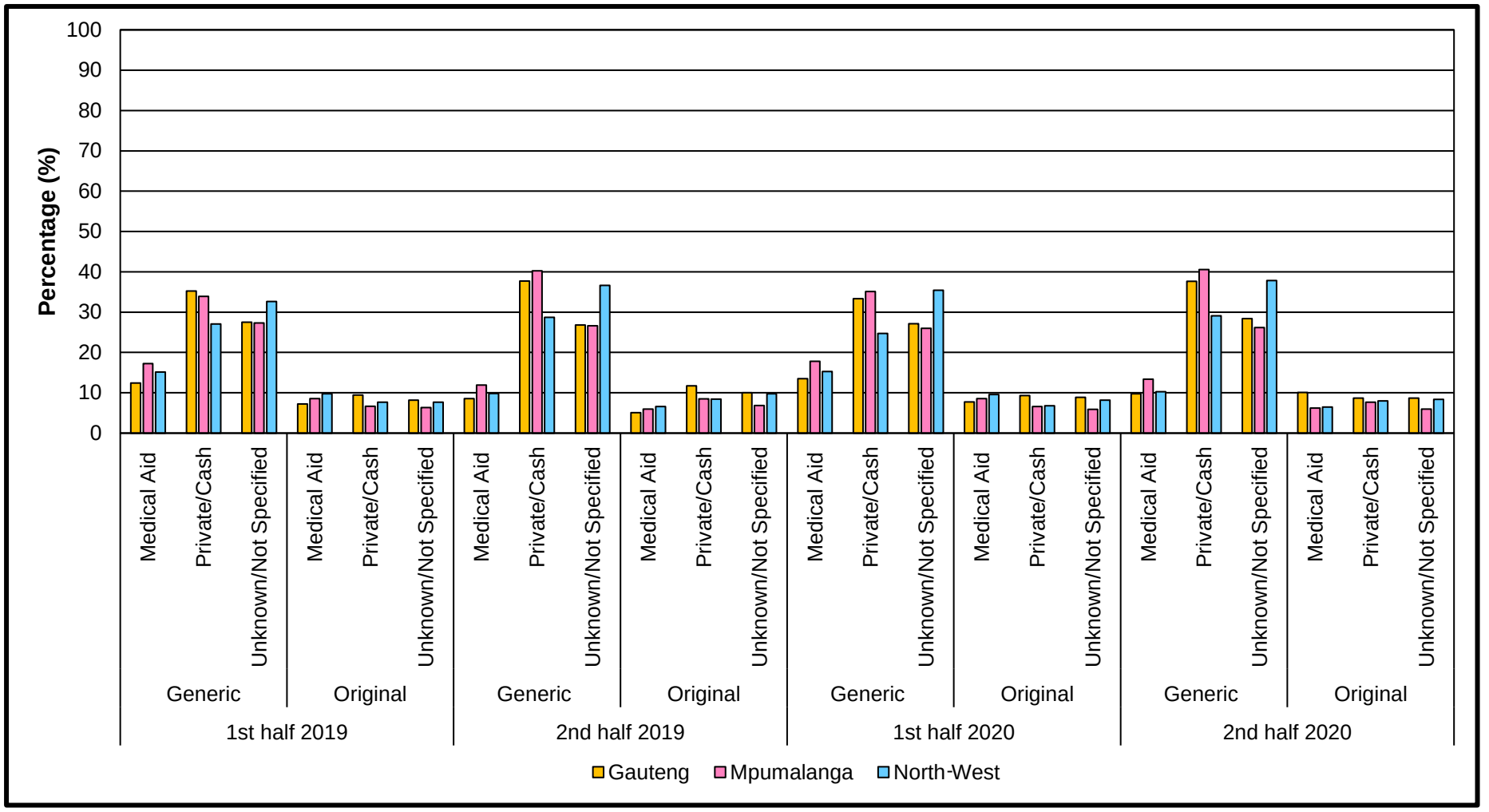
The differences highlighted in Figure 5.2 can be attributed to the availability of inexpensive generic medicine alternatives, costing significantly less than the original medicine option. In the early 2000s, the increase of SEP medicine prices emerged as a significant social concern, primarily driven by inflationary trends over the years (Patel *et al.*, 2012). Consequently, this led to a surge in the generic medicine market, facilitating a broader array of products and pricing options (Patel *et al.*, 2012). Despite the price being the foremost influential factor for consumer choice, literature has

shown that brand-name drugs persist as pharmaceutical market leaders, despite the results evident in this study (Haque, 2017; Håkonsen *et al.*, 2020).

Although many claim that they understand that original and generic drugs offer the same efficacy, there is still a hesitancy to make use of generic drugs as the public believes that generic medicines are inferior in quality to original medicines (Patel *et al.*, 2012). This is untrue (FDA, 2021). This was evident in a study that reported that only 37.6% of participants would purchase a generic product over an original product (Kohli and Buller, 2013). However, as seen in Figure 5.2, generics were strongly chosen over an original product, although, the limitation of more generic products than original products analysed in this study is notable.

A contributor to the decision to choose a generic medicine may be due to the reliance on advice from one's HCP, the highly-esteemed reputation of the company that manufactured the generic, and the lower cost of the OTC product ($p<0.05$) (Patel *et al.*, 2012; Kohli and Buller, 2013). Lower medicine costs are associated with higher number of sales. Choosing to purchase an inexpensive, generic option saves money and the purpose of a generic medicine serves the same therapeutic use as the original product (Nicolosi and Gray, 2009). This enhances fair access and equity for all populations to be able to practice their right of fair access to healthcare (Coovadia *et al.*, 2009).

This chapter's results, **Chapter 5** (as of those in **Chapter 4**), showed that OTC CCM sales were greater during the second half of each year, coinciding with habitual buying in preparation for the South African winter months (Magruder, 2003). Partly, within this '2nd half of [year]', approximately May to August represents part of the South African winter season. During this time, the colder weather increases the risk of cold and flu infections, prompting many members of the public to resort to self-medication with OTC products (or increased doctor visits), including the OTC CCMs analysed in this study (Liu *et al.*, 2013; Insight Survey, 2017). Sales were highest in the second half of both years, but medical aid sales in the first half of each year surpassed those in the second half across all provinces. This drop in medical aid sales from first to second halves of the first year may be attributed to depleted medical aid funds from July to December of each year (Padayachee *et al.*, 2023).



Note: Each individual time period represents 100% of sales for each respective province.

Figure 5.2: Bar graph depicting province, medicine classification and method of payment associations.

As highlighted in Figure 5.2 and Table 5.5, private/cash payment was the preferred method of payment for the OTC CCM purchases. Being a private sector healthcare study, the focus is often motioned towards medical aid methods of payments. However, as seen in the results of this objective (and consistent with those of **objective II**), private/cash payment is unanimously favoured in purchasing these products.

5.4. Linear regressions

Table 5.6 illustrates results produced from univariate linear regressions and a multiple linear regression analysis using data from Gauteng, Mpumalanga and the North-West.

The same categorical and numerical variables were analysed in both regressions, represented side-by-side in Table 5.6. The variables and their respective categories were found to be associated factors that contributed to the sale of OTC CCM products.

5.4.1. Province association and OTC CCM sales

Although all three provinces have been classified as “codeine hotspots”, compared to the Gauteng province, average medication sales significantly decreased in Mpumalanga (adjusted β=-74 sales) and the North-West (adjusted β=-78 sales), respectively. This association was significantly evident in both regression analyses (p<0.001). Although Gauteng is the smallest South African province, most of the population resides in this single province contributing to SA’s GDP, which explains the significantly increased sales of OTC CCMs observed in Gauteng compared to other provinces (Table 5.3, Table 5.5 and Table 5.6). Although the North-West may have a greater land surface area compared to the other provinces, the usage of codeine is sparser and less than in Mpumalanga and Gauteng (Table 5.6) (Nyoni *et al.*, 2022). However, in 2016, North-West was the province that contained the greatest percentage of CCM usage among all South African provinces where codeine prevalence was moderately high (StatsSA, 2016).

Table 5.6: Contributing factors associated with OTC CCM sales.

Variables	Categories	Univariate linear regression			Multiple linear regression		
		β	95% CI	*p*-value	Adjusted β	95% CI	*p*-value
Province	Gauteng	0			**0**		
	Mpumalanga	-223	-248 to -198	<0.001	**-74**	**-89 to -58**	**<0.001**
	North-West	-231	-257 to -205	<0.001	**-78**	**-94 to -62**	**<0.001**
Dosage form	Oral liquid	0			**0**		
	Oral solid	38	9 to 66	0.01	**-56**	**-74 to -39**	**<0.001**
Method of payment	Medical Aid	0			**0**		
	Private/cash	2 621	2 564 to 2 679	<0.001	**269**	**230 to 307**	**<0.001**
	Unknown/Not Specified	1 223	1 178 to 1 267	<0.001	489	460 to 517	<0.001
Medicine classification	Generic	0			**0**		
	Original	-26	-50 to -3	0.029	**-64**	**-79 to -50**	**<0.001**
Bi-annual time	1st half 2019	0			0		
	2nd half 2019	22	-7 to 52	0.142	-2	-20 to 16	0.837
	1st half 2020	7	-22 to 36	0.637	3	-15 to 21	0.731
	2nd half 2020	30	-3 to 57	0.078	4	-14 to 22	0.655
Pack size	-	-0.080	-0.110 to -0.040	<0.001	**-0.38**	**-0.40 to -0.35**	**<0.001**
SEP	-	0.014	0.010 to 0.014	<0.001	**0.014**	**0.014 to 0.014**	**<0.001**
Annual time	2019	0					
	2020	6	-15 to 27	0.577			
Combinations (Medicine classification + Method of payment)	Generic + Medical Aid	0					
	Generic + Private/Cash	**2 807**	**2 741 to 2 875**	**<0.001**			
	Generic + Unknown/Not Specified	1 280	1 228 to 1 332	<0.001			
	Original + Medical Aid	16	-8 to 40	0.183			
	Original + Private/Cash	2 116	2 005 to 2 228	<0.001			
	Original + Unknown/Not Specified	1 080	995 to 1 165	<0.001			

β = coefficient; 95% CI = 95% confidence interval; SEP = Single exit price

Note: Univariate linear regression analysed variables individually, reporting on the individual effects of each variable and their significance. The multiple linear regression analysis adjusted for other variables, reporting on the significance of their effects.

