CODEINE USE IN OVER-THE-COUNTER (OTC) PAIN MEDICATION: A STUDY OF PHARMACIST KNOWLEDGE AND PERCEPTION

NASRENE KHAN

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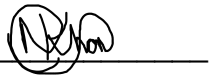
Supervisors:

DR NEIL BUTKOW

MS NEELAVENI PADAYACHEE

DECLARATION

I, Nasrene Khan, declare that this Dissertation is my own, unaided work. It is being submitted for the Degree of Masters in Pharmacy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

 (Signature of candidate) 6th day of August 2018 in Glenvista.

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DEDICATION

I dedicate this dissertation to the Almighty for being the source of my strength and inspiration throughout this process. I also dedicate this to my family for their unconditional love and support. They have encouraged, motivated and cheered for me through great challenges in order for me to reach my goals.

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ABSTRACT

Codeine is an opioid widely available in South Africa's community pharmacy sector in OTC analgesic combination preparations and cough mixtures in low doses. Its widespread availability has led to misconceptions of its therapeutic effect and safety. Pharmacists have primary contact with patients and are therefore able to influence patient perception and utilisation of over-the-counter (OTC) medications. The role of the community pharmacist, when treating general conditions such as pain, their perception of the role of codeine in these available OTC analgesic preparations, as well as their awareness of its misuse and abuse potential in the community, are not available in literature and need to be explored further.

Aim: To investigate the utilisation of codeine-containing analgesic OTC preparations in Gauteng's private healthcare market.

Objectives: To analyse the patterns of utilisation of codeine-containing products in Gauteng's private healthcare market using a national ordering database, as well as to gain an understanding of pharmacist and qualified post-basic pharmacist assistant (QPBPA) perceptions of analgesics.

Study design: A mixed-method approach comprising of both quantitative and qualitative data collection methods.

Data source and participants: Retrospective sales data was extracted from *Orderwise* for a six-month period from 1 January 2016 to 30 June 2016. There were 219 survey respondents comprising of pharmacists and QPBPAs based in Gauteng. In-Depth-Interviews (IDIs) were conducted with eight pharmacists based in Gauteng.

Method: The surveys were distributed to 513 pharmacists in Gauteng. Data from the surveys as well as the *Orderwise* data were transferred to *SAS Enterprise 7.1 Software*. The questionnaire was designed to illicit information based on the following broad categories: treatment preferences when it comes to OTC pain management; knowledge relating to codeine use; and perception and awareness of codeine dependence, misuse and abuse. The interviews were transcribed verbatim. Upon completion of the interviews, emerging themes were gathered via thematic analysis including open and axial coding by

hand. Themes were divided into two broad categories: general pain management and management of OTC codeine use. The three themes that emerged from the data were OTC treatment of non-complicated pain, codeine used for the treatment of pain and codeine misuse and abuse.

Results: *Orderwise* data showed that Gauteng has the second highest codeine-containing product sales distribution in South Africa. A majority (67.2%) of the codeine-containing products sold in Gauteng are indicated for pain. The drug class which includes any product containing paracetamol, the sedative H1 antihistamine doxylamine, and codeine and caffeine, accounts for the majority (59%) of all OTC pain products delivered. Survey and IDI results showed that an overwhelming majority of QPBPAs took drug-marketing into account when treating patients OTC. Patient-request had the second highest level of agreement by pharmacists after evidence-based-medicine. Most respondents said that an 8mg to 10mg dose of codeine is most effective for the analgesic enhancement of both NSAIDs and paracetamol. All interview participants and a majority of all survey respondents found codeine abuse, misuse and dependence to be a significant problem in their community. Half of the participants felt that a challenge in controlling the use and abuse of codeine, was due to the close proximity, and ease of accessibility to different pharmacies without a method of tracking patient use between these pharmacies. Pharmacists and QPBPAs felt that there should be an alternative strategy implemented to prevent OTC codeine abuse.

Conclusion: This study highlights that in Gauteng, there is a huge demand for codeine-containing analgesic medication, especially those in combination with sedative antihistamines. This is met by a large pharmaceutical supply across the province's private community healthcare sector. Codeine's widespread availability OTC has made controlling its use by pharmacists and pharmacy assistants almost impossible and there is a callout for stricter and more proactive control measures placed on codeine-containing product use in South Africa.

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LIST OF ABBREVIATIONS

CCI	Codeine care initiative
CCM	Codeine-containing medication
CCPM	Codeine-containing pain medication
CNS	Central Nervous System
EM	Extensive Metabolisers
IDIs	In-Depth-Interviews
MCC	Medicines Control Council
MIMS	The Monthly Index of Medical Specialties
NC	NSAID and codeine combination
NCCM	Non-codeine-containing medication
NCCPM	Non-codeine-containing pain medication
NPCC	NSAID and paracetamol combination with codeine
NPCWOC	NSAID and paracetamol combination without codeine
NSAIDs	Nonsteroidal anti-inflammatory drugs
OTC	Over-the-Counter
OTCCP	Over-the-Counter codeine preparations
PC	Paracetamol and codeine combination
PDCCC	Paracetamol, doxylamine, codeine and caffeine combination

PM	Poor Metabolisers
PPC	Paracetamol, promethazine and codeine combination
PUS	Pattern of Utilisation Study
QPBPA	Qualified post-basic pharmacist assistant
RDBPC	Randomised double-blinded placebo control
SAMF	South African Medicines Formulary
SAPC	South African Pharmacy Council
UM	Ultra-Metabolisers
URTI	Upper respiratory tract infection
WHO	World Health Organisation

1. INTRODUCTION

1.1 Background

Codeine is a natural opioid found in the poppy plant which is available in many well-known over-the-counter (OTC) analgesic preparations in South Africa. It is also used as an anti-diarrhoeal as well as an antitussive. Although very easy to obtain in South Africa, codeine is structurally similar to the schedule 6 (s6) and much less obtainable-morphine. Despite its structural similarities, codeine is weaker in its analgesic effect due to the weak targeting of the Mu receptor in the central nervous system (CNS). According to studies its weak analgesic effect is due to the fact that just 10% or less of the codeine dose consumed is metabolised in the body to the active metabolite morphine. The rest is believed to be metabolised to the inactive analgesic norcodeine as well as into codeine-6-glucuronide (Armstrong & Cozza, 2003).

Opioids work as analgesics by binding at opioid receptors in the brain and spinal cord. The Mu receptor specifically, is believed to have an analgesic effect in both acute and chronic pain (McQuay, 1989). Due to an increase in the therapeutic use of opioids, the increase in retail opioid supply and sales are mirrored by climbing abuse rates (Manchikanti & Singh, 2008). Even though codeine is considered a weak opioid, it is still associated with dependence and abuse and comes with many side effects.

Many animal and human studies have shown an unpredictable, inconsistent or poor response to treatment with codeine (Williams et al., 2001); however, it is still widely used in the clinical treatment of pain. The unpredictable nature and inter-individual differences of the effect of codeine is due to the fact that it is a prodrug, and its activity is based on its transformation to morphine which varies amongst individuals with different enzyme maturation rates (Williams et al., 2001).

Codeine used appropriately and for its indication incurs little risk; however, excessive or long-term use of codeine contributes to dependence, associated side effects and adverse and life-threatening situations (Bergin et al., 2015). Its widespread availability has made limiting its use very difficult and due to the abundance of combination pain preparations containing codeine available, doctors are constantly prescribing it to treat pain (Pillay et al., 2011).

The abuse liability of codeine is due to its narcotic effect and the rapid development of tolerance to the drug on continued or excessive use (van Hout & Norman, 2015). Some individuals can become dependent on codeine after using it for genuine pain (Hamer et al., 2014).

1.2 Codeine misuse and abuse

The abuse and misuse of products like codeine leads to a strain on the community healthcare system. Fortunately, there is a growing global awareness around the misuse and abuse of codeine and as a result many countries have already re-scheduled codeine-containing preparations and others are on the verge of doing so.

Medication in South Africa is scheduled by the regulatory authority according to the safety profile of the drug. The schedule determines the conditions of which the drug can be sold (MCC, 2014). Codeine in low doses is contained in combination preparations that are classified as schedule 2 (s2) substances in South Africa. This means that these preparations can currently be sold without a prescription but cannot be sold without the direct supervision of a pharmacist.

In South Africa, codeine is available in low doses OTC; however, its use is not properly controlled and the amount of codeine products each customer purchases from different pharmacies currently cannot be recorded or tracked. In some pharmacies, pharmacists are required to insert patient data regarding the sale of such items on site. In many pharmacies this remains a futile exercise for the most part as it does not prevent patients from obtaining their fix from a different pharmacist on a different day, and certainly does not prevent patients from obtaining these products from various pharmacies within the country as their registers are currently not centralised in any way (Le Roux, 2013). The

term called “Pharmacy Hopping” as well as abuse was aimed to be corrected by a strategy known as the Codeine Care Initiative (CCI). This is an innovative idea as all codeine purchases could be tracked through a central database. When a customer reached their limit for a specific time period, the pharmacist must make an informed decision of whether to dispense the product or not (ICPA, 2014). Through this process codeine-containing preparations would still be available as an OTC item, but abuse and misuse would be controlled. The codeine care project is a great initiative; however, the implementation of the project is not easily accepted throughout the country.

In August 2014, the South African Medicines Control Council (MCC) proposed to take action by reducing the amount of codeine allowed in OTC products from 20mg to 10mg per dosage unit in oral solid preparations and in liquid preparations, by reducing the maximum quantity of codeine from 20mg to 10mg per 5ml dose in order to control abuse. Allowing a maximum daily dose of 80mg. The MCC also proposed to “up- schedule” the products containing quantities that do not fall within these proposed restrictions (MCC, 2014). This is still a debatable issue as there are many aspects to consider.

One negating aspect is restricting the access of low income patients to primary care as they will no longer be able to obtain symptomatic relief from the once readily available preparation. According to Gudin and Lee (2013), it could result in the inadequate treatment of pain, prescribing of more potent medication by doctors, and an economic drop within the pharmaceutical industry. In addition, determined abusers will adapt and find ways around the system and it might not solve the misuse and abuse problem, as it will still be available to purchase. On the other hand, removing codeine completely from the OTC shelf as opposed to rescheduling could cause codeine dependent individuals to source stronger more illicit opioids. This could place an even greater burden on the public healthcare system (Foley et al., 2016).

1.3 Codeine as an analgesic agent

Codeine in South Africa is currently available in doses of 8mg to 10mg per dosage unit in combination OTC pain medication. Furthermore, according to the law, the maximum daily OTC dose is 80mg. According to the South African Medicines Formulary (SAMF), a 30mg to 60mg dose taken every four to six hours is needed for an adult to experience the continuous analgesic effect of codeine (Dawn, 2014). There seems to be a disparity between the dose available for the alleviation of pain in OTC combinations, and what evidence suggests is adequate enough to alleviate pain. The lack of evidence from randomised double-blinded, placebo controlled (RDBPC) clinical trials on doses of 20mg or less for the treatment of pain, causes a concern for the potential of misuse and abuse of these products as there is a lack of evidence to support codeine having a significant clinical advantage when added in low doses to OTC products for the treatment of pain (van Hout & Norman, 2014). This prompts the questionability of further codeine dose reductions in OTC pain medication combinations as it implies wasted efforts to keep the medication on the shelf in order to maintain effective pain relief.

1.4 Rationale

Codeine is widely available around South Africa's community pharmacy sector in OTC analgesic combination preparations as an adjunct in low doses. Evidence seems to support the use of codeine for the treatment of pain in doses of 30mg to 60mg; however, there are too many evidence gaps in RDBPC clinical studies and a lack of evidence-based medicine in general to support the dose of codeine currently available in combination OTC products, or on further reduced doses of 10mg or less.

There are common misconceptions on the safety of codeine, due to it being so easily accessible by the public. The impression is that if it is available for use it can be used, and therefore pharmacist intervention at the point of sale is key in the prevention of misuse and even abuse. Pharmacists are key role players in the prevention and mitigation of prescription drug abuse and misuse (Hagemeier et al., 2014) and are in essence the gatekeepers of the dispensing of medications. Community pharmacists in particular, play a pivotal role in influencing the perception and utilisation of OTC analgesics. It is said that the most significant characteristic of community pharmacists is their accessibility as they

are available to the public at all times with no need for appointments or counselling charges and people who are in need of help are not limited by those factors (Gilbert 1998). Pharmacists being the custodians of medicine (Le Roux, 2013), should ensure that the medication they dispense will serve a genuine medical purpose (Joranson & Gilson, 2001). The factors that influence community pharmacists' perception as well as their decision-making when treating patients, especially for conditions such as pain, are scarcely available in literature and need to be explored further (Hagemeier et al., 2014).

Public hospital pharmacies in South Africa provide medication to patients on the receipt of a doctor's prescription only, and due to the many restrictions in terms of the availability of medicines, codeine-containing products are hardly available as treatment for mild to moderate pains in public hospitals. Misuse of opioid pharmaceuticals is emerging as a global public health concern. Codeine use remains high in the retail sector amid calls for revised scheduling and increased pharmacovigilance (van Hout et al., 2014). This study is therefore based on the distribution of codeine-containing products across Gauteng's private healthcare system in particular. Thus far, the role of the private sector community pharmacist in South Africa when treating general pain conditions, their perception of the role of codeine in these available OTC analgesic preparations, as well as their awareness of its misuse and abuse potential in the community is not yet available in literature and need to be explored further.

2. LITERATURE REVIEW

2.1 Introduction

Codeine is an opioid that is used to treat mild to moderately severe pain and it is also indicated as an antitussive and antidiarrheal. Codeine or 3-methylmorphine targets the Mu opioid receptors in the CNS but to a weaker extent than Morphine. Codeine is metabolised in the liver where about 10% is converted to Morphine (Dawn, 2014). The analgesic properties of codeine have been proposed to come from its O-demethylation to morphine, although the exact mechanism of its effect on pain still remains unknown (Drug Index, 2011).

The addictive nature and large side effect profile of codeine make it a potentially dangerous agent; however, codeine's widespread availability in South Africa and many other parts of the world have led to common misconceptions around the safety of the drug. In 2012, data showed that the pharmaceutical industry sold 32 million units of codeine in South Africa (Danetteb, 2013). Globally, the demand for codeine has also risen by approximately 27% over the last decade (van Hout et al., 2014). A majority of these sales are directed to the community sector where it is a component of cough syrups, and it can also be found in combination products that are available OTC to treat symptoms of colds and flu as well as to treat pain.

In South Africa, it is currently permissible to sell codeine-containing products without the issue of a prescription by the patient, and therefore the responsibility lies with the pharmacist as they are meant to safe guard these available medications. However, due to the lack of control over these codeine-containing products, in August 2014, the South African MCC proposed to take action by reducing the amount of codeine allowed in OTC products, as well as by "up- scheduling" the products containing quantities that do not fall within this restriction (MCC, 2015). This enforcement is still a debatable issue as there are many aspects to consider. The shortcomings in terms of placing more restrictions on our healthcare system – will it be efficient enough in preventing misuse and abuse and will the reduced codeine dose be therapeutic?

To get a holistic view on the information currently available, this chapter will aim to review literature based on substance abuse, codeine misuse and abuse, codeine regulations in other countries, as well as the analgesic effect of codeine. In addition, current research based on pharmacist and other healthcare practitioner perceptions of codeine use will be reviewed.

2.2 Substance abuse

Abuse implies that one intentionally uses a substance in an unacceptable manner either habitually or on occasion and not for medicinal purposes. Whereas dependence, according to Perkel et al. (2010), is classified as experiencing tolerance to the drug, having a loss of control, being compelled to take a substance due to one's desire of the effect or relief offered by the drug, as well the need to feed the reward system in the brain. These three factors may be experienced in one patient, though not all is required for dependence to be diagnosed. Misuse is different to abuse and dependence in that it is incorrectly used for a legitimate medical reason, but in higher doses or for longer than the recommended time period (Wazaify et al., 2005).

2.2.1 Substance abuse in South Africa

Empirical evidence collected in the late 1990s pointed to a gradual increase in drug-related problems and substance abuse in South Africa (Ramlagan et al., 2010). South African research has shown that the most common reasons reported for drug use include habit, to alter mood states, to improve health, to cope with personal, social or interpersonal situations, or for the taste or enjoyment (Rocha-Silva et al., 1996).

Socio-economic factors were also considered contributors of substance abuse. An epidemiology study of substance abuse in South Africa found that factors included poverty, unemployment, lack of recreational facilities, being in the presence of substance abusers, and long work days (Ramlagan et al., 2010).

Illicit drug use in South Africa places a great burden on society due to its effects on crime and health. The past divisions of the country still play an important role in its drug abuse patterns today. It is related to age, social class, occupation, school status, gender and very importantly in South Africa, geographic location (Njuho & Davids, 2010).