Bold and highlighted values represent noteworthy data, which are further discussed in the text.

In Gauteng, more than a third of all South African retail pharmacies exist, whilst Mpumalanga and North-West only house approximately 7.5% and 7% of all retail pharmacies respectively (SAPC, 2024). This suggests that access to pharmacies to purchase OTC CCMs is far greater in Gauteng than in Mpumalanga and the North-West.

However, rural locations, like Mpumalanga and the North-West, contain fewer primary healthcare institutions for public use, and therefore, many rural pharmacies are often concerned about making a product sale rather than expressing concern for rational CCM sales (Henricson *et al.*, 1999; Gisev *et al.*, 2016; Parry *et al.*, 2017).

Poorer access to healthcare services, in non-urban and rural areas, suggests a relationship of higher CCM use in these areas, regardless of the limited healthcare services in that location (Gisev *et al.*, 2016). Being largely characterised by rural settings, Mpumalanga and the North-West have fewer opioid treatment centres compared to Gauteng (Harker *et al.*, 2020). Considering this, it may suggest that codeine misusers are cognisant of the greater availability of healthcare services within Gauteng. This may potentially lead misusers to anticipate easier access to treatment centres in the event of possible addiction or overdose, thereby facilitating the decision to increasingly purchase OTC CCMs (Harker *et al.*, 2020). In a South African study, treatment centre admissions for codeine misuse/dependence were highest in Gauteng (29%), followed by the North-West, Northern Cape and Free State (cumulatively 12.9%), with Mpumalanga and Limpopo cumulatively recording the lowest admissions at 5.1% (Dada *et al.*, 2015).

Gauteng is the wealthiest South African province, with a low headcount of adult poverty of 29.3% (StatsSA, 2019). Mpumalanga and the North-West are within the top five provinces having the highest headcount of adult poverty at 54.6% and 59.6% respectively (StatsSA, 2019). Thus, the low socioeconomic statuses contribute to the social deprivation found in Mpumalanga and the North-West, considering the largely rural and sparsely populated factors of each province, ultimately reflecting in their lower respective GDP contributions (Table 5.3).

An English study aimed to demonstrate an association between increased opioid prescribing and an area with low socioeconomic status (Mordecai *et al.*, 2018). The study reported that residents living in areas with a low socioeconomic status were found to have an increased percentage of chronic pain compared to urban areas and thus, the need for the usage of opioids, like codeine, was highly prevalent (Mordecai *et al.*, 2018). Although access and availability to OTC CCMs in rural areas are limited and funds are restricted, this does not prevent rural populations from seeking alternative routes of obtaining OTC CCMs with easier access and wider availability of CCMs in urban pharmacies exhibiting higher rates of CCM abuse, particularly in urban settings (Gisev *et al.*, 2016). Various literature has proven that there is a high rate of rural inhabitants seeking alternative routes to obtain CCMs, by doing whatever inhabitants can, to alleviate pain using OTC CCMs (Gisev *et al.*, 2016; Nyoni *et al.*, 2022). Misuse of CCM habits may 'follow' individuals to their preferred location. Since the North-West and Mpumalanga both neighbour Gauteng, this geographical proximity may benefit these rural residents to work and possibly purchase OTC CCMs in urban Gauteng, contributing to increased OTC CCM sales in Gauteng, yet high prevalence and usage of codeine still exists in provinces like Mpumalanga and the North-West (Nyoni *et al.*, 2022). Therefore, the province regression results mirror literature and other studies, such that urban Gauteng has an association with high sales of OTC CCMs, but non-urban provinces with similar socioeconomic statuses, such as Mpumalanga and the North-West also have an association with increased OTC CCM sales.

Various medicine shortages have prevailed over the years within these non-urban provinces (Zuma, 2022). Contributory factors to these shortages result from poor communication between medicine depots and the province, pharmacies not ordering adequate stock and budgetary issues (Molelekwa, 2021; Zuma, 2022). With large medicine shortages reported in rural South African provinces like the North-West and Mpumalanga, the high prevalence of codeine is surprising (Zuma, 2022). Gauteng, Mpumalanga and the North-West, despite economic differences, share high codeine prevalent rates (StatsSA, 2016; Nyoni *et al.*, 2022). With all three provinces situated in the northern part of SA, with only the North-West bordering a neighbouring country, viz. Botswana, multiple factors have contributed to their "codeine hotspot" status

(Nyoni *et al.*, 2022). While some variables may vary, all three provinces remain highly codeine prevalent provinces.

5.4.2. Dosage form association and OTC CCM sales

Oral solid dosage form products significantly increased average sales by β=38 sales compared to oral liquid sales in univariate analysis (p=0.01). In multiple regression analysis, oral solid dosage form products significantly decreased average sales by adjusted β=-56 sales, compared to oral liquid sales (95% CI [-74 to -39]; p<0.001). Hence, oral liquid dosage forms were most strongly associated with the increased sales of OTC CCMs.

Most oral solid dosage forms are inexpensive, durable and long-lasting but are often found to be less palatable (Vandergriendt, 2019). In comparison, oral liquid dosage form products require stricter storage and packaging measures and are less durable but are often more palatable (Vandergriendt, 2019). While literature shows that oral solid dosage forms are more frequently used than oral liquid dosage forms, the preference for oral solid dosage forms remains predominant due to factors such as convenience, stability and ease of administration (Dada *et al.*, 2015; Richards *et al.*, 2021). Although there are significantly fewer oral liquid products on the South African pharmaceutical market, these formulations are far fewer due to market size limitations and the numerous expensive physiochemical factors that need to be considered during formulation (Glass and Haywood, 2006; Orubu and Tuleu, 2017). However, there is a growing trend, particularly in SA, in the manufacturing and sale of codeine cough syrups (Hart *et al.*, 2014).

Many parameters need to be considered in the design of an oral liquid product, rendering the process complex. Common parameters include physical and microbial stability, palatability, excipient suitability and packaging considerations (Haywood and Glass, 2013; Orubu and Tuleu, 2017). Moreover, driven by convenience and ingredient availability, it has become customary practice to prepare oral liquids from commercially available solid dosage forms, like tablets (e.g. Stilpane® tablets manufactured into Stilpane® syrup) (Haywood and Glass, 2013). Therefore, the manufacture of oral liquid products like syrups and suspensions, is more expensive

than the manufacture of oral solid dosage forms such as tablets and capsules (Lajoinie *et al.*, 2014). Notably, it is ironic that CCM cough syrups are affordable to purchase in pharmacies, according to the public and are known for their ease of accessibility (Essack *et al*., 2020).

Codeine cough syrups are increasingly being purchased by the wrong target group, adolescents (Hart *et al.*, 2014). A South African study aimed to describe factors influencing adolescent use of OTC codeine cough syrups in two rural townships of Mpumalanga and the Free State (Essack *et al*., 2020). The four main factors that resonated with increased adolescent CCM usage were accessibility, affordability, social influences and clandestine usage of codeine syrups (Essack *et al*., 2020). No prescription in SA is required to purchase CCM cough syrups and most bottles range between R 20.00-R 80.00 in price, making codeine syrups an affordable recreational drug in poor communities like Mpumalanga (Carte Blanche, 2018; Essack *et al*., 2020). Codeine liquid forms are preferred by adolescents to “get high and drunk” as they can mix these syrups with alcohol, juice and cold drinks claiming that these syrups “‘have similar intoxicating effects as alcohol’” (Agnich *et al.*, 2013; Hart *et al.*, 2014; Essack *et al*., 2020). These results are supported by the discussions of **objective I**’s ‘Experimentation’ in section 3.2.2.4.1. of **Chapter 3** and in Figure 4.4 of **objective II**’s (**Chapter 4**) findings.

The majority of citizens in an urban province, like Gauteng, would most likely have wide access to various oral liquid OTC codeine products and so these dosage forms are also favoured in urban communities. In developing countries, such as SA, substantial prevalence rates of self-medication of OTC CCMs are observed, particularly in rural communities (Henricson *et al.*, 1999; Gisev *et al.*, 2016). Poorer provinces like Mpumalanga and the North-West are common types of communities that exhibit a lower monthly household income so purchasing inexpensive medicines like OTC CCM oral liquid products to self-medicate is often a more feasible option for residents in these regions (Gisev *et al.*, 2016; Essack *et al*., 2020). This may be a probable contributing factor within these provinces, that witness high misuse and abuse of opioids like codeine (Nyoni *et al.*, 2022). Therefore, a strong association is present in the sale of OTC CCMs when oral liquid dosage forms like codeine cough syrups are purchased.

5.4.3. Method of payment association and OTC CCM sales

Univariate regression analysis shows that compared to medical aids, there was a significant association with increased sales when purchasing products using private funds in the form of cash, followed by unknown/not specified schemes respectively (p<0.001). Similarly evident in multiple regression analysis, compared to medical aids, unknown/not specified schemes significantly increased sales, followed by private/cash method of payment (adjusted β=269; 95% CI [230 to 307]; p<0.001). Whilst these associations are present, the unknown/not specified category does limit the method of payment variable of the data and thus, private/cash payment is strongly associated with increased OTC CCM sales.

Although this is a South African private healthcare sector study, just under a fifth of the South African population are medical aid members (Padayachee *et al.*, 2020). As seen in Table 5.3, an exceedingly small portion of SA's population resides in the North-West and Mpumalanga. Due to the low population percentages in the North-West and Mpumalanga, these provinces have negligible impact on the overall low percentage of medical aid members in SA (Coovadia *et al.*, 2009). This implies that many residents in these areas may lack access to medical aid (Statista, 2023). Consequently, when buying OTC CCMs, a substantial portion of these purchases is made with cash due to the absence of medical aid coverage (Coovadia *et al.*, 2009).

Similarly present in Table 5.5 and Figure 5.2, several reasons may exist for purchasing OTC CCM sales using cash. Purchasing OTC CCMs through a medical aid scheme does lengthen the member's self-payment gap as savings would be depleted quicker, and so, with this knowledge, consumers would opt to pay for OTC CCMs using cash (Nicolosi and Gray, 2009; Discovery, 2024). The addictive properties that codeine possesses may be of concern to some consumers, yet others may be fully aware of these properties and continue misusing them (Van Hout, 2014b). This results in misusers consuming these products "in private", so to keep their usage "a secret" (Van Hout *et al.*, 2017, 2018). Alluding to this behaviour, when purchasing the codeine products, misusers may specifically request to pay cash for these products, and not submit them through their medical aid, as this will create a record of their purchase, therefore, avoiding detection or scrutiny for their misuse of codeine products. Not

relying on this notion, other research may contradict it. For instance, in SA, Padayachee *et al.* (2019), found that 43% of codeine abusers bought CCMs through their medical aid (Padayachee *et al.*, 2019).

5.4.4. Medicine classification association and OTC CCM sales

Univariate (95% CI [-50 to -3]; p=0.029) and multiple regression (95% CI [-79 to -50]; p<0.001) analyses have reported that original medication significantly decreased average OTC CCM sales compared to the purchase of a generic OTC CCM option. There is, therefore, a significant association present between the increase of OTC CCM sales and purchasing a generic product of its kind.

By law, in SA, a pharmacist has to offer a patient the generic option when original products are initially prescribed or requested. A South African study reported that of all the generic products analysed in its study, 67.5% of the generic medicines were more than 40% cheaper, per DDD per month, than their original product, highlighting that the generic market is saving the South African pharmaceutical industry millions of Rands every year (Nicolosi and Gray, 2009). Although this present study reports that generic products were favourably dispensed in pharmacies, another South African study reported that pharmacists tend to favour dispensing original OTC products in PIT compared to when physicians prescribe OTC generic medicines (Padayachee *et al.*, 2020). Pharmacies operate as profit-driven businesses and so some of their tactics may involve capitalising on opportunities to optimise financial gains (Padayachee *et al.*, 2020).

Since companies that produce generic products do not incur the extensive research, testing and marketing costs to produce the innovator drug, generic products are at least 80-85% cheaper (Haque, 2017; FDA, 2021). Multiple companies can produce various generic drugs and hence, market competition exists, resulting in the typical competition for the lowest-costing generic option, affording the public various options of generic products (FDA, 2021). Between 2009 and 2019, the generic medicine market saved the American healthcare system nearly $ 2.2 trillion (FDA, 2021), and in turn, allowed communities better healthcare access for all, allowing consumers to have a wider range of products to choose from (Haque, 2017). While concerns still exist

regarding the therapeutic efficacy of generic drugs compared to their branded equivalents, consumers are slowly increasingly recognising the cost-effectiveness of generics, which can lead to significant monthly savings (Kohli and Buller, 2013; Haque, 2017).

As depicted in Table 5.3 and Table 5.6, wealthier provinces like Gauteng greatly contribute to SA's GDP, primarily through the manufacturing sector, making it a crucial market for pharmaceutical companies (Young, 2020). Consequently, pharmacies in Gauteng are likely to stock and offer a wider range of both original and generic medicines, ensuring broader accessibility and choice for the population (Henricson *et al.*, 1999; Zuma, 2022).

In contrast, rural provinces with limited funds prioritise essential medicines like paracetamol and ibuprofen over costlier options like CCMs (Molelekwa, 2021; Zuma, 2022; Yenet *et al.,* 2023). Provinces like Mpumalanga and the North-West, which face frequent medicine shortages, provide a limited selection of both generic and original products (Gisev *et al.*, 2016; Molelekwa, 2021). Among the available products, generics, being more cost-effective, are prioritised due to economic constraints, resulting in a reduced range of medicines such as OTC CCMs in pharmacies and thus, limited choice for residents (Nicolosi and Gray, 2009; Zuma, 2022).

Unlike Gauteng being an economically stable region, Mpumalanga and the North-West tend to offer fewer and inexpensive generic options due to limited resources, thus providing minimal choice to consumers (Harker *et al.*, 2020; Nyoni *et al.*, 2022). Despite the limited availability of generic options for OTC CCMs in these provinces, the high usage and potential misuse of codeine remain prevalent (Harker *et al.*, 2020; Nyoni *et al.*, 2022). Medicine shortages and the scarcity of specialist substance abuse treatment centres exacerbate the issue of codeine misuse, even though fewer OTC CCM products are available in these provinces (Harker *et al.*, 2020). This correlates with the findings shown in Table 5.5, which indicates a preference for generic options in non-urban provinces.

The availability of multiple generic versions for a single original product inherently leads to a higher ratio of generics to original OTC CCMs on pharmacy shelves (Haque,

2017). Consequently, this increased presence of generic alternatives enhances the probability of consumers opting for a generic over the original OTC CCM, thereby increasing generic OTC CCM sales. In agreement with this present South African study, a Finnish study reported that a lower cost of an OTC generic had an influential impact on purchasing that product (Kohli and Buller, 2013). Literature, and the results of this study, suggest that the South African public is becoming increasingly trusting and accepting of generic medicines (Patel *et al.*, 2012). The cost of living in SA increases annually, and consumers are finding it worthwhile to purchase inexpensive medicines, such as generics, across all types of provinces (viz. Gauteng, Mpumalanga and the North-West), to save on monthly expenses (StaffWriter, 2023a).

5.4.5. Time association and OTC CCM sales

In both bi-annual time regressions, the most notable increase in sales occurred in the second half of 2020, although not statistically significant. Although not statistically significant, annual and bi-annual time regressions both showed a higher number of OTC CCM sales seen in 2020 compared to 2019. This is illustrated in Figure 5.1, showing a R 25 million increase in OTC CCM sales from 2019 to 2020.

As depicted in Figure 5.2, the onset of winter in SA aligns with the beginning of the ‘second half’ of the year. During this time, families typically start stocking up on OTC viral and flu medicines, of which many include CCMs (Al Zoubi *et al.*, 2021). In the initial months of the Covid-19 pandemic in 2020, from July to December (second half of the year), consumer purchasing patterns underwent substantial changes following the onset of the pandemic (Das *et al*., 2022). Lockdown restrictions during the first half of 2020 naturally led to decreased OTC CCM sales as access to places like pharmacies was limited (Kostev and Lauterbach, 2020). The pandemic shifted consumer priorities towards purchasing health products such as OTC CCMs for self-medication purposes (Das *et al*., 2022). This led to an increase in purchases of these products in the latter half of 2020, as indicated by the findings in Table 5.6.

5.4.6. Combinations association and OTC CCM sales

The combination (medicine classification and method of payment) that significantly increased average sales by 2 807 sales, was a generic OTC CCM product purchased

using private funds in the form of cash (p<0.001). Whilst this trend may be evident in the univariate linear regression, such variable analysis was not possible for multiple regression analysis.

Similar factors relating to this association have been previously discussed in sections 5.4.3. and 5.4.4. of **Chapter 5**. Across all three provinces, this regression mirrors the same results and discussions as those found in Table 5.5 and Figure 5.2. However, a summarised list is shown below of the main discussion points regarding the association found in combinations of Table 5.6.

- Medical aid members should consider purchasing OTC medicines using cash or claiming privately, as using medical aid on OTC products depletes savings and extends one's self-payment gap for the year.
- Some individuals who misuse CCMs may opt to pay with cash to avoid creating a record of their purchase.
- Generic medicines undergo a faster and less costly development process, resulting in market prices that are 80-85% cheaper than original medicines.
- Generic medicines offer comparable therapeutic benefits at a significantly lower cost, rendering them a more cost-effective option.
- Those without medical aid must purchase products using cash and choose an inexpensive generic product, thus saving on medicine costs.

5.4.7. Pack size association and OTC CCM sales

Although results showed a minimal effect in both regressions, it was found that as the pack size of an OTC CCM product increased, such as in the number of tablets/capsules/milliliters etc., there was a significant decrease in sales. This finding opposes other available literature. Economically, to save, the majority of South Africans purchase household goods in bulk (more or larger pack sizes of the same product), especially when three or more members are living in the same household (StaffWriter, 2016). This same behaviour occurs when purchasing OTC CCMs. Buying in bulk, or buying larger medicine pack sizes, cost-effectively aids the household budget, as well as being able to use the same pack of medicine for numerous household members at once.

Given their OTC status, individuals can visually observe the various packaging sizes available for a specific CCM and can thus determine which pack size would be more cost-effective for their household. However, another South African study reported that compared to doctors, pharmacists showed a preference for dispensing larger and more expensive pack sizes (Padayachee *et al.*, 2019). This may be especially evident in lower socioeconomic provinces like Mpumalanga and the North-West, where pharmacies are likely to incur higher operational expenses, leading them to dispense OTC CCMs accordingly to optimise business profits (Padayachee *et al.*, 2019). However, in support of this study, Marti and Sindelar's (2015) study suggested that having smaller pack sizes, offers convenience of having these products "on-hand" and available in easy and accessible compartments such as the car, one's pocket or handbag (Marti and Sindelar, 2015).

5.4.8. Single exit price (SEP) association and OTC CCM sales

Although both regression analyses proved to be of minimal effect in this variable, as the SEP of an OTC CCM product increased, a significant increase in OTC CCM sales was shown (adjusted β=0.014; 95% CI [0.014 to 0.014]). Although the conventional idea of an inexpensive product means an increase in sales, this association proves the opposite. Contributing to this association may be the idea of pharmacists encouraging to dispense more expensive products, be it a more expensive generic, the original OTC CCM, or a larger pack-sized product to maximise pharmacy operation returns (Haque, 2017; Essack *et al*., 2020). Certain individuals hesitate to purchase generic products because they believe these products are of lower quality. Therefore, they believe that the higher price of original products ensures the acquisition of superior-quality medicine (Patel *et al.*, 2012).

The price of medicines often triggers a decision-making bias, where a higher cost is equated with superior quality (Moodley and Suleman, 2019). This bias influences consumer to perceive cost as a quality cue and rely on it as a heuristic (Díaz-Lago *et al*., 2023). However, placebo studies have consistently shown that newer, more expensive medicines are not inherently safer or more therapeutically effective than older, less expensive alternatives (Mintzes and Lexchin, 2005; Díaz-Lago *et al*., 2023). Based on the association found in this study, Díaz-Lago *et al*.'s (2023) study, further

supports these results, demonstrating a signinficant moderate effect among their participants of who perceived a more expensive medicine as more effective compared to an inexpensive alternative (*p*=0.039; 95% CI [0.014 to 1.110]) (Díaz-Lago *et al*., 2023). This suggests that the price of a medicine is used “as a surrogate for quality as a decision-making heuristic” (Díaz-Lago *et al*., 2023).