Njuho and David (2010) performed a cross-sectional population-based household survey which targeted all persons over the age of two-years-old in South Africa. The aim of the study was to better understand the extent and influence of illicit drug use in South Africa. The survey results showed that drug use differs considerably by race. They found that white males were 2.3 times more likely to use illicit drugs compared to black males, followed by coloured males. This was also true for the use amongst white and coloured females compared to black females. The interesting result was that females with a higher education were more likely to use illicit drugs compared to those without a formal education. This was also the case with employed and unemployed males. The authors of this study found that urban residents were more likely to report illicit drug use than rural citizens. One of the author's suggestions included an intervention needed to address the high level of drug availability and use.

According to a report done by Peltzer et al. (2010), the most urbanised cities in South Africa such as Johannesburg and Pretoria in Gauteng and Cape Town in the Western Cape have the highest rates of drug abuse.

Dada et al. (2015) investigated the treatment demand in relation to misuse of codeine or codeine dependence in South Africa. The authors of this study found that of the total admission recorded; 29% of admissions for codeine misuse/dependence were in Gauteng, 23.9% in the Eastern Cape and 21.1% in the Western Cape. The central region which consisted of the less urbanised Free State, the Northern Cape and North West province reported only 12.9% of the admissions. Kwazulu-Natal reported 8.0% and Mpumalanga and Limpopo provinces reported 5.1% (Dada et al., 2015).

Peltzer et al. (2010) argued that there was a link between liberation and modernisation of the country. The influx of new cultural trends in the more affluent areas came with an increase in drug use and abuse as well as increases in violent and organised crime (Peltzer et al., 2010).

Demographic factors and personal attributes explained 15% of variances in adolescent drug use (Brook et al., 2006). They also found that psychosocial factors such as environmental stressors and parental drug use, amongst others, influence adolescent drug use in both South Africa and the U.S.

A retrospective study was completed by Myers et al. (2003) on OTC and prescription medication misuse amongst 9063 patients from different substance abuse treatment centres in Cape Town between 1998 and 2000. This study showed that codeine-containing analgesics, which were and mostly still are available OTC in South Africa, were the class of medication abuse that patients were most treated for, second to the benzodiazepine medication class. This study points out the burden that OTC medication abuse places on the healthcare system in South Africa and, as early as the year 2000, drew attention to the need for the up-scheduling of codeine-containing products (Myers et al., 2003).

2.2.2 Codeine use, misuse and abuse

Codeine is an opiate used in almost every part of the world for pain. It is also available OTC in many countries as an adjunct in pain combination packs, cold and flu preparations, as well as in cough syrups as an antitussive. In recent years however, its analgesic as well as antitussive effect has been probed. An assessment of the effect of codeine on the treatment of cough associated with an upper respiratory tract infection (URTI) was investigated by performing a stratified, double-blind, placebo-controlled, parallel-group, clinical trial using three different cough measures such as cough sound-pressure levels, cough severity, and cough frequency (Freestone & Eccles, 1997). Results in this study showed that there was an improvement of all three measures of cough after treatment with 50mg of codeine as well as with the placebo dose. This

revealed that there was no difference in the treatment of URTI associated cough between the codeine single dose and placebo dose (Freestone & Eccles, 1997).

Bolser and Davenport (2007) later concluded that the available evidence on codeine as an antitussive is not enough to support the efficacy of the drug as a cough suppressing agent. They argued that past animal studies did not take into account the complexity of the actual coughing mechanisms in humans (Bolser & Davenport, 2007).

Codeine is still trusted by healthcare practitioners around the world. There is an increase in its demand by patients for its therapeutic as well as CNS effects.

Codeine comes with many CNS side effects due to its narcotic effect. This narcotic effect is also the reason for the abuse liability and quick development of tolerance to the drug on regular or excessive use (van Hout & Norman, 2015). Misuse and abuse is driven by many factors including the widespread availability, misconceptions on product safety, effect and addictive nature (Ling et al., 2011). This can be due to the lack of counselling and education of OTC medications. It can also be the result of over-prescribing from doctors as well as inappropriate dispensing by pharmacists. More factors include self-medicating undiagnosed physical or emotional pain and social influence (Daniulaityte et al., 2006).

Social influence and pressure is a major contributing factor leading to the recreational abuse of codeine which has recently become a global health concern particularly amongst the youth due to the impact of the internet, media and social media. The music industry has played a large role in the encouragement of the use of substances such as codeine through the glamorisation of drugs in Rap music (Yang, 2008). Drug abusers are finding new ways of acquiring their high and are becoming more resourceful in order to keep up with their demand. Codeine is being chemically altered to extract dextromorphan and made into a drug which is commonly known as “Lemon Drop”. Abusers even extract codeine from readily available cold and flu preparations. In a study based on the societal perspectives of OTC medications by Wazaify et al. (2005), a participant reported witnessing the separation of codeine from OTC analgesics using coffee filters to avoid the toxicity of other ingredients in the analgesic combinations. Cough syrups containing

codeine are abused for social intoxication purposes and when added to a mixture of soft drinks, alcohol and candy, it is known as “Purple Drank” (van Hout, 2014), or “Lean” amongst the South African youth. A youth analysis showed that those who use alcohol are nearly nine times more likely to misuse OTC drugs (Steinman, 2006). A study done by Dada et al. (2015) found that 435 treatment admissions in abuse treatment centres around South Africa involved codeine misuse or dependence as a primary or secondary substance of abuse. Only 137 patients (0.8% of the total admissions) had codeine as their primary substance of abuse. The most common primary substance abused by patients who were abusing codeine was OTC/prescription drugs (31.7%), followed by alcohol (21%) and cannabis (14.7%). Interestingly, the same study showed that the most commonly abused codeine-containing medication was Stilpane® (Dada et al., 2015), which should be one of the most difficult codeine products to obtain as it is a schedule 5 (s5) in South Africa and is therefore not issued without an original prescription. Even though it has a lower codeine content than most readily available OTC preparations, its addictive nature is high due to the addition of the anxiolytic drug Meprobamate. Adco-Sinal CO® had a 15mg per dose codeine-content and is ranked at nine out of the ten ranked products and Myprodol® ranked fourth. Perhaps a large contributing factor to the ranking, specifically in community pharmacies, is the cost per product. Stilpane®, although more difficult to obtain, currently costs less than the same amount of the readily available Syndol® or Myprodol® for example. A combination of ingredients that create a deeper euphoric effect such as codeine and doxylamine or codeine and meprobamate compared to codeine in combination with paracetamol and or ibuprofen, could also influence the preferred substance of abuse.

Drug treatment data from the National Drug Treatment Monitoring System (NDTMS) in the UK, the Irish National Drug Treatment Reporting System (NDTRS), and the South African Community Epidemiology Network on Drug Use (SACENDU) showed that 2.5% of people being treated for drug abuse in South Africa had codeine as a primary or secondary drug of abuse in 2014. This is more than that compared to the 1.9% of persons in Ireland between 2008 – 2012 and 2.2% in the UK in 2013 and 2014 (Parry et al., 2015).

2.3 Codeine regulations around the world

There is a growing global awareness around the misuse of readily available products containing codeine. Researchers who were involved in the scoping review of codeine use, misuse and dependence tabulated the global regulations of codeine in thirty-one different countries, both OTC and prescribed, by consulting with the regulatory agency of each country (van Hout et al., 2014). Results from eight of the participating countries, most on separate continents, highlight the variances in global codeine regulations.

2.3.1 Australia

Currently preparations containing less than 12.5mg of codeine can be sold for a period of five days under pharmacist supervision in Australia. However, pharmacies are not allowed to directly advertise the product to the consumer and the label needs to clearly indicate that the total daily codeine dose is 100mg (van Hout et al., 2014).

The new law that will be enforced by the Australian Regulatory agency in February 2018, will see that codeine-containing preparations are schedule 4 (s4) and only sold upon receipt of a doctor's prescription (TGA, 2016).

2.3.2 Canada

Canada allows the sale of OTC codeine combination products available up to 8mg or its equivalent of codeine phosphate per tablet and not more than 20mg or its equivalent of codeine phosphate per 30ml in a liquid preparation. Products may not be displayed and must be kept out of view of the consumer (van Hout et al., 2014).

2.3.3 China – Hong Kong

In Hong Kong, only cough suppressants are permitted to be sold in a pharmacy without a prescription. This is further restricted by only allowing up to 0.1% (5mg per 5ml) codeine-content. A prescription is needed for more than 0.2% codeine-content (van Hout et al., 2014).

2.3.4 Finland

The Finnish Medicines Agency does not permit the sale of any OTC codeine-containing preparations (van Hout et al., 2014).

2.3.5 United Kingdom (UK)

The UK are still fairly lenient when it comes to OTC codeine sales. A dose of 8mg codeine per 500mg of paracetamol as well as 12.8mg of codeine per 500mg of aspirin can be sold OTC under the direct supervision of a pharmacist. Patients are limited to one pack of 32 tablets only. The regulatory authority allows for the display and advertising of the product to the consumer at the point of sale (van Hout et al., 2014).

2.3.6 Ireland

The laws on codeine in Ireland are similar to those in place in the UK; however, in Ireland the advertising and display of the product to the customer at the point of sale is not permitted (van Hout et al., 2014).

2.3.7 The United States of America (USA)

Codeine regulations vary amongst the different states in the USA. Generally, the dose is limited to 10mg per 5ml or 10mg per 1000mg in combination preparations to qualify for OTC sale (van Hout et al., 2014).

Despite the evidence of abuse and misuse of these products, in most parts of the world there is still a lot of resistance from the pharmaceutical industry to restrict codeine availability. Countries such as France, Ireland, Netherlands and Denmark amongst others, still allow the OTC sale of codeine-containing substances. In Denmark, codeine products can be sold in supermarkets and do not need to be sold under the supervision

of a pharmacist. Restrictions however, are placed on the age of the consumer as well as the pack size which are packs that do not contain more than ten tablets (Foley, 2015).

2.3.8 South Africa

In South Africa, ways of tracking, recording and preventing misuse and abuse have been introduced but none have proven successful thus far. In attempts to control abuse, pharmacists may rely on memory or noting of repeat offenders or inserting patient data on site. This remains a futile exercise (Le Roux, 2013), for the most part, as it does not prevent patients from obtaining their fix from different pharmacies within the country as their registers are not centralised in any way.

Due to the ongoing misuse, abuse and dependence of codeine as well as the lack of adherence to the control measures in place, the MCC in South Africa have taken action that align national protocols with some international regulations. This is done by reducing the maximum quantity of codeine per dosage unit in schedule 2 (s2) OTC preparations from 20mg to 10mg. The MCC have limited the maximum daily dose to 80mg for a maximum treatment period of five days for oral solid preparations, reduced the maximum quantity of codeine per 5ml dosage unit from 20mg to 10mg, and limited the maximum daily dose to 80mg and maximum pack size to 100ml for oral liquid preparations (MCC, 2014). The sale of these items must be recorded in the s2 register (Carney et al., 2016).

2.4 The effect of codeine in pain management

Currently in South Africa, for codeine phosphate to be available as a s2 drug and therefore allowed to be purchased without a prescription, it must form part of combination preparations along with more therapeutically active substances in an adult dose unit of 20mg or less; or in doses of 20mg or less per 5ml if available in liquid oral preparations. However, according to the SAMF, a 30mg to 60mg dose taken every four to six hours is needed for an adult to experience the continuous analgesic effect of codeine (Rossiter, 2014). The lack of controlled evidence on doses 20mg or less for the treatment of analgesia raises concerns for the potential of misuse and abuse (Bjune et al., 1996).

There is a lack of evidence from well-controlled clinical trials and therefore treatment decisions for the use of codeine analgesics in chronic non-malignant pain are primarily based on survey data (Arkinstall et al., 1995). There is also a lack of evidence of a significant clinical analgesic advantage of adding codeine in low doses in OTC products (van Hout & Norman, 2015). However, codeine is combined in low doses with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or paracetamol preparations which are available without a prescription for the treatment of pain. According to Derry et al. (2010), codeine does not compare favourably to the above-mentioned alternatives, but is more clinically efficient when combined with paracetamol.

Paracetamol and codeine combination (PC) preparations appear to be more effective than paracetamol alone; however, the combination introduces more side effects and should rather be used for acute rather than chronic pain. A double-blind cross-over study performed by McQuay et al. (1989), showed that 20mg of codeine added to 400mg of ibuprofen had a 30% increase in the analgesic effect. Later, a systematic review performed by De Craen et al. (1996), quantified the pain intensity and relief through visual analogue scales. In most studies, 60mg of codeine was administered along with 400mg to 1000mg of paracetamol and showed that adding codeine leads to an increase in analgesic effect of only 5%. This effect was comparable to the difference in the analgesic effect between codeine and placebo.

A meta-analysis of six studies performed by Derry et al. (2013), showed that a combined formulation of codeine (25.6mg to 60mg) and ibuprofen (400mg) given as a single dose has a good analgesic efficacy, but there was limited data to show the efficacy in lower doses and that the combination is more effective than either drug alone.

Another study showed that codeine in a dose of 125mg, when added to a sub therapeutic dose of imipramine, blocked a mechanism of neuropathic pain called temporal pain summation (Enggaard et al., 2001). This demonstrates the ability of codeine to inhibit this type of pain when combined with imipramine in high doses.

The analgesic efficacy of codeine at higher doses remains favourable and is widely used postoperatively in such doses to treat pain. In a study performed by Bjune et al. (1996) to investigate the effect of codeine added to a dose of 800mg of paracetamol compared to that of 1000mg of paracetamol without codeine given after a caesarean section, confirmed that there is an additive analgesic effect of codeine at 60mg. Doses above 60mg however, have no added efficacy as the drug has a ceiling effect at 240mg per day (Campbell, 2006).

Results extracted from a randomised clinical trial comparing the analgesic and anxiolytic efficacy and tolerability of Stilpane® and Tramacet® after third molar extraction in Gauteng, showed that even though Tramacet® (paracetamol and tramadol) and Stilpane® (paracetamol, codeine, meprobamate and caffeine) have distinctive compositions and work differently, they are equal in their analgesic effect and well-tolerated by patients experiencing moderate to severe acute pain (Outhoff et al., 2015).

The dose of tramadol per tablet is about three times that of the dose of codeine present in Stilpane®. The equivalence of their effect could be due to the way meprobamate plays a part in Stilpane's® analgesic effect. Not necessarily because meprobamate is a strong analgesic, but perhaps by the way it enhances the analgesic effect of the other constituents through an unknown mechanism (Outhoff et al., 2015).

Codeine is known as a prodrug and its analgesic effect is largely dependent on its pharmacogenetic effect. The polymorphic nature of codeine's metabolism reduces the safety of codeine used in young children after surgery (Ciszkowski et al., 2009). For infants and young children in particular, the wrong combination can result in toxic levels of morphine even at standard doses of codeine. This can be deadly possibly due to the maturation differences in the blood–brain barrier (MacDonald& MacLeod, 2010). The authors argue that a direct approach is needed in order to prevent such instances: to stop using the prodrug codeine altogether and instead use its active metabolite, morphine. MacDonald and MacLeod (2010) reason that it is more predictable in its effect and it is more cost effective.

This is also true for adults, whereby some patients may lack this genetically polymorphic enzyme cytochrome CYP2D6 (Kirchheiner et al., 2007). These patients would be poor-metabolisers (PMs) of the drug, and therefore there will be little if any concentration of morphine present in the plasma or urine. Contrasting that are those who are classified as ultra-metabolisers (UMs), and this could be due to a duplicated CYP2D6 gene. Codeine UMs often experience a higher analgesic effect and are more prone to its side effects and addiction (Kirchheiner et al., 2007).

Kirchheiner et al. (2007) analysed the pharmacokinetic differences of codeine between a group of UMs carrying the CYP2D6 gene duplication and extensive-metabolisers (EMs) who carry the wild-type allele. This study concluded that UMs resulted in a 1.5 times higher morphine exposure compared to EMs. Eckhardt et al. (1998) studied a randomised placebo-controlled double-blind trial on the analgesic effect of 170mg of oral codeine and 20mg of oral morphine. They found that even though PMs do not experience the analgesic effect of codeine, at least 7% to 10% of patients will experience its side effects.

An analysis done by Williams et al. (2002) investigated the genotype, phenotype and morphine production from codeine in a small group of an urban UK children population undergoing adenotonsillectomy. This study also compared the analgesia from codeine or morphine combined with an anti-inflammatory drug known as diclofenac. Results showed that after the children were administered with 1.5mg per kg of codeine, morphine and its metabolites were not detected in 36% of these patients. More children required rescue analgesia after codeine than morphine at both two and four hours after administration. The study however, did not show a direct relationship between the phenotype and analgesic effect of codeine as the plasma concentrations of morphine were generally very low one hour after codeine administration for patients of all phenotypes, including those who had normal metabolic capability.