5.4.9. Summary Diagram

In summary, Table 5.6 depicts the statistically significant factors identified in the multiple linear regression model that were associated with increased OTC CCM sales across the three provinces. Significant associations were observed between specific variables and their effect on OTC CCM sales, offering insights into factors influencing sales across several types of economical provinces identified as “codeine hotspots” in SA. Gauteng was the province that depicted the greatest association in codeine use.

Concluding **Chapter 5**, the data from **objective III** facilitated inferential analysis of factors significantly contributing to the sale of OTC CCMs in three South African provinces. From this objective, the data reported on the amount of money spent on the sale of OTC CCMs in Gauteng, Mpumalanga and the North-West in 2019 and 2020. These findings offer insight into the annual expenditure on these medicines in each province. Figure 5.3 provides a geographical representation of the summarised findings found in **Chapter 5**, the findings, and discussions of **objective III** of the study.

As revealed by Figure 5.3, despite economic variations among the analysed provinces, **objective III** revealed that high codeine usage is not consistently linked to a specific economic status or province type. Instead, the findings demonstrate codeine usage across various economic landscapes.

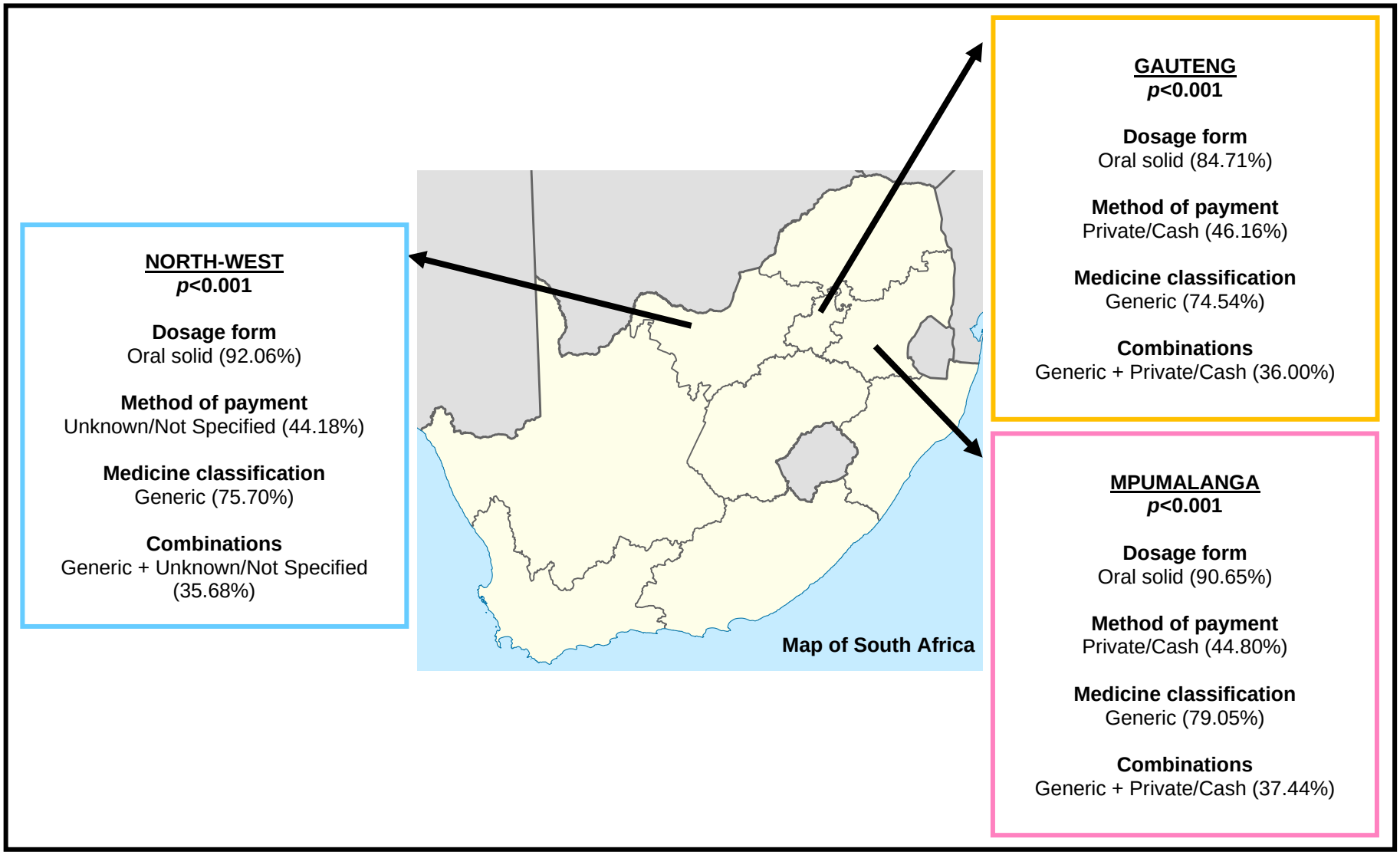


Figure 5.3: Graphical summary of the main results found in objective III.

CHAPTER 6: CONCLUSION, STRENGTHS, LIMITATIONS AND RECOMMENDATIONS

6.1. Conclusion

The study undertaken aimed to review factors contributing to CCM sales and to describe OTC CCM sales trends using retrospective observational analyses of an IQVIA dataset covering retail pharmacies across SA from 1 January 2019 to 31 December 2020. Many factors discussed as contributors to CCM sales were relevant to the descriptive and inferential findings of the study. The results supported existing literature and provided new insights into this research topic. Widespread availability and affordability of OTC CCM products in SA contribute to their misuse, highlighting the urgent need for potential policy reform, education and awareness programmes.

Objective I revealed a considerable proportion of codeine use in SA, posing risks of misuse, dependence and abuse. Despite legitimate therapeutic use of codeine, misuse, abuse, recreational and irrational CCM use are prevalent due to factors such as peer pressure, environmental impacts and societal influences. Various patient-related factors and HCP-related factors have also influenced the sale and usage of CCMs. As custodians of medicine, pharmacists play a pivotal role practising pharmacovigilance in the final decision to dispense an OTC codeine or prescription codeine product at every point of sale. However, in SA, there has seen to be a decrease in HCP intervention, leading to a lack of control and monitoring of OTC CCMs, thereby increasing the potential for irrational codeine use. Figure 3.1 in **Chapter 3**, summarises the factors discussed in **objective I**'s review. This figure outlines the various categories, themes and subthemes in which each factor contributes to the sale of CCMs.

In **Chapter 4** and through descriptive analysis, **objective II** was divided into two parts; **objective IIa** and **objective IIb**. Both **objectives IIa** and **IIb** identified Gauteng, Western Cape and the Eastern Cape as the provinces with the highest OTC CCM sales in this study's period. These sales primarily occurred through cash payments in chain pharmacies, particularly at the onset of the South African winter months. The top-selling OTC CCM products included Adco-Dol® (40s), Mybulen® (30s) and Gen-Payne® (30s) as the top three oral solid OTC CCMs, followed by Broncleer & Codeine® (100 mL) and Benylin & Codeine® (100 mL) as the top two oral liquid OTC CCMs. Figure 4.6 graphically represents a summary of the main findings found within **objective IIa**. Comparing OTC CCM sales before and during the Covid-19 pandemic in SA, observed significant differences across all provinces, payment methods and pharmacy classifications discussed in the study. March 2020 saw the greatest spike in OTC CCM sales for almost all analysed products, highlighting panic buying behaviours in response to the Covid-19 pandemic announcement. Subsequently, April 2020 witnessed a sharp decline in sales for most analysed products, highlighting the impact of the Covid-19 lockdown restrictions and reduced access to pharmacies across SA. Figure 4.10 graphically represents a summary of the main findings found within **objective IIb**.

Objective III in **Chapter 5** inferentially analysed various variables to identify associations with the sale of OTC CCMs in three "codeine hotspot" provinces in SA; Gauteng, Mpumalanga and the North-West. Sales were highest in urban Gauteng, reflecting its large population, followed by lower sales in rural Mpumalanga and rural North-West, where fewer residents reside. The main factors significantly associated with OTC CCM sales in the provinces were the sale of generic, oral liquid dosage form products, paying with cash, and a preference for smaller pack sizes at the point of purchase. Despite their unique economic landscapes, these three provinces exhibited similar trends and associations related to the sale and usage of OTC CCMs. Figure 5.3 provides a graphical representation of the summarised findings associated with **objective III** within each "codeine hotspot" province of SA.

Understanding South African OTC CCM sales trends and associations is crucial for recognising the risks of codeine misuse, dependence and abuse. Collaboration among researchers, HCPs and policymakers is essential to implement effective interventions,

guidelines and strategies for preventing and controlling codeine-related problems and promoting public health safety in SA. Continual monitoring of OTC CCM sales trends, evaluation of intervention programmes, and exploration of innovative strategies are also necessary. Furthermore, ongoing education and awareness initiatives for HCPs and the public are pivotal components of effectively addressing codeine misuse and abuse.

6.2. Strengths

In highlighting the strengths of this study, rigorous methodology and comprehensive data analyses have been instrumental in interpreting key insights of this research topic. The scarcity of literature reporting on sales trends of OTC CCMs across all nine South African provinces, underlines the significance of this study, which addresses a notable public health concern regarding the usage of OTC CCMs and their potential for misuse, dependence and abuse.

Objective I explored several factors contributing to the sale of OTC CCMs, both for legitimate and non-legitimate reasons. The utilised IQVIA data, facilitated a two-year comparison, strengthening the findings on annual sales trends. A major strength of this study, as represented by **objective II**, provided a descriptive overview of OTC CCM sales trends across all nine South African provinces. Additionally, the impact of the first few months of the Covid-19 pandemic on South African OTC CCM sales was also analysed. **Objective III** further explored inferential analysis of three South African “codeine hotspot” provinces, revealing factors associated with OTC CCM sales, despite variations in economic characteristics among the provinces.

Throughout **objectives II** and **III**, the IQVIA data enabled analyses of various variables affecting OTC CCM sales in SA, reflecting on socioeconomic factors contributing to these trends and associations. By utilising a quantitative retrospective observational study in this dissertation, it granted the researcher efficient access to a sizeable dataset, enabling robust analyses of OTC CCM sales trends and associations.