If the metabolism of a drug differs or is altered in an individual or population group, the metabolite could leave the body too quickly and would not reach its therapeutic target. It could also stay in the body longer than normal, producing toxic effects (Smith, 2009). The analgesic effect of codeine is believed to be based on its metabolic conversion to morphine by the genetically polymorphic enzyme cytochrome CYP2D6. The variation of this enzyme in the population leaves codeine's analgesic effect unpredictable unless each individual genotype is evaluated, even then the side effect profile is still unclear as the effects of opioids are also dependent on the biotransformation within the brain (Kirchheiner et al., 2007). Smith (2009) suggests that the way forward, when prescribing opioids such as codeine to patients, is to understand opioid metabolism and thereafter be able to recognise the patient characteristics likely to influence opioid metabolism going as far as the introduction of CYP2D6 genetic screening into the hospital setting. Ducharme (1994) suggests that the evaluation of pain should not be based on the impression of the physician but rather by the use of objective pain scales completed by the patient.

2.5 The healthcare perspective on codeine

2.5.1 The perception of medical doctors on codeine use

Most healthcare professionals believe that codeine, when used for its therapeutic indication, is safe. A perception shared by the general public which is influenced primarily by the widespread availability of codeine in many countries (MacDonald & MacLeod, 2010).

The belief in codeine-containing analgesics however, is not limited to the analgesics available OTC as it is also commonly prescribed by doctors in South Africa. South Africa has a large variety of combination analgesic preparations and therefore its availability influences its prescribing patterns. With this, and the rationale that combining a dose of aspirin with codeine produces an additive analgesic effect and has limited side effects compared to doubling either single constituent, combination preparations have become a popular prescribing choice amongst physicians (Beaver, 1984).

Survey results from a study focused on analgesic use in black adult patients attending an urban general practice in South Africa, showed that the analgesic most used by patients at the time of visiting the doctor was Propain Forte® (42.61%), followed by Stilpane® (26.96%) and Stopayne® (10,43%). Stopayne®, as well as its equivalent Stilpane®, at the time of the study consisted of 8mg codeine per 320mg paracetamol dose, and Propain forte® consisted of 10mg codeine per 400mg paracetamol dose. This study also argued that there was a relationship between psychosocial problems and analgesic use (Pillay et al., 2011). Codeine is not the only ingredient in combination preparations like those above, with the potential for misuse and abuse. Meprobamate is a tranquilizer that is used to treat anxiety which could be associated with pain; however, it also has some analgesic properties which contribute toward the analgesic efficacy of Stilpane® (Kanto et al., 1973). The South African MCC proposed to reschedule meprobamate from s5 to s6 in order to improve the monitoring of drug use due to its abuse potential and addictive nature (MCC 2003). The addictive effect is doubled with two potential abuse substances in one analgesic combination preparation such as the commonly prescribed s5 product in South Africa.

Skurtveit et al. (2008), using the Norwegian prescription database, explored the use of codeine analgesics in individual patients in Norway. Approximately 99% of the overall codeine consumption in the country is made up of the combination analgesic preparations. Results showed that many Norwegian patients who were prescribed the combination analgesic preparations containing codeine, were also prescribed other potential substances of abuse (Skurtveit et al., 2008).

A cross-sectional study involving open and close-ended questionnaires designed to determine prescriber perceptions on codeine-containing medication use, found that of the 300 participants based in primary care and pain settings, about 40% agreed that they found it difficult to identify problematic use of codeine without being advised by the patient. Participants suggested that the slow or gradual withdrawal of codeine was the preferred method of managing dependence (Foley et al., 2016).

Thorough patient evaluation including the investigation of patient medical history is extremely important before writing a prescription. Patients are usually on medication already, and drug-drug interactions are significant when prescribing analgesics. The polymorphism of codeine as a prodrug makes its effectiveness unstable. It is therefore so imperative for doctors to make informed decisions based on factual evidence when prescribing. As concluded by Radford et al. (2016) it is of the utmost importance to consider an individual's CYP2D6 phenotype when prescribing analgesic prodrugs such as codeine-containing preparations to manage persistent pain.

2.5.2 Pharmacist perception of codeine use

Being a pharmacist is not merely the dispensing of prescribed medications; pharmacy is a multidisciplinary profession and has over the years become very patient-centred. In a paper done on the role of pharmacists in developing countries by Azhar et al. (2009), it was concluded that even though pharmacists play a vital role in the healthcare sector, their role was being underutilised. The main reason for this was that there was a lack of communication between the pharmacist and the public.

A cross-sectional study also done in Pakistan by Azhar et al. (2011) compared the medication counselling and dispensing practices at community pharmacies in different cities. The study focused on the process of prescription handling at community pharmacies in terms of patient dispenser interaction, prescription validation, and medication counselling. A comparison of practices was also made between pharmacists, pharmacist assistants and pharmacy salesmen (with no medicinal education). Results showed that no counselling at all was given to the patient by the dispenser in 52.7% of cases and complete counselling was provided in only 3.1% of the cases. The study found that there was no significant difference in the practice between the different dispensers such as the pharmacists, pharmacist assistants and salesmen.

Further investigation into the literature revealed studies based on pharmacy perception including a questionnaire given to the pharmacist and patient by Oshima et al. (2016). The study was performed in order to compare patient and pharmacist perception on the role of pharmacists as an advisor on drug therapy. Questions were based on the pharmacist's interaction with the patient and involved finding out whether patients were made to feel comfortable, if each party was properly understood, and whether or not the pharmacist protected the patient from the adverse effects of the dispensed medication.

Results showed a discrepancy between the perception of the pharmacist and of the patient regarding the role of the pharmacist in understanding the effects of drugs given to patients, the health changes caused by the drugs, as well as protecting patients from the side effects of drugs. Pharmacists issued a high rating, whilst patients gave a lower rating for these three aspects (Oshima et al., 2016).

Another study focused on the competence standard of community pharmacists in monitoring adverse drug reactions, adherence to pharmacy regulations, and the extent that pharmacists engage in patient counselling. The results of this study showed a need for the improvement of pharmaceutical care within that sector (Al-Hassan, 2011).

Wazaify et al. (2005), through their study of societal perspectives on OTC medicines in Ireland, found that patients were usually aware of the abuse potential of codeine. This, according to Wazaify et al. (2005), signifies the need for pharmacists to take the initiative and be more pro-active when managing inappropriate OTC drug use.

In Australia, codeine-containing analgesics were classed as a s2 drug and therefore readily available OTC; however, in the year 2010 combination analgesics containing codeine were up-scheduled to s3. A study done by Hamer et al. (2014) involved a qualitative investigation on the impact of the up-scheduling of these medications on community pharmacy practice by doing semi-structured interviews with eleven different community pharmacists in an area. The findings showed a change of the role of the pharmacist including an increased workload due to an increased involvement in sales and sometimes even experiencing some resentment from purchasers due to this (Hamer et al., 2014). Participants mentioned that they were more aware of codeine

misuse and abuse due to observing an increase in requests of these products. Some were able to intervene in cases of misuse; however, these participants were unsure of how to intervene and where to refer dependent people for help. All participants mentioned that they referred the patient to a doctor if they suspected over-use.

Participants also mentioned that purchasers felt judged having to justify their therapeutic need and participants found it difficult within a small amount of time to obtain and validate a therapeutic need. This study also highlighted a need for more effective ways of monitoring and assisting codeine-dependent people, such as increased partnerships with doctors (Hamer et al., 2014).

A Northern Ireland study based on the factors that influence the treatment decisions of pharmacists when dispensing OTC medication included, to a large extent, patient choice as long as the product was deemed safe by the pharmacist. Pharmacists also admitted that they seldom considered evidence on the drug's effectiveness when dispensing the OTC product (Hanna & Hughes, 2010).

The most recent study was based on pharmacist perception of the management of OTC and prescription codeine misuse in Ireland, the UK and South Africa. Their method involved focus groups with a few community pharmacists in each country and discussed the general experience of being a community pharmacist, monitoring codeine-containing medications, customer support in relation to this, relationships with other healthcare professionals, and training needs amongst others (Carney et al., 2016).

Carney et al. (2016) found that the response of the pharmacist in each area was influenced by the regulations within that area. Pharmacists found it difficult to intervene when customer and commercial demand was so high and when prescribers issue pain medication without considering the effects on the patient holistically. They also found difficulties in effectively identifying customers that have a problem with codeine misuse and abuse. Patient access to different prescribers and dispensers was a large issue, as well as public awareness of the safety of codeine. The study highlighted the need to improve current tactics to regulate the sale of codeine in each of these countries.

One limitation of this purely qualitative study however, was that the cross comparison of pharmacist views in each of these countries were based on the focus group session conducted on a small number of pharmacists in each country and could not generalise the opinions of the pharmacists in each of these countries (Carney et al., 2016).

2.6 Conclusion

The misuse of codeine in South Africa is a result of the widespread availability of the drug which has led to mistaken beliefs around the safety of codeine. This has led to over self-medicating, dispensing, and even the prescribing of codeine for the treatment of pain. Socio-economic factors, chronic emotional or physical pain, social influence, peer pressure and the influential role of the media have led to the abuse of codeine. Peltzer et al. (2010) mentioned the correlation between the urbanisation of areas and drug abuse.

The abuse liability of prescription as well as OTC medications places a huge burden on the general well-being and health of the population as well as the countries healthcare system. The cost of restrictions that need to be put in place as a result have both social and economic implications.

There are too many evidence gaps in controlled clinical studies as well as a lack of evidence-based medicine to support the dose of codeine currently available in combination OTC products or on further reduced doses. Codeine used for the treatment of pain remains favourable in doses of 30mg to 60mg, and according to some studies, enhance the effect of paracetamol. This is opposed by the systematic review results found by De Craen et al. (1996), who argued that adding a dose of 60mg to paracetamol had a similar effect to the placebo.

Some studies suggest the phasing out of codeine, especially in young children, as it has unpredictability in its therapeutic as well as toxic effects. In South Africa, OTC products containing codeine are already restricted to lower doses and some cough preparations have a warning label preventing its use in children under the age of six years.

The regulation of codeine-containing products varies across countries. Furthermore, within countries there exists contradictory opinions on its use and abuse potential (Bergin et al., 2015; van Hout et al.,2014).

Pharmacists are key role players in the prevention and mitigation of the impact of prescription drug abuse and misuse (Hagemeier et al., 2014). Pharmacists are in essence the gatekeepers of these medications. Pharmacists have a final say on whether the patient receives the medication or not, or whether dispensing a prescription order will serve a legitimate medical purpose and be in the usual course of professional practice (Joranson & Gilson, 2001). However, available studies suggest contradictory views between patients and pharmacists on the responsibility of the pharmacist (Oshima et al., 2016).

There is also a need for an improvement in the monitoring of adverse drug reactions, adherence to pharmacy regulations, and effective patient counselling and intervention methods (Al Hassan, 2011; Hamer et al., 2014).

There is not much supporting literature on pharmacist perceptions (Hagemeier et al., 2014), and even though some later studies have investigated pharmacist perception around codeine use in other countries, there are still no studies, to my knowledge, that are based on pharmacist perception of codeine use in South Africa. Codeine is widely available in South Africa and it is dispensed by pharmacists all around the country. Pharmacist perception of codeine use in OTC analgesic medicines, as well as the factors that influence their treatment decisions related to pain, need to be explored further.

3. METHODOLOGY

3.1 Study Aim and Objectives

3.1.1 Aim

The aim of this study is to investigate the utilisation of codeine-containing analgesic OTC preparations in Gauteng's private healthcare market.

3.1.2 Objectives

- To analyse the patterns of utilisation of codeine-containing products in Gauteng's private healthcare market using a national ordering database.
- To gain an understanding of pharmacist and qualified post-basic pharmacist assistant (QPBPA) perceptions of codeine for analgesia by conducting surveys and semi-structured in-depth-interviews.

3.2 Type of study

This was a mixed-method study that incorporated both quantitative and qualitative type research methods. The qualitative aspect serves to provide additional information for a more detailed understanding of the quantitative data (Sutton & Austin, 2015).

3.3 The construction and implementation of the data collection procedures

This study involved three different methods of data retrieval involving three different data sets. The first, purely quantitative aspect was the retrospective data-captured analysis of codeine-containing product utilisation from a national ordering database *Orderwise.* The second set of information was retrieved by handing out mixed quantitative/qualitative surveys to community pharmacists in Gauteng. Lastly, the purely qualitative data was obtained by doing semi-structured in-depth-interviews (IDIs) with community pharmacists in Gauteng.

3.3.1 The pattern of utilisation study (PUS): using the *Orderwise* database

Retrospective data was received for a six-month period starting from January 2016 to June 2016. Data was extracted from an electronic procurement system database called *Orderwise. Orderwise* is a system which connects manufacturers, wholesalers and retail pharmacies, and allowed for an all-inclusive data record involving the different pharmacy sectors. To my knowledge, it is the only online ordering system in South Africa that allows any pharmacy to order from any supplier in the country. The data retrieved was specifically focused on the pattern of utilisation of codeine-containing products in the Gauteng province. Data was extracted based on the product name and schedule number. Data included month of delivery, price, pack-size, quantity ordered, quantity delivered, as well as the pharmacy of delivery. The relevant information was extracted from the raw data and was imported into Microsoft Excel where it was organised (Appendix F). The data was then transferred to *SAS Enterprise 7.1 Software* for final analysis.

3.3.2 The survey: mixed quantitative-qualitative

The mixed quantitative-qualitative surveys used for this study based on pharmacist and QPBPA perceptions on codeine used for pain management was designed on an online survey platform called *Typeform.*

The questionnaire was divided into two sections (Section A and Section B) and included both open and closed-ended questions.

Section A included both open and close-ended questions based on pharmacist and QPBPA perceptions of general pain management. Questions in this section were developed to help evaluate the participant's pain related treatment preferences. It also included open-ended scenario-based questions to ensure that the respondents were free to answer their first preference of medication without being influenced to choose a specific type of medication mentioned.

Section B consisted of questions relating specifically to the utilisation of codeine for pain management. Majority of the questions were close-ended using the Likert scale format, and related statements could be ranked according to level of agreement on the scale. Questions were based on codeine utilisation, misuse and abuse. Questions relating to codeine-content, dose and side effects were designed to identify any gaps in knowledge.

3.3.2.1 Distribution of surveys

The link to the *Typeform* survey as well as a soft copy (for slow internet connections) were first distributed to a random sample of over 513 community pharmacists and qualified QPBPAs around Gauteng via email. However, the response rate was very low after the first batch of emails as less than 20 responses (<3.8%) were received. The ideal response sample size of 385 was due to the assumption of a 75% response rate. In order to improve the response rate, the pharmacists were given a telephonic reminder and the emails were sent again. The response rate improved, however not adequately enough. Hard copy surveys were then delivered personally to pharmacies in Gauteng. The surveys were distributed evenly between each region in Gauteng as with the emails on the first and second attempt. Therefore, a stratified sampling technique was employed. The Gauteng regions included the north, south, east and west of Johannesburg, as well as the Johannesburg CBD, Pretoria and Vereeniging. The hand delivered surveys were then collected a minimum of three hours after it was dropped off, taking into account the busy nature of the pharmacy and any interruptions occurring due to that. The study population included pharmacists as well as QPBPAs as they are heavily involved in the sales of OTC products and therefore their input contributed to the research as well.

3.3.3 In-Depth Interviews (IDIs): Qualitative

In support of the data retrieved from the questionnaires, IDIs were conducted with pharmacists based in the Gauteng area in order to further explore the reasons for their treatment decisions. The qualitative data, themed and coded using the thematic analysis approach, assisted in identifying and filling any quantitative evidence gaps for a well-rounded collection of information for analyses (Turner, 2010).

The interview designed was semi-structured and during every interview, the researcher made use of the interview guide which consisted of approximately twelve open-ended questions and on average took 15 minutes to 30 minutes per interview. Encompassing both open-ended experience-based questions as well as theoretically driven questions, the semi-structured design of the interview allowed for a variation of responses by participants (Galletta, 2013). Every interview was recorded using an Android recorder. All interviews took place in a quiet area within the pharmacy with just the interviewer and participant present. Pharmacists were contacted telephonically and if they agreed to take part, an interview time was scheduled according to the availability of both parties. The IDIs were restricted to qualified pharmacists.

The interview session began with a short introduction of this investigation and an overview of the confidentiality of the interview. Participants were then asked to sign the recording consent form (Appendix E). This preceded background questions based on pharmacist experience, qualification and location. In closing the interviews, participants were asked if they would like to talk about anything else regarding the topic and were thereafter thanked for their participation.

The guide included nine open-ended questions which were used to obtain participants' views and beliefs regarding pain treatment, codeine used for pain, and codeine use and abuse in their community (Appendix B). To allow for a detailed and in-depth response on the scenario-based questions on pain treatment within the interview time frame, fewer scenarios were discussed as compared to those asked in the questionnaire (Appendix A).

3.4 Sampling and selection of participants

3.4.1 The PUS

Orderwise data included information on all s0-s2 orders during a six-month period. Specifically, this included all the pharmacies who made use of the *Orderwise* ordering system to order s0-s2 items during a six-month period from 1 January 2016 to 30 June 2016. The six-month period started at mid-summer and ended during mid-winter and therefore could take into account the seasonal influences on medication orders.

Pharmacies who use *Orderwise* use them throughout the year and therefore this was a fair representation of their usual pharmacy clientele.

3.4.2 The questionnaire participants

The questionnaires were piloted on a group of ten pharmacists whose responses were not included in the study. Clarity and structure corrections were made and retested on the same group. A random sample of 513 Gauteng based community pharmacists and QPBPAs were chosen for the study using a directory obtained from the South African Pharmacy Council (SAPC). The sample size was calculated using the sample size calculator taking into account the number of pharmacists based in Gauteng as well as a confidence interval of 95%.

3.4.3 The IDIs

IDIs were piloted on two pharmacists in the Johannesburg CBD area and the findings from those interviews were not included in the study. The recordings for the pilot were transcribed to identify and remove any ambiguities in the questions and were also used as test rounds to ensure that correct interview techniques were used. The interviews were conducted on a sample size of eight pharmacists based around the Gauteng area in an attempt to mirror the local distribution of the surveys. The IDIs were conducted as a means of possibly enhancing the data received from the surveys (the themes developed were very similar amongst the different interviews) and therefore stopped at the eighth interview. Using a method of purposeful sampling in order to include an equal number of newly qualified pharmacists (<1 year to six years of experience), as well as experienced qualified pharmacists (seven years to more than 30 years of experience) working in the private sector in order to take their work experience into account.

3.5 Data analysis

3.5.1 PUS data analysis

Retrospective sales data from the *Orderwise* database from January 2016 to June 2016 were extracted and transferred to a Microsoft Excel spreadsheet.

The raw data supplied by *Orderwise* included the following variables:

- Product name;
- The pharmacy who ordered that product;
- The quantity of the product ordered by the pharmacy;
- The supplier who would deliver the product to the pharmacy;
- The quantity delivered to the pharmacy;
- The current price per product sold; and
- The month in which the product was sold.

The raw data had to be sorted and each order could be further classified according to the following (Appendix A):

- Codeine-content of product;
- Dosage form;
- Treatment indication;
- Medication composition/classification; and
- Province.

The codeine-content column was obtained by using the monthly index of medical specialties (MIMS) as well as the SAMF to determine whether or not each product contained codeine. The codeine-containing medicines were then further classified according to their codeine-content per tablet/capsule in solid dosage forms or in the case of mixtures, the codeine-content per 5ml was used. This could then be used to determine the total codeine-content per product ordered. The *South African Medical Directory* as well as *Google Maps* was used to determine each ordering pharmacy's provincial location by using the customer name and supplier information from the *Orderwise* data.

The organised data was then transferred to the *SAS Enterprise 7.1 Software* for descriptive statistical analysis in order to gather geographical information regarding the areas of most and least codeine utilisation as well as the sale trends for popular codeine-containing OTC products.

3.5.2 The questionnaire: data analysis

The close-ended questions in the questionnaire was originally designed in the 5-level Likert scale format; however, upon analysis this had to be reduced to the 3-level Likert to receive optimum response frequencies. This meant that answers which were '*strongly agree'* and '*agree'* had to be combined as '*agree'*, the same was done with '*strongly disagree'* and *'disagree'*. The neutral response '*Not sure'* remained the same. This should not result in any significant reduction in the reliability or validity of the data (Jacoby & Matell, 1971).

The data from the *Typeform* questionnaires were downloaded directly from the online data capture page to *SAS Enterprise 7.1 Software*. Data-captured in paper format were entered manually and combined with the data captured online (Foley et al., 2016). Chi-square tests were used to examine and compare categorical variables. The questionnaire was designed to illicit information based on the following broad categories: demographics of participant pharmacist and QPBPA; OTC pain related treatment preferences; knowledge relating to codeine use; as well as perception and awareness of codeine dependence, misuse and abuse.

3.5.3 The IDI: data analysis

Each interview was transcribed verbatim. Upon completion of the interviews, emerging themes were gathered from the interviews via thematic analysis including open and axial coding by hand. To ensure validity, half of the transcripts were coded independently by another researcher. Member checking was performed by sending four of the interviews along with the coding sheet to four of the respective interviewees, they returned them with no amendments. This ensured that the developed themes were based on their intent meaning which was another way of verifying plausibility (Carlson, 2010). Themes were divided into two broad categories: general pain management and management of OTC codeine use. The three themes that emerged from the data were OTC treatment of non-complicated pain, codeine used for the treatment of pain, and codeine misuse and abuse. The twelve sub-themes developed from the data can be seen in Table 4.15.

3.6 Ethical clearance

Ethical clearance for the questionnaires, IDIs and for the collection of existing data on the utilisation of codeine from the *Orderwise* database was approved by the Medical Human Research ethics committee of the University of the Witwatersrand. The information acquired from participants will remain completely anonymous and did not require participants to disclose any personal information. All questionnaires were the same and used for data analysis equally. The ethical clearance number is M160317.

4. RESULTS

4.1 OTC codeine-containing product trends

4.1.1 National overview

For purposes of this study pain medication preparations were classified according to its general composition (Appendix G).

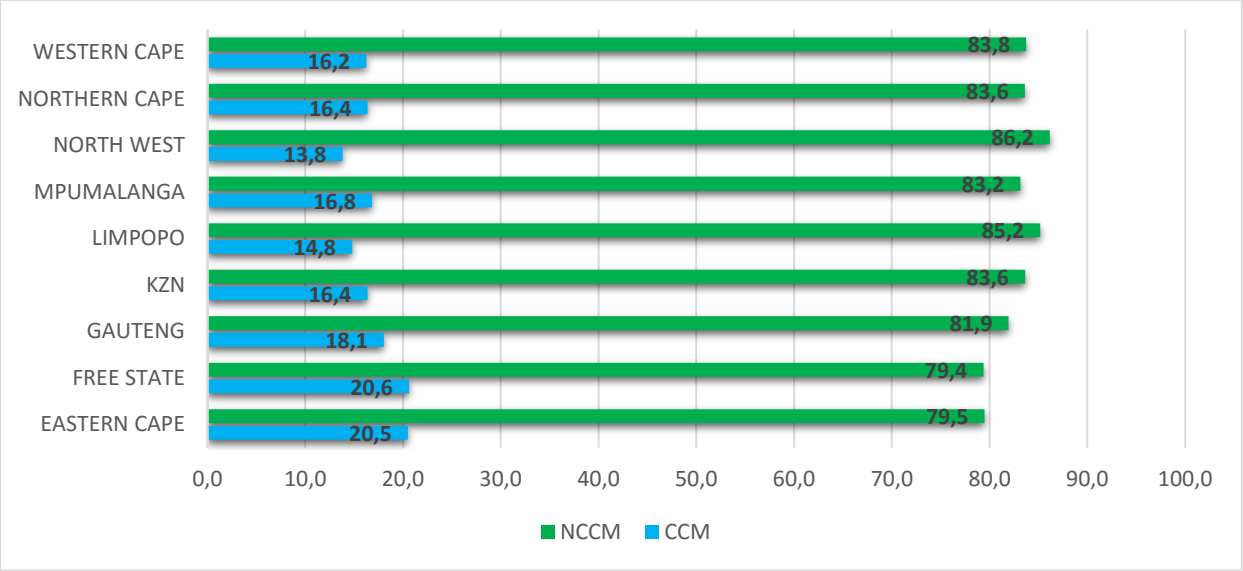

Figure 4.1: Percent distribution of the total OTC products sold within each province between 1 January 2016 to 30 June 2016.

Figure 4.1 above shows the CCM and NCCM percent distribution of the total OTC product deliveries within each province over the study period 1 January 2016 to 30 June 2016. The Free State and Eastern Cape have the largest distribution of CCM deliveries of their total OTC product deliveries with percentages of 20.6% and 20.5% respectively. Gauteng has the second largest CCM distribution of 18%. The North West and Limpopo provinces have the lowest CCM distribution with percentages of 13.8% and 14.8% respectively. Percent distribution of each provinces' total OTC sales allows the data not to be largely influenced by the population size of each province.

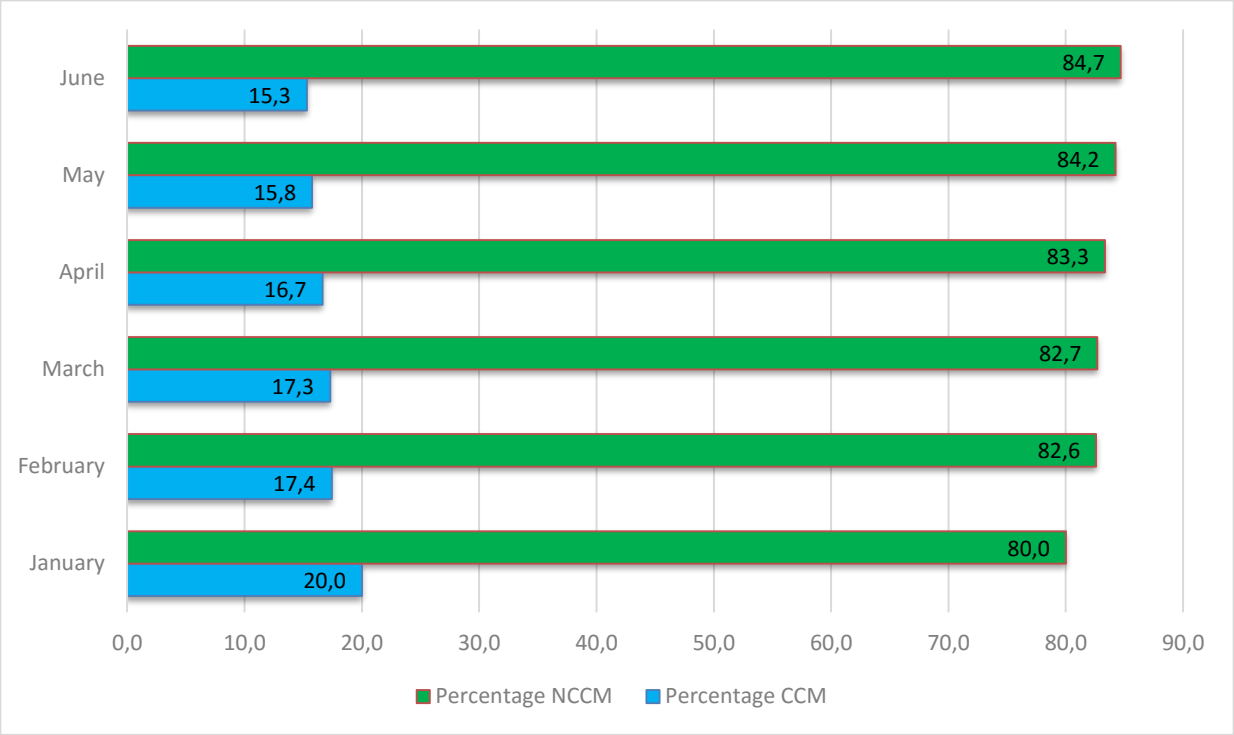

Figure 4.2: The percent distribution of CCM and NCCM deliveries per month from 1 January 2016 to 30 June 2016.

Figure 4.2 above shows a relatively consistent monthly distribution. January however, has the highest proportion of CCM sale deliveries. In January, CCM accounted for 20% of the total deliveries. There was a decrease in the CCM sales in May and June where the CCM percent delivered was around 15%. The national average monthly percent distribution of codeine-containing products is 17% of the total OTC medication deliveries. Figure H.1 shown in Appendix H, indicates that out of all the types of OTC pain medication products delivered, 28% of the product types delivered are codeine-containing and 72% of product types delivered do not contain codeine.

4.1.2 Gauteng analysis

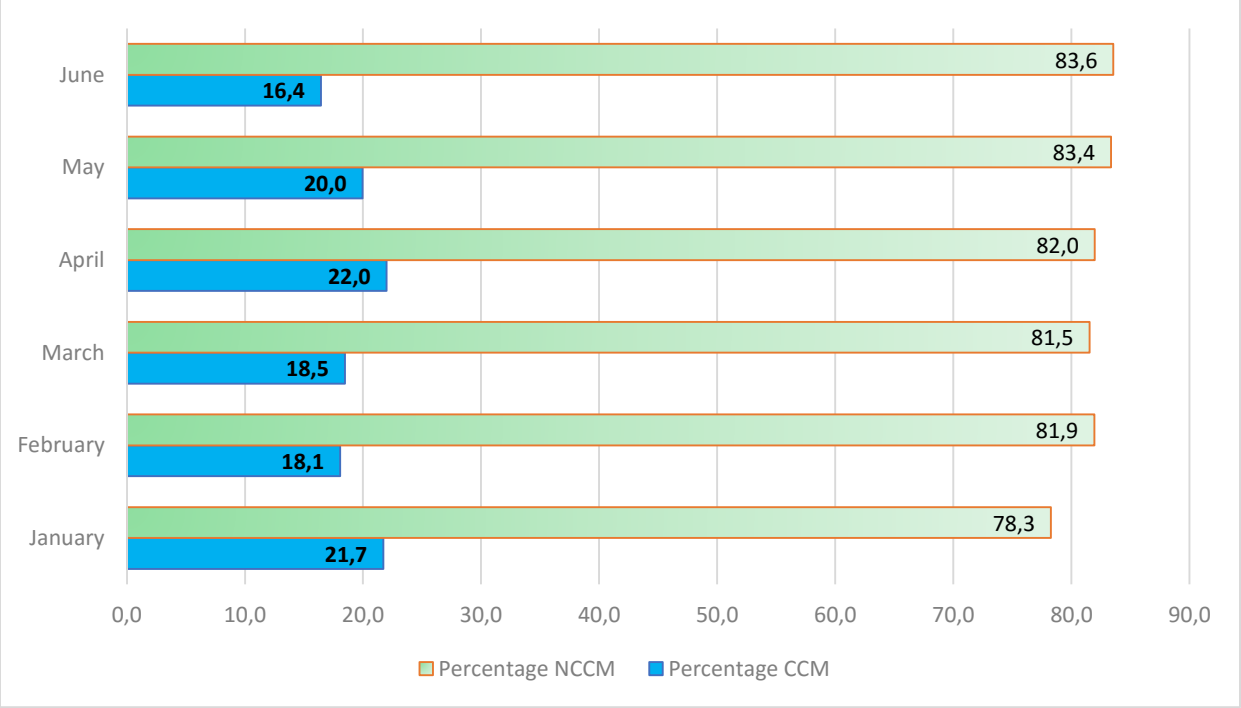

Figure 4.3: The percent distribution of CCM and NCCM deliveries per month from 1 January 2016 to 30 June 2016.

Figure 4.3, as with the nationwide results, indicates a consistent total sales distribution between the six months. The average monthly percent distribution of codeine-containing products was 19% of the total OTC medication deliveries. The highest proportion of CCM deliveries also happened in the beginning of the year, where CCM in January accounted for approximately 22% of the total OTC deliveries. The CCM sales decreased by almost 4% from January to February. The CCM sales distribution decreased to 16.4% in June.

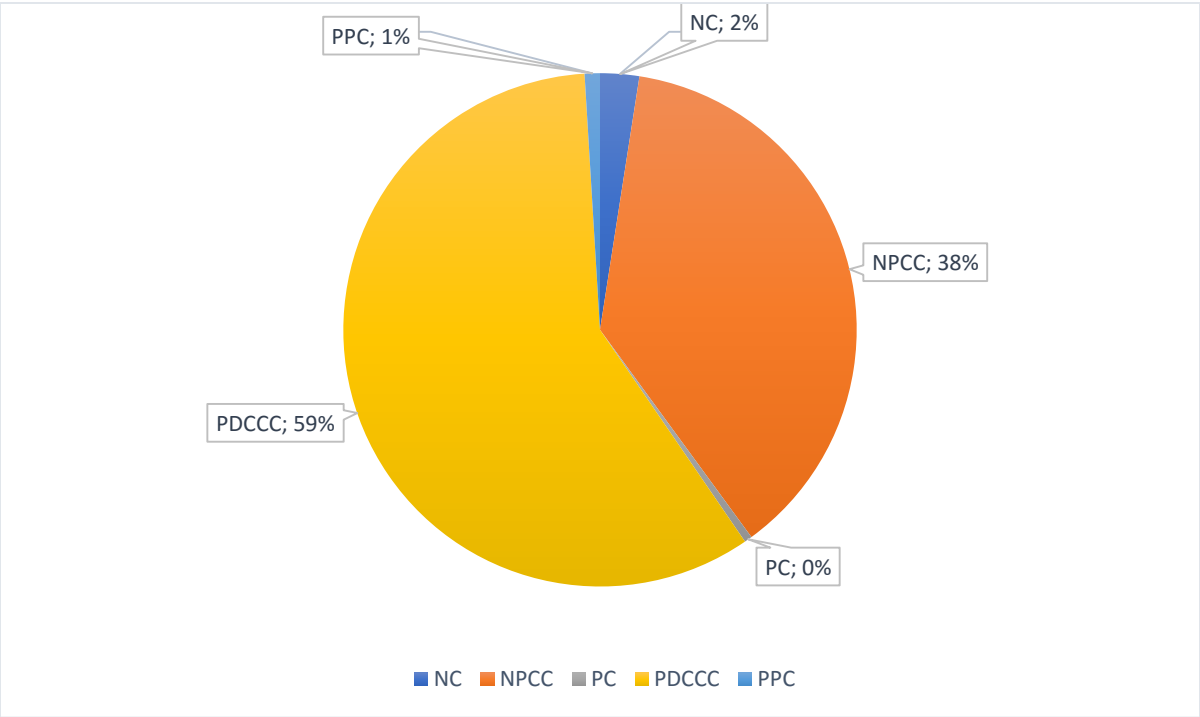

Figure 4.4: The medication class distribution of the total CCPM deliveries in Gauteng for the period 1 January 2016 to 30 June 2016.