6.3. Limitations

Acknowledging and addressing the limitations found within the study, enhance the credibility and applicability of the study's findings. The utilised IQVIA data only covered a 24-month period from 2019 to 2020. With passing time, there may most certainly be variations to the present OTC CCM sales trends and associations and may not necessarily reflect current trends, capture recent developments or advancements within this field of study. Furthermore, the data period only encompassed the first ten months of the Covid-19 pandemic in SA, which may not necessarily provide a comprehensive reflection of OTC CCM sales patterns throughout the Covid-19 pandemic.

Additionally, it is possible that this study did not encompass all available OTC CCM products available on the South African pharmaceutical market. This may have been either due to the unavailability of certain products from manufacturers or suppliers, or their exclusion from the IQVIA data. It is also important to recognise that while the data includes numerous pharmacies across SA, it may not offer a fully comprehensive representation, as not every registered pharmacy may have consented to IQVIA collecting such data.

Another limitation pertains to the few inaccuracies in the IQVIA data, including recording errors and or missing specifications, posing challenges to the interpretation of the results. Although the IQVIA data was intended to include only OTC products containing codeine, an IQVIA database error resulted in the inclusion of a product containing no codeine, necessitating its exclusion for this study. Furthermore, within the IQVIA data, some products were excluded in this study since they did not fall within the S0-S2 OTC selection.

The study was limited by the absence of certain variable data due to pharmacies withholding information from being linked with the IQVIA data. A substantial portion of the 'Method of payment' variable, contained entries such as "-" or "Unknown/Not Specified" making it challenging to interpret the results of this variable accurately and statistically. Similarly, within the 'Pharmacy classification' variable, some pharmacies were labelled as "Undisclosed Pharmacies" in IQVIA, indicating the non-consent of

these pharmacies sharing information in the data. Consequently, this impacted the results of this variable too, categorising them as “Unknown/Not Specified” data within this study.

Considering the above-mentioned limitations, it is of utmost importance to interpret the study’s findings cautiously, recognising the limitations present in the data and methodology employed.

6.4. Recommendations

6.4.1. Improved prescribing and dispensing practices

Improved screening procedures should be implemented by all HCPs to deter irrational purchases and usage of CCMs. At the point of PIT, dispensers could promote the sale of non-codeine containing products or combination products with low codeine dosages and higher doses of non-opioid analgesics, such as aspirin, ibuprofen and or paracetamol (Van Hout and Norman, 2016). This strategy may help discourage dependence on codeine products. Healthcare professionals should advocate for holistic, non-pharmacological treatments that consider the entire body, rather than resorting to potential irrational prescribing and purchasing of codeine analgesics, which can increase the risk of misuse and abuse. These alternatives may include in promoting a healthy diet, hydrotherapy, exercise and rest (Builders, 2016).

6.4.2. National centralised database

A national centralised database with an alarm detection for the S2 register should be implemented as a compulsory feature in all registered South African pharmacies. The implementation of such an automated database could be integrated into current pharmacy software and enhance the current S2 register, acting as an audit and monitoring system for dispensers. This may improve pharmacist intervention, identify potential codeine misusers, and prevent the phenomenon of ‘pharmacy hopping’ within communities.

6.4.3. Considerations for future control policies

Careful evaluation of the existing regulatory framework for OTC medicines containing codeine in SA is essential (Essack *et al*., 2020). Globally, discussions and debates have arisen regarding the potential up-scheduling of all CCMs to prescription-only status (Hockenhull *et al.*, 2022; Voigt, 2022). Various arguments regarding codeine policy reform have been presented, with a consensus emerging for comprehensive review (Singu and Verbeeck, 2021; Hockenhull *et al.*, 2022; Voigt, 2022).

Singu and Verbeeck (2021) advocate for the removal of all CCMs from the WHO's EML. Their rationale stems from the definition of essential medicines as those that are "the most efficacious, safe and cost-effective" for priority conditions (Hockenhull *et al.*, 2022). While codeine may be affordable, Singu and Verbeeck (2021) assert that it is not the most efficacious or safe analgesic available. Removing codeine from the EML would signal to HCPs that CCMs should be a last resort for prescribing or point of sale (Singu and Verbeeck, 2021). This effect might prompt prescribers to refrain from repeatedly prescribing CCMs on subsequent prescriptions. However, such a shift could affect legitimate patients who cannot afford monthly visits to obtain a new prescription for CCMs.

Professor Charles Parry, from the South African Medical Research Council, suggests that instead of up-scheduling all OTC CCMs in SA, SAHPRA should consider implementing stricter limitations on the quantity of tablets/capsules or bottles a purchaser may obtain in a single purchase (de Villiers, 2020). Evidence indicates that countries with less stringent regulations on access to and sale of CCMs have experienced increased prevalence of irrational sales and usage (Hockenhull *et al.*, 2022). Policymakers should carefully consider policy reforms designed to restrict codeine sales, ensuring that legitimate access to OTC medicines remains available for legitimate patients.

The complete up-scheduling of CCMs to prescription-only status may hinder legitimate access to healthcare, infringe upon individuals' right to health, and restrict freedom of choice regarding OTC purchases (Ino and Nakazawa, 2022). Furthermore, it could pose financial challenges for pharmacies and potentially exacerbate the burden on the

healthcare system (Padayachee *et al.*, 2019). Further debates, discussions and research need to be explored before such potential policy reform can take place in SA.

6.4.4. Enhanced HCP education on CCMs

Healthcare professionals have emphasised the importance of enhanced education on codeine misuse and dependence. Multidisciplinary face-to-face workshops specifically focused on codeine use, are deemed most beneficial for HCPs to educate patients and promote rational CCM sales and usage (Builders, 2016; Parry *et al.*, 2017; Byrne *et al*., 2018). These workshops should aim to augment HCPs' understanding and knowledge of CCMs, enabling them to effectively communicate the associated risks to patients during prescribing and or dispensing. By participating in such training, HCPs may reconsider their approach to prescribing and or dispensing CCMs, opting instead for non-codeine alternatives.

6.4.5. Enhanced public education on CCMs

There is an urgent need to address the lack of public awareness and education regarding the adverse effects and addictive properties of codeine (Essack *et al*., 2020). Urgent action is required to develop comprehensive public educational campaigns and programmes aimed at informing all purchasers of codeine about its potential harms and risks (Builders, 2016; Cherian *et al.*, 2018; Richards *et al.*, 2021). These initiatives should highlight the dangers of excessive codeine use and advocate for strategies to prevent the development of a codeine misuse endemic within communities (Nyoni *et al.*, 2022). In support of this proposal, between 2015 and 2019, in Denmark, the sale of opioids decreased due to enhanced education and public awareness (Pottegård *et al.*, 2023).

Country policymakers should analyse the patterns of CCM usage within their country, specifically targeting communities at higher risk of codeine dependency and misuse. This analysis would aim to enhance policies regarding rational CCM usage. Additionally, regulatory measures should be implemented to restrict misinformation about codeine in advertising and on social media platforms, thereby reducing the encouragement of irrational purchases and usage (Cherian *et al.*, 2018).

The above-mentioned recommendations are essential for potential informed policymaking, market interventions and public health strategies aimed at optimising healthcare access and outcomes with rational CCM usage.

6.5. Concluding remarks

In conclusion, this study effectively identified several factors contributing to the sales of CCMs in SA and provided a detailed analysis of OTC CCM sales trends between January 2019 and December 2020. The findings supported existing literature and offered new insights, particularly highlighting the widespread availability and affordability of OTC CCMs as key contributors to misuse and dependence. Despite its contributions, the study faced limitations due to the relatively short data period, potential inaccuracies within the dataset and the incomplete representation of South African pharmacies. Consequently, the findings should be interpreted with caution.

Given the limitations, further research is recommended to expand on this study's findings. Future investigations should explore more recent sales data and examine the long-term impact of the Covid-19 pandemic on OTC CCM sales trends. Additionally, there is a need for enhanced HCP education, improved prescribing and dispensing practices, and the implementation of a national centralised database to better monitor CCM sales and prevent misuse. Finally, potential policy reforms, including stricter regulations on the sale of CCMs, should be carefully evaluated to ensure a balance between safeguarding public health and maintaining access for patients with legitimate therapeutic needs.

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APPENDICES

Appendix A: Ethical waiver clearance certificate.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Innovation)

21/08/2023

Ref: W-CBP-230511-01

TO WHOM IT MAY CONCERN

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical)

Investigator: Ms F Giuricich
Student No. (if appropriate): 2095435
Staff No. (if appropriate):

Supervisor: Ms R Shaikh

School: Therapeutic Sciences
Department: Pharmacy and Pharmacology
Division: Pharmacy Practice
Medical School
University

Project title: *Sales of over-the-counter codeine-containing medicines in South Africa, 2019-2020: a retrospective observational study*

Reason: Review of information in the public domain
No human participants will be involved in the study

Professor P Ruff
Chairperson: Human Research Ethics Committee (Medical)

Research Office Secretariat:
Third Floor, Phillip Tobias Building, corner of St Andrews and York Roads, Parktown, Johannesburg 2193
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Appendix B: Permission to use Figure 3.2 (Cooper, 2011).

Gmail

Federica Giuricich <fedgiuricich1@gmail.com>

Permission request to cite Figure from RJ. Cooper Research Paper

5 messages

Federica Giuricich <fedgiuricich1@gmail.com> Tue, Jun 13, 2023 at 10:48 AM
To: "richard.cooper@sheffield.ac.uk" <richard.cooper@sheffield.ac.uk>

Good day

I trust you are well.

My name is Federica Giuricich and I am a Master's in Pharmacy (MPharm) student at the University of the Witwatersrand (Wits University), Johannesburg, South Africa. My primary supervisor is Ms Rubina Shaikh, from the division of Pharmacy Practice in the Department of Pharmacy and Pharmacology at Wits University. I am conducting my Master's research on the sales of over-the-counter codeine-containing medicines in South Africa.

Whilst browsing the internet for literature, I came across your Research Paper **entitled:** "'I can't be an addict. I am.' Over-the-counter medicine abuse: a qualitative study.". I am therefore writing to you to request permission to cite your Figure 1 from this Paper in my MPharm dissertation (**entitled:** Relationship between over-the-counter medicine use and prescribed medicines.")? All referencing protocols will be adhered to. This figure has been useful as a pertinent figure which very nicely describes in pictorial format various relationships of prescribed and dispensed OTC medicines which ties in consistently to the research that I am conducting in my MPharm.