Figure 4.4 indicates that the PDCCC class accounts for 59% of the total CCPM deliveries in Gauteng. The second highest class distributed in Gauteng are products that fall within the NPCC class (38%). The PC class still contributes least to CCPM deliveries (0.96%).

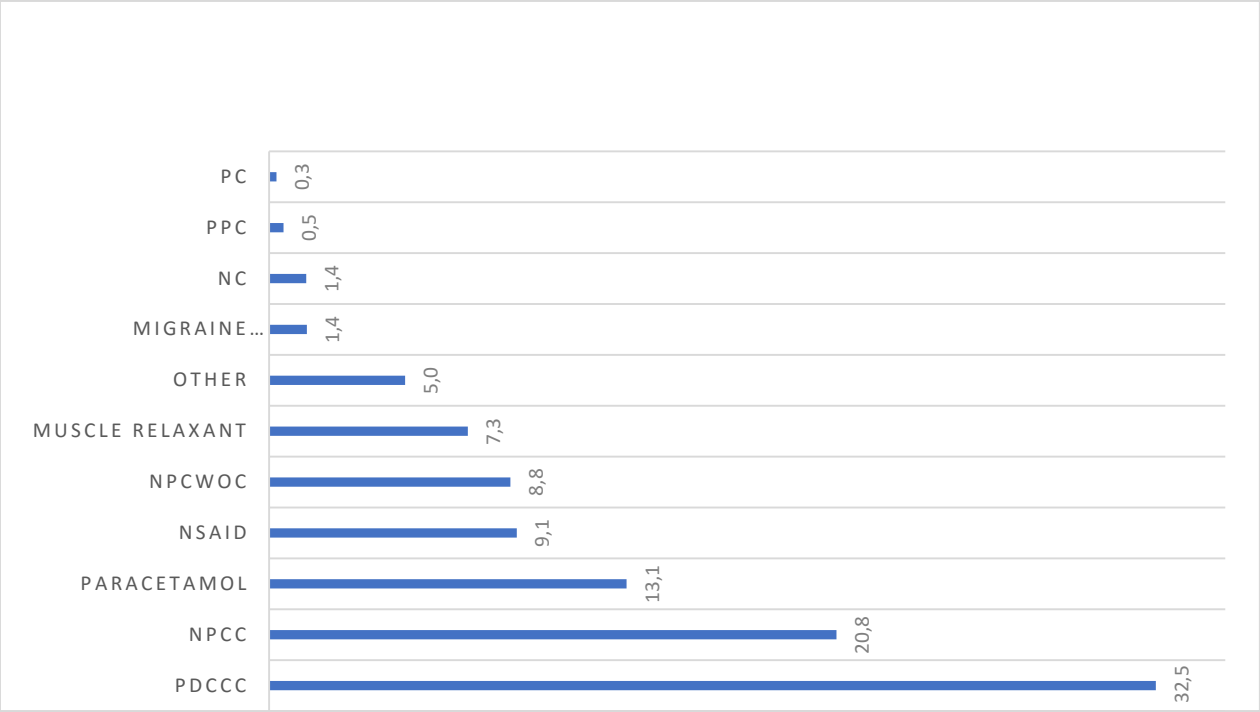

Figure 4.5: The medication class distribution of the total analgesic OTC medications delivered in Gauteng from the 1 January 2016 to 30 June 2016.

Figure 4.5 indicates the medication class distribution of all the OTC analgesic products (CCM and NCCM) sold to pharmacies within Gauteng. PDCCC is still the largest distributed OTC analgesic class with 32.5%, followed by NPCC of 20.8%. The NC (1.4%), PPC (0.5%) and PC class (0.3%) contribute the least to the OTC pain medication sales.

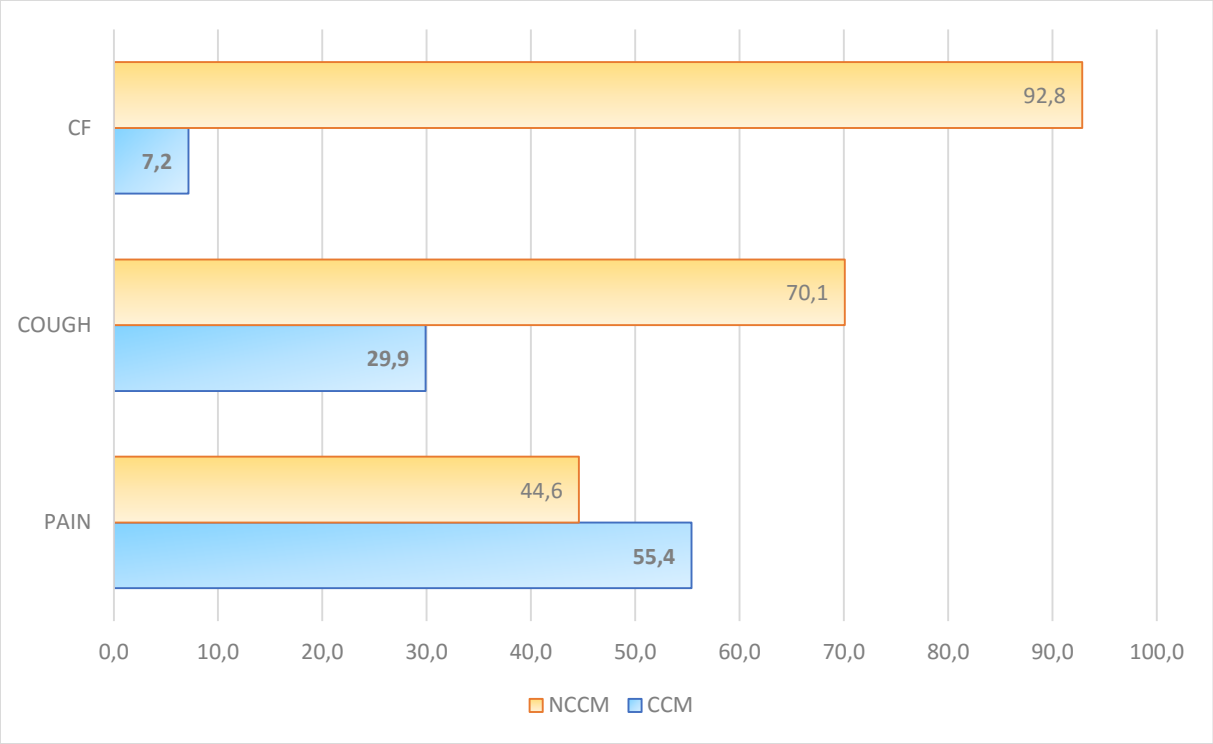

Figure 4.6: Percent distribution of the total OTC products delivered in Gauteng per treatment indication for the period 1 January 2016 to 30 June 2016.

Figure 4.6 above indicates that codeine-containing analgesic products accounts for majority of analgesic OTC sales (55.4%). Codeine-containing cough medications account for 29.9% of the total cough product sales in Gauteng. Only 7.2% of the cold and flu (CF) products sold are codeine-containing.

Table 4.1: CCM delivered percent frequency distributed according to its treatment indication.

Treatment indication	CCM delivered frequency (n)	Percent (%)
Cold and Flu (CF)	80375	6.5%
Cough	326627	26.3%
Pain	834587	67.2%

Table 4.1 above shows that the majority of codeine-containing products, sold to pharmacies in Gauteng using the *Orderwise* system, are indicated for the treatment of pain (67.2%).

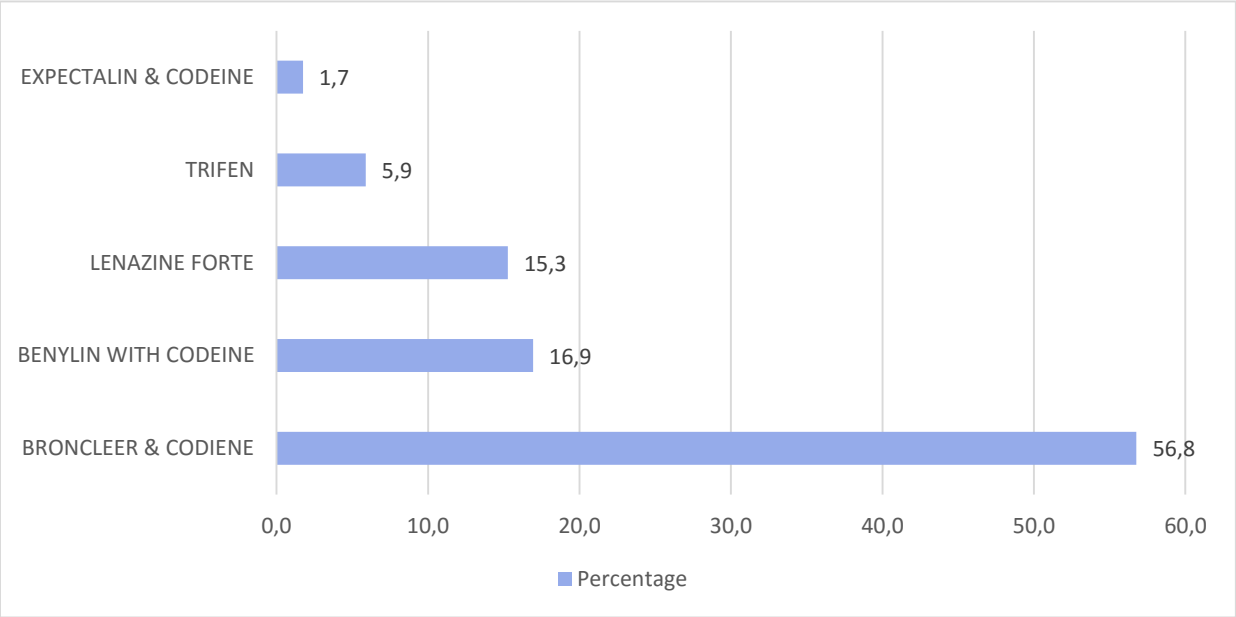

Figure 4.7: Codeine-containing cough products delivered in Gauteng with the top five highest percent frequency for the period 1 January 2016 to 30 June 2016.

Figure 4.7 above shows that Broncleer & Codeine® make up majority of the OTC cough syrup sales (56.8%). Benylin® with codeine accounts for 16.9% and Expectalin & Codeine® account for the least of the top five products (1.7%). The top five products in the figure above make up 96% of the OTC codeine-containing cough product deliveries in Gauteng.

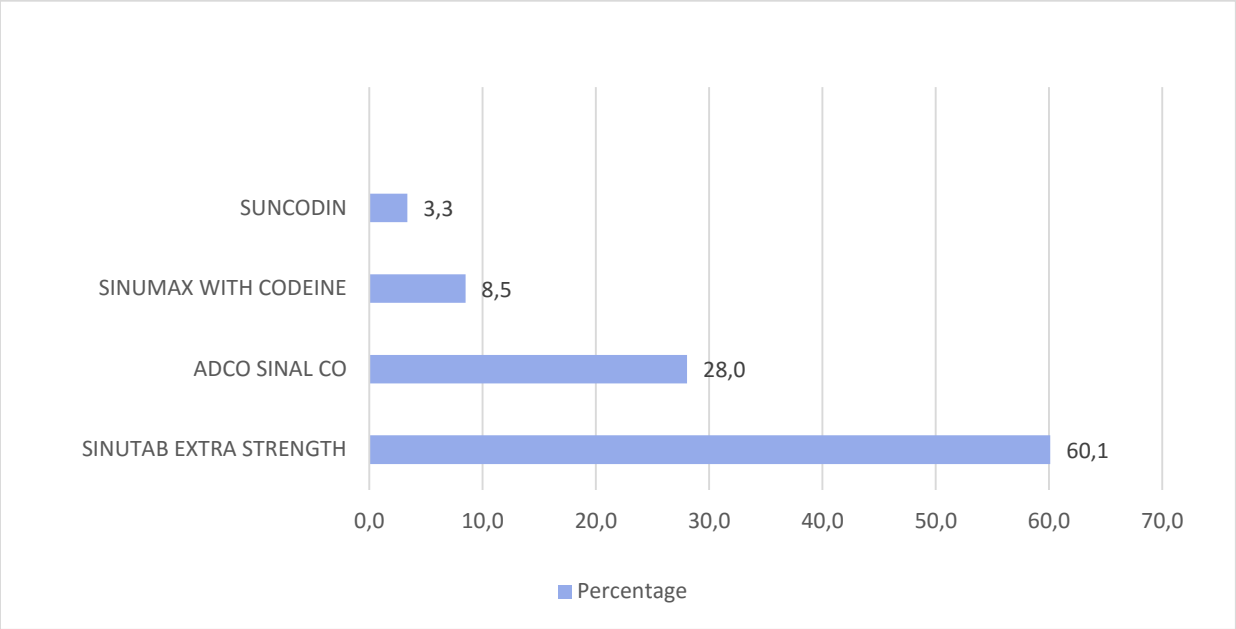

Figure 4.8: Codeine-containing cold and flu products delivered in Gauteng with the top five highest percent frequency for the period 1 January to 30 June 2016.

Figure 4.8 above shows that the product with the highest contribution to codeine-containing cold and flu preparations in Gauteng is Sinutab Extra Strength® (60.1%) which is a combination of codeine, chlorpheniramine maleate, pseudoephedrine and paracetamol. Sinutab Extra Strength®, Adco-sinal co®, and Sinumax with codeine® make up 96.6% of the OTC codeine-containing cold and flu product deliveries using *Orderwise* in Gauteng.

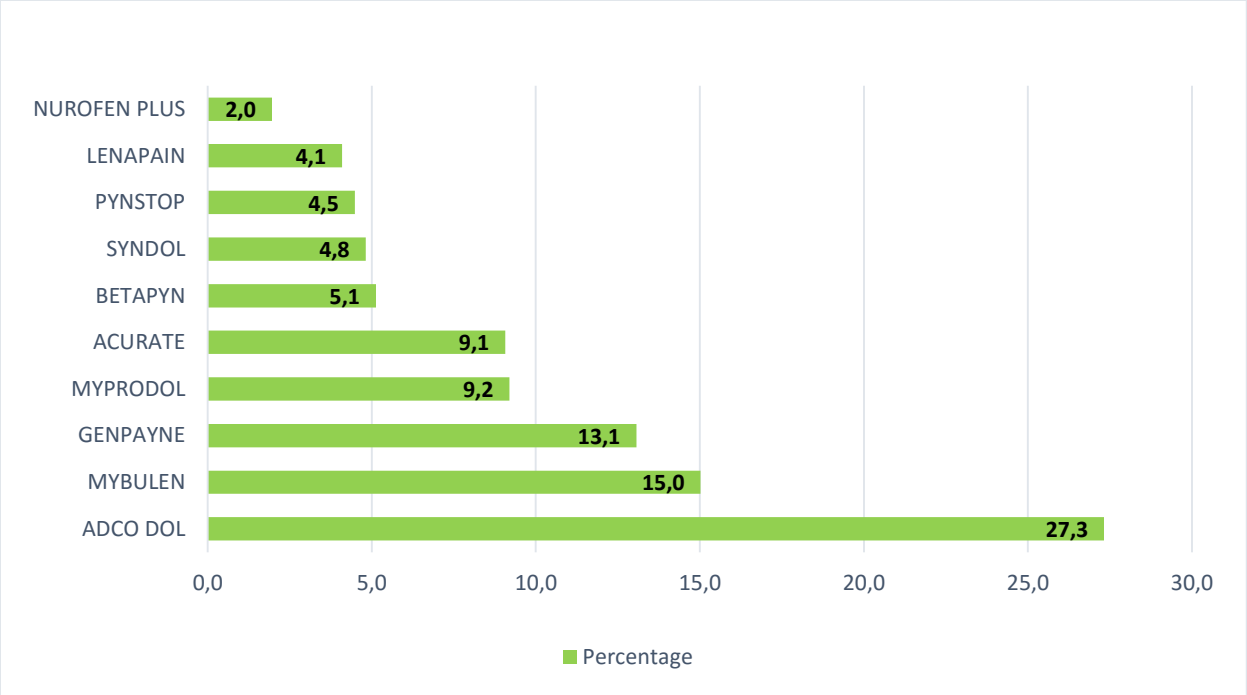

Figure 4.9: CCPM products delivered in Gauteng with the top ten highest percent frequency for the period 1 January 2016 to 30 June 2016.