Thanking you kindly and I look forward to your favourable response.
Have a lovely day further.

Kind regards
Federica Giuricich
MPharm Candidate

Richard Cooper <richard.cooper@sheffield.ac.uk> Thu, Jun 15, 2023 at 12:13 PM
To: Federica Giuricich <fedgiuricich1@gmail.com>

Hi Federica,
Thanks for checking but I suspect it is actually BMJ Open who have to agree as the copyright resides with them. I've also attached the larger (and earlier) report linked to the project which has the same figure in and was sent to PPRT the funder but looking at this is is also copyright protected. So, what I've also attached are:
- PPT pof presentation which has the figure in it
- an unpublished executive summary report which I feel is owned be me/University of Sheffield and I'm fine for you to use that.

I think the citation for the attached would be Cooper RJ (2011) Unpublished Report 'Respectable Addiction' - A

qualitative study of over the counter medicine abuse in the UK. Executive Summary' if you need to show this in your final report.
The research sounds interesting and I hope it goes well!
Best wishes,
Richard
PS Do you need access to any other published papers from the work? There was a literature review and also the Surveillance and Uncertainty one I think about pharmacy staff - let me know.
PPS Also a book chapter I wrote for The Prescription Drug Abuse Epidemic edited by Schepis (2018). ISBN **978-1440852640**

Dr. Richard Cooper
Senior Lecturer in Public Health
Director of Education
School of Health and Related Research (ScHARR)
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Appendix C: Skeleton of data extraction table used to create the review.

Summary Table: Article review

PROJECT TOPIC: *Review* – **Factors contributing to codeine-containing medicine sales.**
PROJECT REVIEWER & RESEARCHER: Federica Giuricich

STUDY	STUDY TYPE	ASPECTS/ OBJECTIVE /FOCUS	LOCATION / PERIOD	STUDY CRITERIA	LIMITATIONS & DISCUSSION POINTS	OUTCOMES

Appendix D: List of all Medical Schemes classified under “Medical Aid”.

Scheme Names	
Aeci Medical Aid Society	Medcor (GEMS)
Affinity Health	Medicover (Liberty)
African Unity Health (Insurance)	MediHelp
Aid for Aids (Medscheme)	Medimed Medical Scheme
Allcare	MediPos Medical Scheme
Alliance Midmed Medical Scheme	Medisense Medical Scheme (Gold Fields)
Anglo Medical Scheme (GoldMed & AACMed)	Medshield Medical Scheme
Anglovaal Group Medical Scheme	Metropolitan Medical Scheme
Bankmed	Momentum Health Medical Scheme
Barloworld Medical Scheme	Moto Healthcare (Automed & Mimed)
Bestmed Medical Scheme	Mutual & Federal Medical Aid Fund (Nedgroup Medical Aid Scheme)
BHP Billiton SA Medical Scheme	NAMPAK (SA) Medical Scheme (Amalgamated with Discovery)
BMW Employees Medical Aid Society	Naspers Medical Fund
Bonitas Medical Fund	National Independent Medical Aid Society (NIMAS – Amalgamated with Resolution Health)
BP Medical and Society	Nedgroup Medical Aid Scheme (Nedcor Medical Aid Scheme)
Building & Construction Industry Medical Aid Fund (BIMAF)	Netcare Medical Scheme
Cape Medical Plan	Old Mutual Staff Medical Aid Scheme
Carecross (part of Momentum)	Optimum Medical Scheme (OPMED)
Chartered Accountants (SA) Medical Aid Fund (CAMAF)	Oxygen Medical Scheme
Community Medical Aid Scheme (COMMED)	Parmed Medical Aid Scheme
Compcare Wellness Medical Scheme	Pathfinder Medical Scheme
CSIR Medical Scheme	PG Group Medical Scheme
Day1 Health	Pharos Medical Plan (Topmed)
De Beers Benefit Society	Pick & Pay Medical Scheme
Dischem Medical Aid	Platinum Health
Discovery Health (Afrox Medical Aid Society)	Premier Medical Plan
Discovery Health Medical Scheme	Prime Cure
Emerald	Pro Sano Medical Scheme (Amalgamated with Bonitas)
Enablemed	Profmed
Engen Medical Benefit Fund	Protea Medical Aid Society
Essential Med	Purehealth Medical Scheme (NBC)
Fedhealth Medical Scheme (Fedsure)	Quantum Medical Aid Society
Fish-med (Fishing Industry Medical Scheme)	Rand Water Medical Scheme
Food Workers Medical Benefit Fund	Remedi Medical Aid Scheme
Furnmed	Renaissance Health Medical Scheme
Genesis Medical Scheme	Resolution Health Medical Scheme
Gen-health Medical Scheme	Retail Medical Scheme
Getmed	Rhodes University Medical Scheme (Aranda Medical Scheme)
Glencore Medical Scheme (was Xstrata)	Rx Health – Umvuzo Health Medical Scheme
Golden Arrows Employees Medical Benefit Fund	SA Breweries Medical Aid Society
Government Employees Medical Scheme (GEMS)	SABC Medical Aid Scheme
Grintek Electronics Medical Aid Scheme (GEMAS)	SAPPI Medical Aid Scheme (Amalgamated with Bestmed)
Hairdressing Sick Benefit Fund	Sasolmed

Scheme Names	
Horizon Medical Scheme	SEDMED
Hosmed Medical Aid Scheme	Selfmed Medical Scheme
Impala Medical Plan	Siemens Medical Scheme
Imperial Group Medical Scheme	Sisonke Health Medical Scheme
Ingwe Health Plan (Momentum Health)	Sizwe Medical Fund (MSP Sizwe Medical Fund)
Kaelo	South African Municipal Union National Medical Scheme (SAMUWMED)
Keyhealth (Global Health)	South African Police Service Medical Scheme (POLMED)
Keyhealth (Munimed)	Spectramed
LA – Health Medical Scheme	Stocksmed
Libcare Medical Scheme	Suremed Health
Liberty Health Medical Scheme	TFG Medical Aid Scheme (Foscini Group Medical Aid)
LifeMed Medical Scheme	Thebemed Medical Aid Scheme (Odyssey)
Lonmim Medical Scheme	Tiger Brands Medical Scheme
Makoti Medical Scheme (Goodhope Medical Aid)	Topmed Medical Scheme (Pharos)
Malcor Medical Scheme	Transmed Medical Fund
Mamoth Health	Tsogo Sun Group Medical Scheme
Mascom (Chamber of Mines)	Umvuzo Health Medical Scheme
Massmart Health Plan (Makro Medical Scheme)	University of Kwa-Zulu Natal Medical Scheme
MBMED Medical Aid Fund (DCMED)	Witbank Coalfields Medical Aid Scheme
	Wooltru Healthcare Fund

Appendix E: Permission to use Figure 3.3 (Nyoni *et al.*, 2022).

Gmail

Federica Giuricich <fedgiuricich1@gmail.com>

Permission request to cite Figure from Nyoni et al. Research Paper

4 messages

Federica Giuricich <fedgiuricich1@gmail.com> Mon, Feb 27, 2023 at 8:56 AM
To: "princessnyoni942@gmail.com" <princessnyoni942@gmail.com>
Cc: Rubina Shaikh <rubina.shaikh@wits.ac.za>

Good morning

I trust you are well.

My name is Federica Giuricich and I am a Master's in Pharmacy (MPharm) student at the University of the Witwatersrand. My primary supervisor is Ms Rubina Shaikh, from the division of Pharmacy Practice in the Department of Pharmacy and Pharmacology at Wits University. I am conducting my Master's research on the utilisation of codeine sales data across South Africa.

Whilst browsing the internet for literature, I came across your Research Paper **entitled:** "Spatial clustering of codeine use and its association with depression: a geospatial analysis of nationally representative South African data". I am therefore writing to you to request permission to use your Figure 1 from this Paper in my MPharm dissertation (**entitled:** Spatial distribution and cluster identification of codeine-containing medications in South Africa. Locations of the codeine use clusters (hotspots) illustrated in red circles, superimposed into a continuous surface map of codeine use prevalence generated using kernel interpolation technique.")? All referencing protocols will be adhered to. This figure has been useful as a geosaptial representation of which provinces in South Africa are prone to codeine misuse, which ties in consistently to the research that I am conducting in my MPharm exploring sales data of codeine use across South Africa.

Thanking you kindly and I look forward to hearing back from you.

Kind regards
Federica Giuricich
MPharm Candidate

Nyoni et al., 2022; Spatial clustering of codeine use and its association with depression, A geospatial analysis of nationally representative SA data.pdf
1878K

princess nyoni <princessnyoni942@gmail.com> Mon, Feb 27, 2023 at 9:17 AM
To: Federica Giuricich <fedgiuricich1@gmail.com>

Hi Fedeica,

Thanks for the interest in our study.

Please feel free to cite the figure.

Kind regards,
Princess
[Quoted text hidden]

Appendix F: The remaining 21-55 OTC CCM of the national product sales between 1 January 2019 to 31 December 2020.