The products in Figure 4.9 above shows that Adco-dol (27.3%) contributes the most to the total CCPM product deliveries in Gauteng, followed by Mybulen (15%) and Genpayne (13.1%). Approximately 94% of the total OTC CCPM product deliveries for Gauteng are made up by these top ten products.

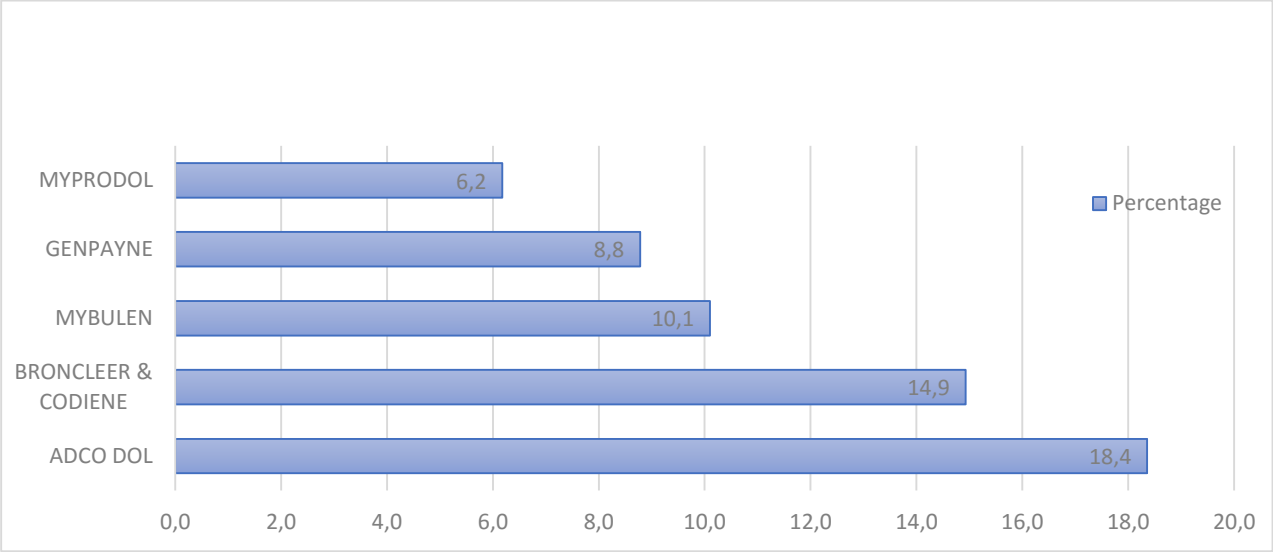

Figure 4.10: Frequency distribution of all OTC-CCM product deliveries in Gauteng for the period 1 January 2016 to 30 June 2016.

Figure 4.10 above indicates that Adco-dol® (18.4%) contributes the most to the overall OTC codeine-containing product sales in Gauteng. Broncleer & Codeine® cough syrup is the second most popular OTC codeine-containing product in Gauteng (14.9%), followed by the therapeutic equivalents Mybulen® (10.1%), Genpayne® (8.8%) and Myprodol® (6.2%).

4.2 Questionnaire results

Table 4.2: Demographic details and information pertaining to profession, location and education.

	Frequency (n)	Percent (%)
Gender		
Male	72	32.88
Female	147	67.12
Age		
<29	88	40.18
30-39	68	31.05
40-49	39	17.81
50-59	16	7.31
60+	8	3.65
Highest graduate qualification		
Masters in Medicine	9	4.55
Masters in Pharmacy	16	8.08
Bachelor of Pharmacy	158	79.8
Doctorate in Pharmacy	5	2.53
Matric	5	2.54
Frequency missing = 26		
Pharmacy role		
Intern Pharmacist	24	11.32
Locum Pharmacist	52	24.53

	Frequency (n)	Percent (%)
Permanent Employee Pharmacist (PEP)	49	23.11
Pharmacy Manager	43	20.28
Pharmacy Owner	5	2.36
QPB Pharmacist assistant (QPBPA)	39	18.4
Frequency missing = 7		
Location		
Johannesburg East	43	19.63
Johannesburg West	29	13.24
Johannesburg North	56	25.57
Johannesburg South	59	26.94
Johannesburg CBD	6	2.74
Vereeniging	5	2.28
Pretoria	21	9.59

The survey based on pharmacist perception of codeine use in OTC pain medication recruited 219 participants of a total 513 pharmacists who were contacted during June 2016 to September 2017 providing a 43% overall response rate. The age of the respondents varied from twenty-three years old to over sixty years old where about 40% of respondents were under twenty-nine years old (n=88) and almost 4% of respondents were over sixty years old (n=8). The Gauteng province was divided into seven regions based on geographical location. Johannesburg was divided into north, south, east and west. Pretoria and Vereeniging were also included as regions. Responses from each region in Johannesburg were spread fairly equally, the responses from Pretoria and Vereeniging were slightly lower.

Locum pharmacists, permanently employed pharmacists (PEP) and pharmacy managers contributed most toward the response rate from all participants, followed by QPBPAs and intern pharmacists, with the fewest responses received from pharmacy owners.

Table 4.3: Basis for general treatment decisions.

Statement	n	%agree	%disagree	%not sure
I base my general treatment decisions on evidence-based medicine	217	93.09	1.84	5.07
I base my general treatment decisions on patient request	214	67.29	21.97	10.75
I base my general treatment decisions on anecdotal evidence	206	53.4	16.5	30.1
I base my general treatment decisions on the marketing of a drug	217	47	46.54	6.4

Table 4.3 above shows the factors likely to influence participant treatment decisions in the pharmacy. The statements are ranked in order of the level of agreement. The highest level of agreement was for the use of evidence-based medicine (93.09%) and second was the influence factor of “patient request” followed by the use of anecdotal evidence (53.4%). The “drug- marketing” medication sales influence seems to divide respondents equally with 47% agreeing and disagreeing, leaving the rest of the responses (6.4%) at “not sure”.

Table 4.4: The drug-marketing effect on treatment decisions per pharmacy role type.

Statement: I base my general treatment decisions on the marketing of a drug				
Pharmacy Role	**%agree**	**%disagree**	**%not sure**	**%total**
QPBPA	73.68	23.68	2.63	100.00
Pharmacy manager	52.38	47.62	0.00	100.00
PEP	44.90	44.90	10.20	100.00
Intern pharmacist	37.50	54.17	8.33	100.00
Locum pharmacist	30.77	57.69	11.54	100.00

Table 4.4 above indicates in detail the percent contribution of each pharmacy role on the agreement level of the drug marketing effect on treatment decisions. Majority of QPBPAs (73.68%) and pharmacy managers (52.38%) base their treatment decisions on the marketing of the drug. Majority of the locum pharmacists (57.69%) however, disagree with the influence of drug-marketing on their treatment decisions. Figure 4.5 below indicates that overall, QPBPAs were most likely of all the respondents to base their decisions on drug-marketing (29%). Pharmacy managers (23%) and PEPs (23%) contributed second most to the agreement with drug-marketing.

Table 4.5: Respondents most likely to be influenced by drug-marketing.

Statement: I base my general treatment decisions on the marketing of a drug			
Pharmacy Role	**%agree**	**%disagree**	**%not sure**
Intern pharmacist	9	13	14
Locum pharmacist	16	30	43
PEP	23	22	36
Pharmacy Manager	23	20	0

Statement: I base my general treatment decisions on the marketing of a drug			
Pharmacy Role	**%agree**	**%disagree**	**%not sure**
Pharmacy Owner	0	5	0
QPBPA	29	9	7
Total	100	100	100
P value= 0.00005 for the interaction between agreement and pharmacy role type			

Table 4.6: Anecdotal evidence influence on treatment decisions per pharmacy role type.

Statement: I base my general treatment decisions on anecdotal evidence				
Pharmacy Role	**%agree**	**%disagree**	**%not sure**	**Total %**
QPBPA	61.76	5.88	32.35	100.00
Permanent pharmacist	47.83	15.22	36.96	100.00
Pharmacy owner	40.00	40.00	20.00	100.00
Pharmacist manager	51.22	19.51	29.27	100.00
Locum pharmacist	57.14	20.41	22.45	100.00
Intern pharmacist	58.33	12.50	29.17	100.00

Table 4.6 above indicates that majority of the QPBPAs (61.76%), locum pharmacists (57.14%), and pharmacy managers (51.22%) agreed to being influenced by anecdotal evidence when recommending treatment.

Table 4.7: Pharmacist and QPBPA awareness of codeine side effects.

Statement	n	%agree	%disagree	%not sure
The side effects of codeine include nausea	212	71.23	13.68	15.09
The side effects of codeine include diarrhoea	214	14.49	78.04	7.48
The side effects of codeine include respiratory depression*	218	77.06	11.01	11.93
The side effects of codeine include increased heart rate	215	35.35	40.47	24.19
The side effects of codeine include indigestion*	215	51.16	18.6	30.23
The side effects of codeine include dizziness*	215	77.21	8.37	14.42
The side effects of codeine include pruritic*	217	39.17	20.74	40.09
The side effects of codeine include Miosis *	213	42.86	12.9	44.24
The benefits of codeine outweigh its side effects when providing symptomatic relief	213	53.05	30.05	16.9

**correct statements*

S/E test results	n	Total Respondent %	Pharmacy Owner %	Pharmacy manager%	Locum Pharmacist%	PEP%	Intern Pharmacist %	QPBPA%
100%	8	3.65	0	0	4.08	4.08	8.33	4.88
80-99%	24	10.96	20	9.52	20.41	6.12	4.17	9.76
60-79%	87	39.73	40	54.76	34.69	34.69	58.33	29.27
50-59%	47	21.46	0	21.43	20.41	22.45	20.83	19.51
<50%	53	24.2	40	14.29	20.41	32.65	8.33	36.59
total	**219**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

P value<0.0001 for the interactions between pharmacy role (Pharmacy managers, Locum pharmacists, PEP, Intern pharmacists and QPBPA) and test results.

As can be seen from Table 4.7 above, many respondents were unsure of all the codeine side effects. More than 30% of respondents answered not sure to 3/7 (42%) of the related statements. The total respondent results for the codeine side effect test indicates that only 3.65% of the respondents knew of all the listed codeine side effects and majority of the respondents (39.73%) scored between 60% to 79% for the test whereas 24.2% responded to less than 50% of the side effect statements correctly.

Majority of the pharmacy managers (54.76%), pharmacy interns (58.33%), locum pharmacists (34.69%), and PEP (34.69%) scored between 60% to 79% for the side effect test whereas majority of the QPBPAs (36.59%) scored less than 50%. The second highest frequency QPBPA score was 60% to 79% (29.27%), closely followed by QPBPAs receiving between 50% to 59% for the test (19.51%).

Table 4.8: Pharmacist and QPBPA perception of the analgesic dose of codeine.

Statement	n	%agree	%disagree	%not sure
NSAIDS				
8-10mg of codeine works best to enhance the analgesic effect of Non- steroidal anti- inflammatory drugs (NSAIDs)	216	81.02	6.94	12.04
10-20mg of codeine works best to enhance the analgesic effect of Non- steroidal anti- inflammatory drugs (NSAIDs)	184	38.04	36.96	25
>20mg of codeine works best to enhance the analgesic effect of Non- steroidal anti- inflammatory drugs (NSAIDs)	191	13.09	57.07	29.84
PARACETAMOL				
8-10mg of codeine works best to enhance the analgesic effect of Paracetamol	209	81.34	6.22	12.44
10-20mg of codeine works best to enhance the analgesic effect of Paracetamol	199	49.25	31.16	19.6
>20mg of codeine works best to enhance the analgesic effect of Paracetamol	191	14.14	57.07	28.8

Table 4.8 shows the participant opinions on the questions relating to their perception of the dose of codeine needed to enhance the analgesic effect of NSAIDs and paracetamol ranked in order of the level of agreement for each drug category. Approximately 81% of respondents agreed with the statement: “8-10mg of codeine works best to enhance the analgesic effect of NSAIDs” and 81.34% agreed with the same dose range for paracetamol. High levels of disagreement were found with the statement: “>20mg of codeine works best to enhance the analgesic effect of Non-Steroidal Anti-Inflammatory drugs (NSAIDs)” as well as “20mg of codeine works best to enhance the analgesic effect of paracetamol” (57.07%). Many respondents were not sure if 10mg-20mg codeine added to NSAIDs (25%) and paracetamol (19.6%) enhanced analgesia.

Table 4.9: Pharmacist and QPBPA perception of codeine dependence, misuse and abuse in the community.

A: Statement	**n**	**%agree**	**%disagree**	**%not sure**
Codeine dependence is a significant problem in the community	213	93.9	2.35	3.76
Codeine misuse is a significant problem in the community	213	93.43	3.29	3.29
Codeine abuse is a significant problem in the community	216	91.67	2.31	6.02
B: Statement	**n**	**%agree**	**%disagree**	**%not sure**
Codeine works synergistically with analgesic agents in combination therapy.	214	86.92	2.34	10.75
The pharmacy s2 register is a useful tool when monitoring codeine abuse	216	77.31	15.74	6.94

**discrepancies due to missing values*

Table 4.9 above indicates pharmacist and QPBPA perception of the codeine abuse, misuse and dependence problem in the community. Approximately 94% and 93.43% of respondents agreed to codeine dependence and codeine misuse being a significant problem in the community respectively. A high level of agreement was also found with "codeine abuse being a significant problem" (91.67%).

It can be seen in Part B of Table 4.9 that almost 87% of respondents agree with codeine's synergistic analgesic effect in combination therapy. There was a lower, but still a significantly high level of agreement to the statement "the s2 register is a useful tool when monitoring codeine abuse".

Table 4.10: Codeine misuse or abuse intervention methods at point of sale.

Statement	n	%agree	%disagree	%not sure
I would counsel a patient I suspect of misusing or abusing codeine by recommending alternate medication	218	95.87	2.75	1.38
I would counsel a patient I suspect of misusing or abusing codeine by warning the patient by limiting their use at my pharmacy for a specific time period.	215	80.93	15.81	3.26
I would counsel a patient I suspect of misusing or abusing codeine by a referring them to a doctor.	214	76.17	17.29	6.54
I would counsel a patient I suspect of misusing or abusing codeine by a refusing to dispense the product.	211	73.93	17.06	9
I would counsel a patient I suspect of misusing or abusing codeine by a referring them to a rehab facility.	214	43.46	31.78	24.77

Table 4.10 above shows the level of agreement of participants to the counselling or intervention methods they would use when suspecting a patient of misusing and or abusing codeine. The highest level of agreement (95.87%) is with the statement "I would counsel a patient I suspect of misusing or abusing codeine by recommending alternate medication." High levels of agreement were found for limiting patient use for a specific

time period (80.93%), doctor referral (76.17%) and refusal of sale (73.93%). The highest level of disagreement (31.78%) was found for “referral of patients to a rehab facility”.

Table 4.11: Pharmacist and QPBPA perception of codeine regulations in South Africa.

Statement	n	%agree	%disagree	%not sure
In order to prevent codeine misuse and abuse, the South African Medicines Control council have reduced the maximum quantity of codeine per dosage unit, in schedule 2 preparations, from 20mg to 10 mg (MCC,2014).				
The proposal above will have no impact on the Healthcare system	216	80.09	7.41	12.5
There should be an alternative strategy to prevent OTC codeine abuse in South Africa.	216	80.09	7.41	12.5
The proposal above will have a negative impact on the Healthcare System	214	16.82	64.02	19.16
The proposal above will have a positive impact on the Healthcare system	215	11.16	71.63	17.21

As can be seen from Table 4.11, there are high levels of disagreement found for both dose reduction having a negative (64.02%) as well as positive (71.63%) impact on the healthcare system. Similarly, 80% of participants feel that the dose reduction of codeine in OTC pain medication will in fact have no effect on the healthcare system. Approximately 80% of respondents also feel that there should be an alternative strategy to prevent OTC codeine abuse in South Africa.

Table 4.12: Product codeine-content awareness questions.