Ranking position	Product	Dosage form	Pack size	SEP per product	Frequency of sales	Distribution (%)
21st	Sinutab Sinus Pain ES®	Tab	12	R 35.27	324 307	0.94
22nd	Pynstop®	Tab	20	R 36.03	263 978	0.76
23rd	Mybulen®	Cap	30	R 66.35	260 129	0.75
24th	Tensodol®	Tab	20	R 14.57	256 505	0.74
25th	Lenapain®	Tab	18	R 22.00	245 307	0.71
26th	Tensopyn®	Tab	40	R 38.76	207 192	0.60
27th	Lenadol®	Tab	40	R 51.85	206 800	0.60
28th	Tensopyn®	Tab	20	R 19.38	159 341	0.46
29th	Lenadol®	Tab	18	R 23.33	104 096	0.30
30th	Tensopyn®	Paed Syr	100 mL	R 37.70	76 753	0.22
31st	Adco-Napacod®	Tab	5 000	R 2 473.72	71 756	0.21
32nd	Stopayne®	Syr	100 mL	R 59.34	71 484	0.21
33rd	Syndol®	Tab	10	R 19.32	48 216	0.14
34th	Ibucod®	Tab	30	R 62.76	42 938	0.12
35th	Propain®	Tab	18	R 38.66	21 690	0.06
36th	Acurate®	Tab	100	R 72.94	21 286	0.06
37th	Ibucod®	Tab	18	R 37.65	20 972	0.06
38th	Tensopyn®	Eft	18	R 42.98	20 797	0.06
39th	Benylin & Codeine®	Syr	200 mL	R 113.22	20 346	0.06
40th	Propain®	Tab	40	R 85.91	17 773	0.05
41st	Adco-Dol®	Tab	100	R 101.70	9 780	0.03
42nd	Broncleer & Codeine®	Syr	200 mL	R 30.48	9 335	0.03
43rd	Pynstop®	Tab	18	R 32.41	5 396	0.02
44th	Pynstop®	Tab	100	R 180.28	1 576	0.00
45th	Betapyn®	Tab	100	R 215.26	1 529	0.00
46th	Adco-Dol®	Tab	500	R 508.49	1 359	0.00

Ranking position	Product	Dosage form	Pack size	SEP per product	Frequency of sales	Distribution (%)
47th	Lenadol®	Tab	100	R 104.66	980	0.00
48th	Syndol®	Tab	100	R 193.28	458	0.00
49th	Lenapain®	Tab	100	R 98.70	206	0.00
50th	Tensodol®	Tab	100	R 67.00	170	0.00
51st	Lenapain®	Tab	500	R 493.48	106	0.00
52nd	Tensopyn®	Tab	100	R 96.91	98	0.00
53rd	Propain®	Tab	54	R 115.97	91	0.00
54th	Propain®	Tab	100	R 214.76	18	0.00
55th	Lenadol®	Tab	500	R 523.32	7	0.00

ES = extra strength; Tab = tablets; Cap = capsules; Syr = syrup; Paed Syr = paediatric syrup; Eft = effervescent tablets; SEP = Single exit price
Note: Frequency of sales is indicative of the number of packs or bottles of a product sold.

Appendix G: Numerical results of the number of OTC CCM sales over time per province.

		Province								
Month and Year	**Total OTC CCM sales**	**Eastern Cape**	**Free State**	**Gauteng**	**KwaZulu-Natal**	**Limpopo**	**Mpumalanga**	**North-West**	**Northern Cape**	**Western Cape**
Jan ‘19	1 390 238	120 747	67 039	556 301	172 457	40 225	88 154	70 026	32 031	243 258
Feb ‘19	1 316 708	110 092	66 174	540 002	153 560	35 806	57 404	69 067	30 829	223 774
Mar ‘19	1 474 297	122 561	73 886	598 775	172 098	41 636	98 292	75 242	35 013	256 794
Apr ‘19	1 475 439	125 231	73 406	605 427	171 540	42 667	100 150	79 391	35 092	242 535
May ‘19	1 556 444	129 687	83 198	633 699	176 847	45 144	107 043	85 175	38 688	256 963
Jun ‘19	1 546 289	120 405	73 425	657 896	178 134	47 483	107 825	86 413	35 387	239 321
Jul ‘19	1 522 268	121 117	72 092	642 833	184 810	46 073	103 367	79 634	34 490	237 852
Aug ‘19	1 502 260	122 412	73 400	601 546	194 171	45 277	102 169	83 886	35 525	243 874
Sept ‘19	1 367 140	102 207	65 514	561 777	165 150	40 769	94 055	77 274	31 448	228 946
Oct ‘19	1 364 266	108 907	65 997	556 184	165 211	39 074	88 178	76 746	31 231	232 738
Nov ‘19	1 371 221	105 952	64 856	572 177	162 981	40 771	89 720	74 880	29 646	230 238
Dec ‘19	1 540 880	125 527	69 224	629 062	196 106	48 896	100 630	82 178	33 510	255 747
Jan ‘20	1 495 810	122 279	76 959	601 193	185 423	47 270	101 330	85 622	35 574	240 160
Feb ‘20	1 356 914	108 333	67 431	557 247	159 661	40 317	94 179	77 452	32 128	220 166
Mar ‘20	1 727 744	132 835	84 554	718 760	205 488	51 345	120 020	98 983	39 692	273 067
Apr ‘20	1 272 673	110 178	65 737	502 560	155 990	42 545	90 206	77 288	32 010	196 159
May ‘20	1 389 722	118 395	70 987	557 615	158 154	44 521	101 044	82 703	35 910	220 393
Jun ‘20	1 364 189	116 849	67 528	554 042	162 502	44 664	93 002	79 703	33 546	212 353
Jul ‘20	1 532 796	124 147	77 582	625 599	191 469	52 515	108 931	91 374	36 100	224 079
Aug ‘20	1 429 329	108 393	73 735	586 817	171 529	48 365	102 535	87 561	33 424	216 970
Sept ‘20	1 328 904	102 757	64 751	550 910	156 302	41 391	90 348	78 255	32 208	211 982
Oct ‘20	1 412 542	105 821	68 996	587 743	166 341	44 363	96 378	82 706	34 205	225 989
Nov ‘20	1 319 569	103 478	64 058	544 596	158 065	39 070	87 469	76 199	31 455	215 179
Dec ‘20	1 552 913	111 768	73 908	627 268	205 696	50 349	105 723	90 323	35 427	252 451

Appendix H: Numerical results of the number of OTC CCM sales over time per pharmacy classification.

	Pharmacy classification			
Month and Year	**Chain**	**Independent Pharmacy**	**Independent Pharmacy Groups**	**Unknown/Not Specified**
Jan ‘19	832 342	398 006	158 844	0
Feb ‘19	773 356	388 191	153 933	0
Mar ‘19	870 924	426 000	176 382	0
Apr ‘19	871 402	434 052	169 002	0
May ‘19	927 857	444 592	182 903	0
Jun ‘19	898 908	471 069	174 720	360
Jul ‘19	881 475	464 576	174 844	364
Aug ‘19	913 991	426 794	160 078	415
Sept ‘19	846 214	368 446	151 187	373
Oct ‘19	837 044	373 848	151 928	497
Nov ‘19	829 100	386 710	153 940	410
Dec ‘19	955 464	427 255	156 921	359
Jan ‘20	875 553	449 340	169 186	528
Feb ‘20	802 450	396 597	156 532	281
Mar ‘20	1 021 771	507 613	193 470	416
Apr ‘20	727 268	396 478	147 269	569
May ‘20	817 025	405 603	165 195	778
Jun ‘20	787 770	413 702	160 948	841
Jul ‘20	893 744	458 978	177 114	1 644
Aug ‘20	839 329	421 924	165 120	1 912
Sept ‘20	750 734	407 888	167 461	1 766
Oct ‘20	835 045	401 788	171 944	2 647
Nov ‘20	786 962	373 126	156 937	1 545
Dec ‘20	970 119	402 732	176 885	2 118

Appendix I: Numerical results of the number of OTC CCM sales over time per method of payment.

	Method of payment		
Month and Year	**Medical Aid**	**Private/Cash**	**Unknown/Not Specified**
Jan ‘19	376 429	598 354	414 406
Feb ‘19	332 812	572 401	410 553
Mar ‘19	343 498	656 903	472 825
Apr ‘19	359 826	658 207	456 303
May ‘19	376 199	703 213	475 685
Jun ‘19	336 067	695 575	513 471
Jul ‘19	295 318	711 060	514 755
Aug ‘19	272 165	734 114	494 997
Sept ‘19	228 870	699 656	437 714
Oct ‘19	207 376	707 450	448 602
Nov ‘19	190 709	710 042	469 760
Dec ‘19	227 986	796 464	515 597
Jan ‘20	410 914	624 653	458 884
Feb ‘20	355 785	586 512	413 443
Mar ‘20	474 678	709 919	538 563
Apr ‘20	329 769	523 242	418 302
May ‘20	330 063	619 581	438 808
Jun ‘20	311 828	607 804	443 379
Jul ‘20	348 074	687 766	495 524
Aug ‘20	267 333	690 984	469 877
Sept ‘20	230 962	633 071	463 820
Oct ‘20	231 619	719 351	460 599
Nov ‘20	204 708	690 835	423 272
Dec ‘20	270 042	828 487	453 395

Appendix J: Numerical results of the monthly sales over time per OTC CCM product (Group 1).

	Product										
Month and Year	**Adco-Dol®**	**Mybulen®**	**Mybulen® Suspension**	**Gen-Payne®**	**Acurate®**	**Sinutab Sinus Pain ES®**	**Broncleer & Codeine® Syrup**	**Benylin & Codeine® Syrup**	**Stilpane® Syrup**	**Betapyn®**	**Tensodol®**
Jan ‘19	448 216	204 245	15 454	138 388	117 365	64 115	57 347	38 232	33 199	54 775	23 943
Feb ‘19	422 243	175 652	14 566	137 471	111 812	65 567	62 518	37 610	37 592	49 537	20 840
Mar ‘19	466 641	194 531	16 456	160 786	129 769	70 979	78 830	39 263	38 813	55 612	24 828
Apr ‘19	453 300	209 916	16 919	150 509	135 780	77 492	82 700	41 050	39 622	55 683	25 056
May ‘19	471 829	215 715	19 888	162 115	146 977	93 991	63 497	49 793	48 636	56 797	27 186
Jun ‘19	447 407	206 626	19 965	154 602	139 075	94 627	110 837	50 720	44 818	52 588	28 782
Jul ‘19	462 949	203 473	14 261	146 242	138 654	87 542	97 876	49 120	44 440	54 672	32 314
Aug ‘19	481 654	196 528	26 193	159 183	147 827	89 415	22 788	74 051	32 041	56 934	31 033
Sept ‘19	440 523	176 774	14 103	150 628	139 341	81 320	1 453	84 046	24 638	50 347	29 333
Oct ‘19	458 020	182 777	12 946	141 335	140 581	68 648	326	73 925	29 209	52 227	30 103
Nov ‘19	451 074	173 397	12 462	150 667	143 053	59 593	38 347	58 822	32 058	52 954	32 568
Dec ‘19	494 384	225 678	14 362	161 900	147 154	72 324	82 116	47 739	22 153	58 829	29 395
Jan ‘20	469 072	218 319	15 953	171 541	149 255	74 533	57 303	45 485	31 959	55 422	29 643
Feb ‘20	428 396	199 468	15 239	147 559	136 798	69 831	51 239	41 510	25 109	50 127	28 559
Mar ‘20	514 817	240 251	22 732	206 844	173 901	113 023	59 104	48 166	43 637	61 569	37 407
Apr ‘20	401 518	179 365	10 876	130 064	131 709	77 781	41 242	39 866	29 929	49 180	31 287
May ‘20	450 554	186 971	10 246	149 281	148 158	78 722	42 706	43 972	36 281	53 041	37 854
Jun ‘20	427 799	189 006	10 500	141 240	148 632	78 284	42 249	45 619	34 176	50 359	38 563
Jul ‘20	469 202	206 538	12 013	168 462	158 223	98 292	48 291	57 421	40 687	54 961	45 755
Aug ‘20	451 967	187 205	9 148	150 764	151 299	78 869	59 806	42 743	42 249	52 308	39 866
Sept ‘20	419 141	168 448	8 975	143 993	144 184	72 891	58 120	36 158	37 103	48 153	34 618
Oct ‘20	442 280	179 842	9 717	153 038	154 470	75 396	57 306	41 247	42 826	49 207	41 187
Nov ‘20	411 064	156 685	8 854	160 607	151 021	66 380	48 150	34 893	39 791	45 897	40 711
Dec ‘20	478 982	212 110	12 807	192 243	156 443	87 441	46 858	43 013	44 907	53 831	47 510

ES = extra strength

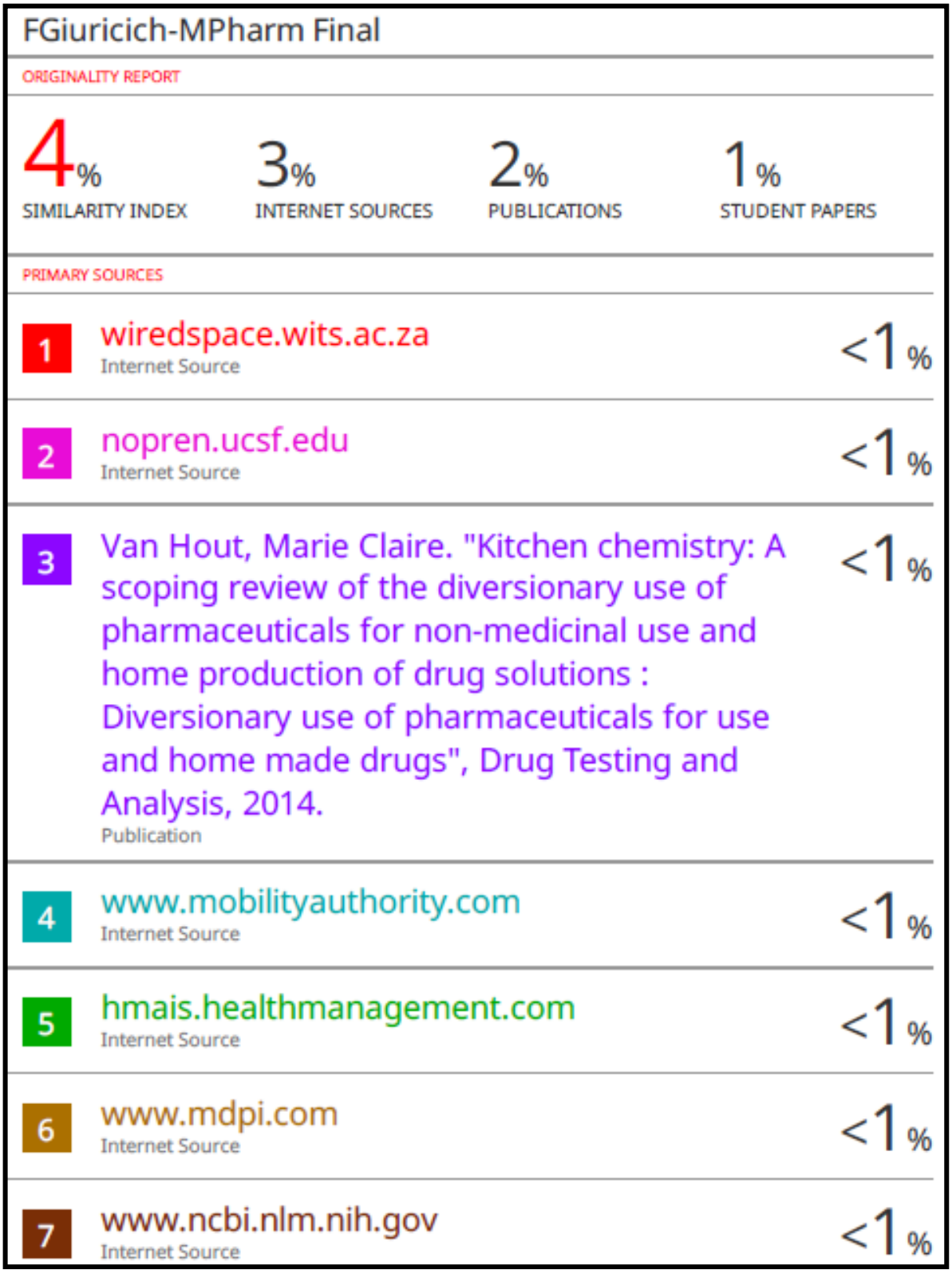
Appendix K: Numerical results of the monthly sales over time per OTC CCM product (Group 2).

	Product										
Month and Year	**Lenapain®**	**Adco-Napacod®**	**Pynstop®**	**Syndol®**	**Nurofen Plus®**	**Tensopyn®**	**Tensopyn® Paediatric Syrup**	**Lenadol ®**	**Stopayne® Syrup**	**Ibucod®**	**Propain®**
Jan ‘19	35 148	22 971	32 402	37 599	16 146	26 710	2 930	14 277	3 634	3 136	6
Feb ‘19	32 828	21 827	29 927	35 146	15 610	23 601	3 152	13 178	3 137	2 882	12
Mar ‘19	37 598	23 461	33 713	37 864	17 701	20 879	3 726	14 692	4 338	3 259	558
Apr ‘19	36 233	25 462	32 647	37 285	17 433	11 757	3 294	14 266	3 982	3 445	1 608
May ‘19	37 780	28 762	33 530	38 546	17 696	15 128	4 823	14 945	3 151	3 798	1 861
Jun ‘19	36 335	27 860	32 450	36 255	16 852	18 375	4 877	13 831	4 077	3 509	1 821
Jul ‘19	37 560	26 519	32 742	37 651	17 087	13 340	2 874	14 198	3 656	3 108	1 990
Aug ‘19	35 361	26 639	33 340	37 667	16 940	5 507	4 104	14 469	5 551	3 023	2 012
Sept ‘19	32 906	23 265	30 907	34 833	15 017	10 309	3 977	13 070	6 041	2 556	1 753
Oct ‘19	33 416	23 750	31 012	35 811	15 197	8 828	3 405	13 444	5 249	2 339	1 718
Nov ‘19	32 882	22 945	30 991	35 008	14 789	4 413	2 966	13 754	4 473	2 293	1 712
Dec ‘19	33 291	23 390	33 177	37 430	17 583	12 048	3 300	13 952	6 289	2 501	1 885
Jan ‘20	31 364	22 637	31 252	35 176	18 168	14 279	2 594	13 460	3 692	2 798	1 905
Feb ‘20	28 185	21 769	28 522	31 829	15 908	14 563	2 922	12 211	2 832	2 593	1 745
Mar ‘20	34 591	26 455	36 104	39 572	18 813	19 384	5 918	14 730	2 478	3 056	2 192
Apr ‘20	26 226	19 887	26 660	30 154	12 941	16 067	2 917	10 641	648	2 048	1 667
May ‘20	28 889	22 100	28 296	21 974	14 057	17 880	2 430	11 833	398	2 229	1 850
Jun ‘20	27 556	21 885	27 804	31 649	13 407	16 999	2 499	11 627	233	2 283	1 820
Jul ‘20	29 239	27 125	29 725	34 324	14 363	18 216	2 955	12 235	188	2 584	1 997
Aug ‘20	28 431	23 437	29 722	32 531	13 445	17 694	2 244	11 346	130	2 314	1 811
Sept ‘20	26 996	20 954	28 351	31 987	13 633	17 491	1 992	10 946	807	2 080	1 883
Oct ‘20	27 852	22 299	29 675	32 486	14 077	20 429	2 190	11 450	1 543	2 070	1 955
Nov ‘20	25 531	20 263	27 821	30 548	12 795	20 134	2 038	10 652	1 973	1 924	1 837
Dec ‘20	27 974	24 069	31 328	33 524	15 016	23 397	2 626	11 794	2 984	2 082	1 974

Appendix L: Numerical results of the province, medicine classification and method of payment associations.

Bi-annual time period	Medicine classification	Method of payment	Province			*p*-value
			Gauteng	Mpumalanga	North-West	
1st half 2019	Generic	Medical Aid	12.44	17.22	15.14	<0.001
		Private/Cash	35.23	33.92	27.07	
		Unknown/Not Specified	27.49	27.30	32.63	
	Original	Medical Aid	7.20	8.55	9.78	
		Private/Cash	9.47	6.67	7.68	
		Unknown/Not Specified	8.18	6.35	7.70	
2nd half 2019	Generic	Medical Aid	8.59	11.89	9.83	<0.001
		Private/Cash	37.74	40.24	28.73	
		Unknown/Not Specified	26.80	26.60	36.64	
	Original	Medical Aid	5.09	5.93	6.60	
		Private/Cash	11.75	8.50	8.44	
		Unknown/Not Specified	10.03	6.83	9.76	
1st half 2020	Generic	Medical Aid	13.51	17.82	15.25	<0.001
		Private/Cash	33.37	35.11	24.73	
		Unknown/Not Specified	27.15	25.99	35.46	
	Original	Medical Aid	7.76	8.59	9.59	
		Private/Cash	9.31	6.62	6.79	
		Unknown/Not Specified	8.89	5.87	8.18	
2nd half 2020	Generic	Medical Aid	9.79	13.36	10.30	<0.001
		Private/Cash	37.64	40.59	29.08	
		Unknown/Not Specified	28.41	26.17	37.82	
	Original	Medical Aid	10.07	6.19	6.46	
		Private/Cash	8.69	7.70	7.99	
		Unknown/Not Specified	8.69	5.99	8.36	

Appendix M: Turnitin report[1].



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[1] Full report available upon request.