Codeine-content statement:	n	%Yes	%No	%Not sure
Genpayne contains codeine	217	98.16	0.92	0.92
Nurofen contains codeine	216	5.56	93.06	1.39
Empacod contains codeine	218	90.83	5.5	3.67
Broncleer cough syrup contains codeine	215	85.12	11.16	3.72
Sinutab c/extra strength contains codeine	212	67.45	22.64	9.91
Allergex contains codeine	214	96.73	0.93	2.34

Table 4.13: Product codeine-content awareness test result totals distributed per pharmacy role.

Product codeine content: awareness test results			Pharmacy role					
Total Respondents	**n**	**%**	Pharmacy Owner%	Pharmacy Manager%	Locum Pharmacist %	PEP %	Intern Pharmacist %	QPBPA %
100%	**101**	**46**	80	52	54	35	36	46
80-99%	**83**	**38**	20	36	29	49	28	44
60-79%	**25**	**11**	0	7	8	16	20	7
50-59%	**6**	**3**	0	5	2	0	12	0
<50%	**4**	**2**	0	0	6	0	0	2
Total	**219**	**100**	100	100	100	100	100	100

**discrepancies due to missing data. P value<0.0001 for interactions between pharmacy roles and codeine-content awareness test results.*

Table 4.13 indicates the respondent test scores on product codeine-content awareness. It can be seen that majority of most pharmacy role types answered all the related questions correctly. Pharmacy owner (80%), locum pharmacist (54%), pharmacy managers (52%), QPBPAs (46%), interns (36%) and lastly PEPs (35%).

Table 4.14: Treatment indication for codeine product requests by patients.

Statement	n	%agree	%disagree	%not sure
Patients visiting your pharmacy, are more likely to insist for codeine-containing preparations for pain.	216	86.11	12.04	1.85
Patients visiting your pharmacy, are more likely to insist for codeine-containing preparations for the treatment of cough.	213	66.20	30.05	3.76
Patients visiting your pharmacy, are more likely to insist for codeine-containing preparations for sinus.	213	66.20	31.92	1.88
Patients visiting your pharmacy, are more likely to insist for codeine-containing preparations for sleep problems.	209	46.89	49.28	3.83
Patients visiting your pharmacy, are more likely to insist for codeine-containing preparations for common cold.	213	43.19	53.52	3.29
Patients visiting your pharmacy, are more likely to insist for codeine-containing preparations for anxiety	210	20.48	72.86	6.67

Table 4.14 above indicates that highest levels of agreement were found by pharmacy personnel with patients requesting CCM for the treatment of pain (86.11%). Approximately 66.2% of respondents agreed with patients requesting CCM for cough and sinus treatment, and the lowest level of agreement was found with patients requesting CCM for anxiety.

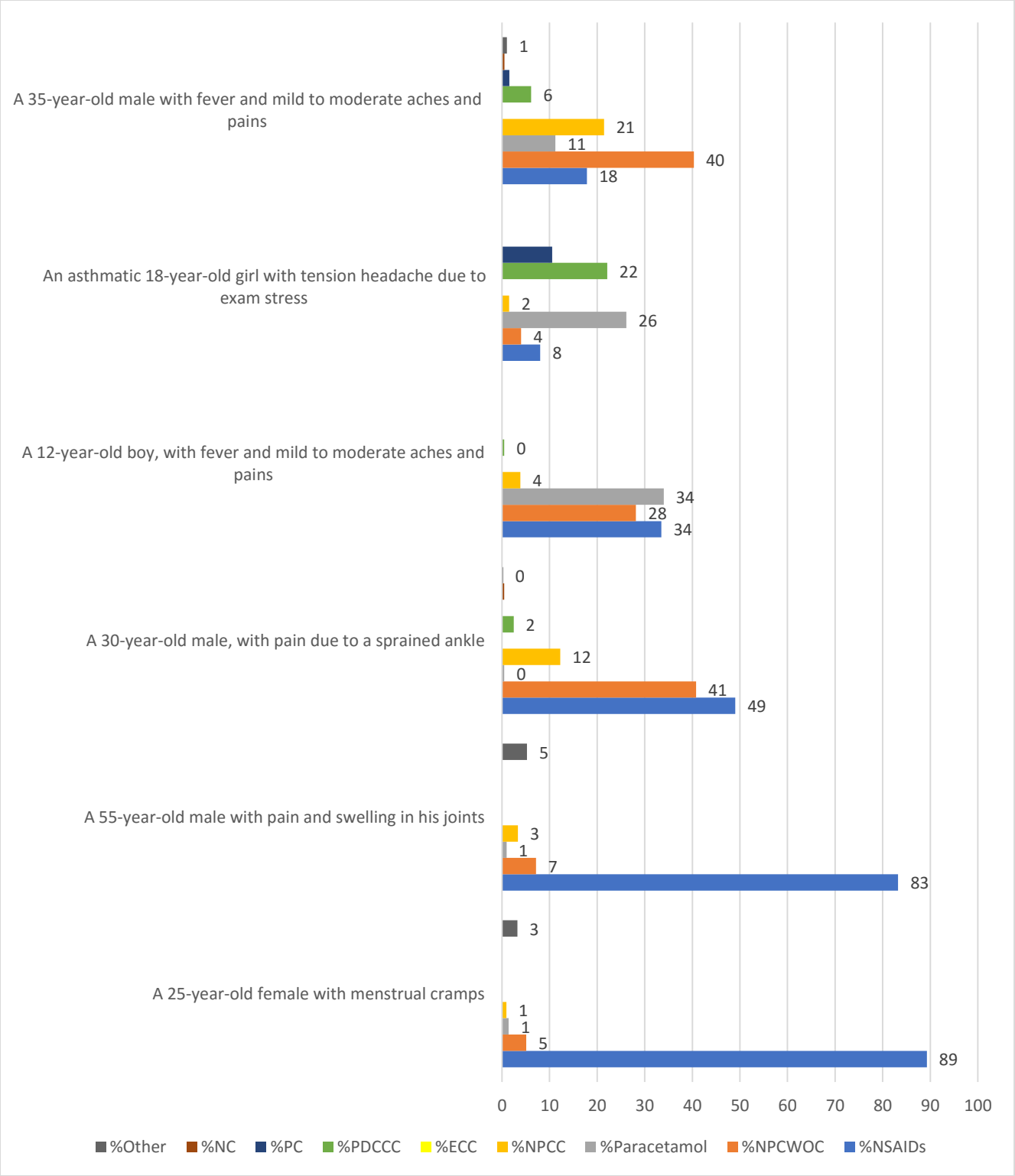

Figure 4.11: Pharmacist medication class preference for OTC pain scenarios.

Figure 4.11 shows the results to the open-ended scenario-based questions on the questionnaire regarding the treatment of OTC pain symptoms. Respondents were asked to give their first line drug of choice for the following conditions: a 25-year-old female with menstrual cramps; a 55-year-old male with pain and swelling in his joints; a 45-year-old male with a migraine (Appendix I); a 30-year-old male with pain due to a sprained ankle; a 12-year-old boy with fever and mild to moderate aches and pains; an asthmatic 18-year-old girl with tension headache due to exam stress and lastly a 35-year-old male with fever and mild to moderate aches and pains. The drug of choice stated by the respondent was then classified according to its composition or type seen in Appendix G.

An overwhelming majority of respondents would give NSAIDs alone to half of the above scenarios. “a 25-year-old female with menstrual cramps” (89%); a 55-year-old male with pain and swelling in his joints (83%); 12-year-old boy, with fever and mild to moderate aches and pains (34%).

PDCCC class was only significantly recommended by respondents for an asthmatic 18-year-old girl with tension headache due to exam stress (22%), and a 35-year-old male with fever and mild to moderate aches and pains (6%).

In general, CCPM such as the PDCCC, NPCC, NC and PC class were recommended by less than 25% of the respondents in all cases and did not account for more than 7% in most cases. Response types did not vary significantly amongst pharmacy roles (Appendix I)

4.3 IDI results

Table 4.15: Categories, themes and sub-themes developed from IDI data.

Categories	Themes	Sub-Themes
General pain management	OTC treatment of non-complicated pain	OTC NSAID use for the treatment of non-complicated pain
		The suggestion of a NSAID, paracetamol and codeine combination for the OTC treatment of non-complicated pain
		Non-pharmacological treatment of non-complicated pain
Management of OTC codeine use	Codeine used for the treatment of pain	Pharmacist preference of codeine use for different pain forms
		Pharmacist perception of the most effective codeine dose for pain
	Codeine misuse and abuse	Pharmacist awareness of codeine misuse and or abuse in the area
		Pharmacist perception on the severity of codeine misuse and or abuse in the area
		Pharmacist distinction between misuse and abuse
		Pharmacist interventions in the management of misuse and abuse
		Profit influence on OTC codeine sales
		Location and accessibility to pharmacies
		Codeine regulation method

Eight (n=8) community pharmacists, two males (n=2), and six females (n=6), aged between 23-year-old and 59-year-old were interviewed between January 2017 and November 2017. Their years of experience as pharmacists varied between ten months and thirty-five years. The role of the pharmacists was spread between four (n=4) pharmacy managers, two (n=2) permanently employed pharmacists, one (n=1) community pharmacy owner and one (n=1) locum pharmacist.

4.3.1 OTC treatment of non-complicated pain

All participants' (n=8) preferred drug of choice when treating most OTC pain symptoms fell within the NSAID medication class.

"…as an experienced pharmacist, only mefenamic acid, that is definitely the drug of choice." Participant 2

A couple (n=2) of those participants preferred the NSAID choice to be in combination with codeine and paracetamol and thus their drug of choice also fell within the (NPCC) group. Those two (n=2) participants also mentioned that they would, in addition to OTC treatment, give non-pharmacological advice.

"...so, it's more correcting the lifestyle and eating habits and things like that...exercise, exercise and stretches, water and warm/cold therapy because I go by that myself." Participant 4

4.3.2 Codeine used for the treatment of pain

Of all the (n=6) participants who felt that codeine has a place in pain health care, half of the participants (n=3) stated that it works more efficiently for specific pain types only. A couple (n=2) of those participants said that it should be used for acute pain alone and only one (n=1) participant stated that it should be used for chronic pain. A few (n=3) participants felt that it was effective for pain but did not give a specific pain type preference. Even though participants mentioned that codeine should only be used for a specific type of pain, there was a lack of consensus between the participants on their argued type.

"I think unless you have a problem with chronic pain or you have serious acute pain, I don't think you need to use codeine all that much". Participant 1

"I think it has a place, especially short term…" Participant 2

I don't have any objectives to it if it is a chronic condition and if the situation necessitates it, because you've got people with chronic migraines and people who really need it for pain relief, where the condition necessitates it, it's not a problem for me at all". Participant 6

All participants were not sure when giving a response on their opinion on the most effective codeine dose when used in combination OTC therapy for pain. Most participants (n=5) felt that 8mg to 10mg was the preferred dosage which is currently the allowed OTC dose per tablet.

"Yoh... you're asking a very technical question; most items have what? 10mg?" Participant 5

Half of the participants who felt that 8mg to 10mg was enough reasoned that more than that could lead to abuse or tolerance.

"hmm, is it 10mg or less? Because more than that, the customer is prone to being addicted to it". Participant 8

One (n= 1) participant felt that 10mg to 20mg would be the most effective and one participant stated that he did not know which dose would be most effective.

4.3.3 Codeine misuse and abuse

All participants (n=8) were aware of the severity of codeine abuse in their pharmacies community and all of the participants felt that codeine use in the area was a large concern.

"Rife (laughs), it's rife. There's no other word for it". Participant 2

"Wow! Wow! Codeine, our customers they love it. They want it by name; they will kill you for it. So, our community, they are so susceptible to codeine use". Participant 8.

Almost all (n=7) participants said there was a difference between codeine misuse and codeine abuse, most participants felt that they were usually more successful at counselling a misusing patient than an abusing patient.

"I think abuse is the recreational effect, the using of codeine where it's not necessarily needed. Misuse is when the patient is unaware of codeine and its side effects and pharmacists are not properly counselling the patients thoroughly on how to use codeine". Participant 7

"It's difficult, you can counsel them, but people who are abusing it, you're not going to touch them. They just want the stuff and want to go. People who are misusing the item, if you can get to a point of identifying them, you can counsel them, tell them about the side effects…" Participant 5

Almost all (n=7) participants used counselling methods on patients as a first line form of intervention if they suspected abuse.

Counselling methods involved finding out the reasons for this product use, informing patients on the side effects, and tapering down the dose.

"… so basically, at the end of the day, your duty as a health professional is to you know, help someone's health. It's hard, because he's (the patient) addicted and he's been doing it for years, but like slowly you can get to him. Eventually what I did was; tried to taper down the dose, so I tried to explain the side effects of codeine…" Participant 7

"I didn't say anything at the time, but I did make a point to tell him (the patient) not to use six to eight tablets a day and they might make him drowsy and there can be some dependence and addiction". Participant 1

A few of the participants would further intervene by referring suspected abusers or misusers to the doctor. One (n=1) participant would refuse the sale if their intervening methods did not work.

"I actually took her (the patient) aside and tried to ask her why was there such a need for her to be taking huge quantities every single week. Um, we can only do so much as far as to counsel the patient or gather information but they can be evasive. It got to a point where I recommended she speak to a doctor…" Participant 6

Almost half of the participants mentioned that sale targets and profit chasing play a huge role in the sale and thus abuse and misuse of codeine-containing products.

"I'd blame pharmacists themselves, because they're inconsistent. They know the law, but they want to make a profit. Patients end up not knowing who's right and who's wrong." Participant 5

"… I have refused sales. I also refuse to give any cheap codeine-containing products because the price of course is a big driver. It's far cheaper to buy a codeine-containing cough mixture than it is to buy any other substance of abuse. So, you stop keeping your lines, and you stop selling except on scripts, and of course if you address the people and you're a locum, you're not invited back (laughs)." Participant 2

Half of the participants (n=4) reasoned the challenge of control on the use of codeine, to be due to the close proximity, and ease of accessibility to different pharmacies without a method of tracking patient use between these pharmacies.

"Codeine use is a big problem, because we have retail pharmacies which are pretty close to each other, so people tend to go from one store to another, so even if we can restrict or limit use at our store, they can go down the road and buy the same medication, so we can't really stop that." Participant 6

"Even if you try to do your part and don't give them, and advise them otherwise, but we know retail pharmacies are like mushrooms everywhere, so they will leave you and go next door." Participant 4

Codeine control and regulation was a recurrent sub-theme. Abuse and misuse were felt to be the result of the lack of control of OTC codeine-containing products nationwide. Of the (n=6) participants who felt that there needs to be some change in the control or regulation of codeine, more than half (n=4) felt the solution would be the further up-scheduling of codeine-containing products and a couple of them (n=2) felt that a centralised tracking register of codeine use could be of help.

"If I had my way, all codeine shouldn't be s2 it shouldn't be s3 even…If you want your fix, pay and go see your doctor who will be responsible for your addiction should you come to that level of addiction. Your doctor who prescribes it to you, must account." Participant 4.

"… I do think it should be prescribed um, it should be a s3 and above, it should definitely not be available over-the-counter." Participant 7

5. DISCUSSION

The objective of this study was to analyse codeine use in Gauteng's private healthcare sector and to further explore the practices around its use by gaining an understanding of pharmacist perception of analgesics, more specifically OTC codeine-use for analgesia, by conducting surveys and IDIs with pharmacists around Gauteng.

5.1 OTC codeine product trends

National trends show that Gauteng has the second highest CCM product sales distribution in South Africa. The Free State and Eastern Cape have the largest distribution of CCM sales and the North West and Limpopo provinces have the lowest. Nationally, codeine-containing products contribute a monthly average of 17% of the total OTC product deliveries. Additionally, 28% of all OTC products available on the ordering system contain codeine. This is more than a quarter of all the available OTC products which continue to increase along with the global demand of codeine-containing products (INCB, 2012). The large availability of codeine-containing products in South Africa is consistent with countries in the European Union where codeine is permitted without a prescription (Foley et al., 2015).

Gauteng, known as one of the more urbanised provinces in South Africa, has a slightly higher monthly average distribution of codeine-containing products than the national average.

The Gauteng codeine utilisation trends show that the PDCCC drug class, which includes any product containing paracetamol, the sedative H1 antihistamine doxylamine, and codeine and caffeine, accounts for the largest portion of all OTC pain products delivered in the six-month period. Products in this class include, Adco-dol®, Syndol® and Acurate® amongst many others. The second largest portion of OTC pain medication sales is made up of the NPCC class. These are medications consisting of an NSAID, paracetamol and codeine. Popular brands such as Genpayne®, Mybulen® and Myprodol® fall within this class. However, noticeably the smallest percentage of OTC pain medication deliveries in Gauteng are products containing only paracetamol and codeine. The low portion of codeine and paracetamol combined product sales exist, even though according to recent

studies, codeine-paracetamol combinations are more favourable for analgesia compared to codeine-NSAID combinations (Derry et al., 2010), and according to Franceschi et al. (2013), should be the treatment of choice for mild to moderate pain.

Global OTC analgesic medication sales make up a significant proportion of the total OTC sales. In 2012, market figures in the United Kingdom indicated that OTC medication for adult analgesia alone accounted for 63% of all OTC sales (PAGB, 2012). Analgesics also post the highest sales amongst OTC drugs in the United States (Abbott & Fraser, 1998). Skurtveit et al. (2008) found that approximately 99% of the overall codeine consumption in the country is made up of the combination analgesic preparations. Results from the present study indicates that pain medication containing codeine accounts for 67.2% of all OTC codeine-containing medication sales in Gauteng. Furthermore, approximately 55% of the total analgesic OTC products delivered were codeine-containing. In Gauteng, analgesic codeine-containing products make up four out of the five most distributed CCM products. Adco-dol® (PDCCC class) constitutes the largest proportion of CCM deliveries in Gauteng. Genpayne ®, Myprodol® and Broncleer & Codeine® also make up the top five CCM products.

Results from a previous study where data was collected from centres participating in the South African Community Epidemiology Network on Drug Use showed that out of all the OTC codeine-containing products that were frequently reported as being misused or causing dependence, Adco-dol® was ranked the highest. Myprodol® was ranked third after Benylin® syrup with codeine (Data et al., 2015). The present study shows that the cough syrup Broncleer & Codeine® accounts for majority of the OTC cough syrup sales (56.8%) in Gauteng. It is also the second most distributed codeine-containing product after Adco-dol®.

The Free State and Eastern Cape provinces followed by Gauteng, according to present results, have the largest distribution of CCM deliveries of the total OTC products delivered within each province. With percentages of 20.6%, 20.5% and 18% respectively. According to the South African Community Epidemiology Network on Drug use study in 2014, the Eastern Cape had the most rehabillitation centres treating more than ten patients for primary or secondary codeine abuse along with the Free state and Gauteng

which fell within the central area (Dada et al., 2015), possibly associating availability with the abuse prevelance.

5.2 Pharmacist perception: The IDI and questionnaire

According to the present study, when treating patients OTC, majority of the respondents claim to base their treatment decisions on factual information from evidence-based medicine. Most however, still state that they are influenced by anecdotal evidence and that many of their sales are also influenced by drug-marketing. According to recent studies, continued medical education, which should be evidence-based, is very closely linked to the marketing of pharmaceuticals. Pharmaceutical companies are detailing pharmacists and pharmacy personnel on a daily basis on the effects of their products; however, due to the blurred lines between promotion and education, the integrity and credibility of the company and thus the product can be questioned (Relman, 2001). Majority of the pharmacists said that they were not influenced by drug-marketing; however, an overwhelming majority of the QPBPA respondents said that drug-marketing and anecdotal evidence influenced their treatment decisions, and therefore the drug recommendation they would give to the patient. This could be due to the lack of effective formal training of assistant pharmacy personnel which might result in the need for the pharmacist assistants to rely on other sources of information.

The request by patients for medicine, powerfully drives prescribing decisions (Mintzes et al., 2002). In the retail pharmacy setting, where sales are also a predominant driving force, it can be significantly worse. In the present study, “patient request” has the second highest level of agreement by pharmacists indicating that when patients request a specific product for their symptoms, they are very likely to receive it by pharmacists. Results are comparable to that of the Northern Ireland study by Hanna and Hughes (2010). Similarly, pharmacists in Northern Ireland were to a large extent influenced by patient choice. In contrast to the present study however, pharmacists admitted that they seldom considered evidence on the drug’s effectiveness when dispensing OTC products.

Patients who are dependent, misuse or abuse OTC substances usually ask for it by name. Futhermore, consumer drug advertising can largely influence a treatment choice for the

patient. Advertisements, for medication that is allowed to be advertised in South Africa, should show all the benefits and all the potential harms and adverse effects of the advertised medication so that patients get a holistic idea based on factual information of the drug they are requesting.

Many interview participants felt that sale targets and profit goals were additional challenges in controlling codeine-containing substances. This is an issue in many countries and is not a new challenge with possible conflicts of commercial and public interests long existing in the healthcare industry. Brennan et al. (2006) proposed stricter regulations around sales incentives, pharmaceutical samples as well as continuing medical education by pharmaceutical companies as market incentives seemed to be posing considerable challenges to the principles of medical professionalism in the USA. The community pharmacist in the private healthcare system is conflicted on a daily basis by their role as a sales person and health care giver, and therefore the South African pharmaceutical care industry could also benefit by these suggestions.

The codeine side effect awareness test results show that majority of the respondents were aware of the most common codeine side effects such as nausea, constipation, dizziness as well as respiratory and heart rate depression; however, only 3.65% of all respondents were aware of all of the listed side effects.

Majority of the respondents scored between 80% to 100% for the product codeine-content aspect of the questionnaire, showing that there is a high level of awareness amongst most pharmacy staff members on codeine verses non-codeine-containing products.

A 60mg dose of codeine in combination with paracetamol is most commonly used in clinical studies and thus as well as in clinical practice (Koren et al., 2006; Moore et al., 1997). There is a lack of evidence-based medicine to support the use of codeine in doses less than 20mg. That being said, there is a disparity between what evidence suggests is the most effective dose, and what pharmacists perceive as the most effective dose. The survey results show that 81% of respondents agreed with 8mg to 10mg of codeine being the most effective dosage unit range for the analgesic enhancement of both NSAIDs and paracetamol. Only 13% and 14% agreed that more than 20mg per dose unit of codeine works best to enhance the analgesic effect of NSAIDs

and paracetamol respectively. This can be compared to the results from a similar study performed in the United Kingdom based on the prescribing practitioner's perspectives on prescribed and OTC medicines containing codeine. The cross sectional study showed that less than 20% of the doctors in the UK agreed that doses below 30mg are not very effective in treating mild-to-moderate pain (Foley et al., 2016). The IDI results revealed that many of the pharmacists felt that 8mg to 10mg of codeine was the most effective dosage unit because it was the most available dosage unit. Futher clinical studies should identify the efficacy of codeine in doses less than 10mg whilst taking into consideration the variability of codeine's metabolism and thus therapeutic effects within a population (Zhou, 2009).

A majority of pharmacists would not recommend codeine-containing OTC analgesics as first line treatment for acute pain and anti-inflammatory symptoms. Almost all (n=6) interview participants would recommend a single NSAID for uncomplicated pain and inflammation. An overwhelming majority of the questionnaire respondents did not recommend codeine-containing products as first line treatment in pain management either. Respondents instead recommend a single NSAID, or paracetamol or NSAID-paracetamol combination, but most respondents did not feel that any of the listed OTC pain scenarios required any codeine-containing pain medication combinations. This further complicates the possible reasons for high PDCCC and NPCC sales in South Africa as well as the reasoning toward pharmacist perception of codeine's efficacy.

Survey results show that most respondents (87%) agreed with codeine working synergistically to enhance analgesic agents in combination therapy. Interview results correlate with this as majority of the participants (n=6) felt that codeine is effective for pain and has a place in pain healthcare. The circumstance for its use in pain however, was less unanimous amongst interviewees as half of the participants felt it should be used for acute pain. A couple (n=2) of the participants felt it worked better for chronic pain and the remaining participants (n=2) who felt that it works for pain did not specify a type.

Pharmacist perceive codeine dependence, misuse and abuse to be a significant concern in the commmnity. A large majority (93%) of all survey respondents found codeine misuse and dependence to be a significant problem and 91% felt that codeine abuse was also a

substantial issue in the community. All interviewed pharmacists felt that codeine abuse in their community was a large concern and described codeine use in their pharmacy as severe. Majority of the questionnaire respondents (77%) however, still said that the s2 register kept in the pharmacy is useful in the monitoring of codeine abuse. This could possibly be expained with results from the interview participants who felt that they were able to identify patients who abused codeine on a daily basis, but found it difficult to control it at their pharmacy level with the ease of availabilty of the substance and a lack of solid control on a national level. A s2 register is compulsory for all pharmacies in South Africa; however, the recorded information is only specific to that particular pharmacy and cannot be used by authorities and therefore cannot be used to control the misuse or abuse of these drugs.

Almost all interview participants were able to distinguish between misuse and abuse. Their disctinction of misuse was in line with Wazaify et al. (2005), who described misuse as medicine that is incorrectly used for a legitimate medical reason. That is, in higher doses or for longer than the recommended time period. Many participants felt that at a pharmacist level, they were more successful at counselling a patient they suspected of misusing, rather than abusing codeine, as they were able to provide them with knowledge on the side effects of the product and hopefully deter their use. This is similar to the Australian study by Hamer et al. (2014), based on pharmacist perception of the effect of CCPM product up-scheduling in the community, where participants also felt that they were more able to intervene in cases of misuse.

General suggestions of interventions in the present study included informing patients on the adverse effects as well as tapering the dose of codeine-containing medications. The study by Foley et al. (2016) showed that majority of the UK doctors also used the process of dose tapering, as well as education and counselling techniques, as intervention methods.

The intervention aspect of the questionnaire found highest levels of agreement for recommending alternate medication, followed by limiting patient product use at their pharmacy for a specific time period, referal to a doctor and lastly refusal of sale. These methods still do not prevent individuals aqcuiring the drug from other pharmacies and

according to Albsoul-Younes et al. (2010), this problem could be minimised if pharmacists networked more frequently with one another whereby a suspected abuser would be reported to other pharmacies in the area. Majority of the respondents disagreed with intervening when suspecting abuse by referring patients to a rehabilitation facility. This could complement results found in the Data et al. (2015) study whereby only 26.7% of primary or secondory codeine abuse admissions in South African treatment centres, were referred by health professionals. One of the barriers to treating patients experiencing codeine misuse and dependence, reported by addiction treatment providers who were linked to the South African Community Epidemiology Network on Drug Use, was that patients were not sure where to go for treatment (Parry et al., 2017).

Participants in the study by Hamer et al. (2014) also felt they were unsure of how to intervene and where to refer dependent people for help. However, all participants in the Australian study compared to 76% of questionnaire respondents in the current study, did state that they referred the patient to a doctor if they suspected over-use.

Majority of the respondents (80%) agreed that there should be an alternative strategy to prevent OTC codeine abuse. Many respondents felt that the new South African regulation involving dose and pack size reduction on OTC sales will have neither a positive nor negative effect on the healthcare system in South Africa. About 80% of the respondents agreed that the regulation will actually have no impact on South African healthcare. The IDI results enhance this as most participant pharmacists felt that there should be a change in the method of codeine control in South Africa. Majority of these participants felt that the change should be the complete up-scheduling of all codeine-containing products, the remaining participants (n=2) felt that the change should be a centralised tracking register that could be used to monitor the use of codeine on a national level.

5.3 Summary

- Codeine-containing products, especially those indicated for pain, are widely available and distributed in Gauteng. OTC codeine-containing analgesic medication make up more than half of the total OTC analgesic medications delivered in Gauteng.

- The PDCCC and NPCC class accounts for more than half of all the OTC pain medication deliveries and the PC class accounts for less than 1% even though many studies suggest that the PC combination is most likely to be effective for pain.
- Adco-dol® sales are the highest in Gauteng. Adco-dol is also the most reportedly abused OTC pain product according to data from centres involved in the South African Community Epidemiology Network on Drug Use (Data et al., 2015).
- An overwhelming majority of respondents said that their treatment decisions are evidence-based. Anecdotal evidence as well as drug-marketing still influence many pharmacist treatment preferences; however, majority of QPBPAs' treatment decisions are influenced by drug-marketing and anecdotal evidence.
- The community pharmacist in the private healthcare system is conflicted on a daily basis by their role as a sales person and health care giver. Sale targets and profit goals are additional challenges in controlling codeine-containing substances.
- There is some awareness amongst respondents of the common codeine side effects. However, almost all of the respondents were not aware of all the listed codeine side effects. There is a high level of awareness amongst most pharmacy staff members on which products contained codeine and which did not.
- There is a disparity between what evidence suggests is the most effective codeine dose, and what pharmacists perceive as the most effective codeine dose. Majority of the questionnaire respondents as well as the interview participants felt that 8mg to 10mg of codeine was the most effective dose unit range for the analgesic enhancement of NSAIDs and paracetamol.
- Majority of the participants in the study perceive codeine abuse, misuse and dependence to be significant issues in the community and find it difficult to control it at a pharmacy level.
- Pharmacists felt that they could get involved if they suspect a patient of misusing codeine by counselling them on its adverse effects. Pharmacists were least likely to refer patients they suspected of abuse to a rehabilitation facility.
- Pharmacists perceive codeine to work synergistically with OTC combination analgesics and consider it to be effective in pain management at low doses.

However, there should be more control over its use and that the control should come from a national level.

- Similar to past studies, the present study highlights that there is a callout from pharmacy personnel for tighter monitoring systems and restrictions placed on codeine use (Hamer et al., 2014; Carney et al., 2016). Majority of participant pharmacists want codeine to be prescription acquired only, but drawbacks to that suggestion according to Gudin and Lee (2013), is that it could result in the prescribing of more potent medication by doctors and cause an economic drop within the pharmaceutical industry. In addition, determined abusers will adapt and find ways around the system. This would be a viable option if patient interest is the main concern along with the fact that it's OTC availability appears wasted due to a lack of significant evidence of codeine's efficacy in dosage units less than 10mg.
- The up-scheduling of codeine would also be beneficial if there was a way of introducing CYP2D6 genetic screening in clinical practice, this could allow prescribers an opportunity to test a patient's genotype before prescribing codeine-containing products, as its analgesic effect is largely dependent on the variation of the patient genetics and would thus provide a means of preventing irrational use.

5.4 Strengths and limitations of the study

A number of limitations of this study have been identified. The PUS does not represent trends everywhere in Gauteng as it was just based on the *Orderwise* database. In addition, the PUS excludes pharmacies, wholesalers as well as manufacturers who do not use this facility in this time frame. The PUS may not have included all available products on the South African market due to factors such as manufacturer and or supplier availability. In addition, the method of questionnaire distribution had to change due to the low response rate via email on the first attempts. The response rate was then limited to the visits to each individual pharmacy.

There is a possibility that pharmacists with an interest in the topic or who have been experiencing problems with codeine use, abuse and dependence in their pharmacy may have been more likely to participate in the study. This study, to our knowledge, is the first in South Africa to provide information on pharmacist perceptions of OTC codeine use and abuse and can be used to provide information for future studies.

6. RECOMMENDATIONS AND CONCLUSION

6.1 Recommendations

6.1.1 Future control policy considerations

The complete up-scheduling of codeine-containing medication should be considered by the MCC, along with the implications it would have on South African healthcare. There should be a review of the CCI national database as an audit and monitoring system. The CCI database should not serve as a replacement but as an enhancement of the s2 register. Further consideration should be placed on its implementation being compulsory in all pharmacies.

6.1.2 Pharmacist intervention programs

Updated guidelines incorporating innovation as recommended by Parry et al. (2017), for addiction treatment providers, should also be developed for pharmacists and assistants to ensure that patients with an abuse or dependence problem receive a uniform and proven treatment option. Standard guidelines and awareness campaigns should also be developed for pharmacists and pharmacist assistants for the correct counselling and referral of patients with codeine abuse or misuse.

6.1.3 Future study recommendations

There is a lack of evidence to support codeine's significant clinical advantage when added in low doses to OTC products for the treatment of pain (van Hout & Norman, 2014). Further RDBPC clinical trials should be conducted to investigate the analgesic effectiveness of doses of 20mg or less. Further clinical studies should investigate the health implications of using codeine and antihistamine combinations in managing acute pain. The reason for the high level of codeine product sales need to be investigated and compared to the product abuse prevalence in the community.

6.2 Conclusion

This study highlights that in Gauteng, there is a huge demand for codeine-containing analgesic medication, especially those in combination with sedative antihistamines. The demand is met by a large pharmaceutical supply across the province's private community healthcare sector. Pharmacists are the custodians of medicine and thus are key role players in the prevention of codeine misuse and abuse at a community level. Codeine's large availability OTC however, has made controlling its use by pharmacists and pharmacy assistants almost impossible.

Pharmacists perceive that there is a need for codeine in low doses for pain management; however, there is a lack of evidence-based medicine to support this view. Further RDBPC clinical trials should investigate the analgesic efficacy of codeine in doses lower than 20mg. The short and long-term health implications of using low-dose codeine in combination with sedative anti-histamines should also be studied.

There is a callout from pharmacy personnel for stricter and more proactive control measures placed on codeine-containing product use in South Africa. Stringent controls should be enforced on the detailing of pharmacy personnel, especially QPBPAs, by pharmaceutical companies on codeine-containing products. Information on all the possible adverse reactions and the short and long-term effects of codeine-containing products should be included in the detailing process to enhance the awareness these products. The close proximity of pharmacies and the ease of accessibility of codeine-containing products within each pharmacy potentiates abuse. If the implementation of a compulsory tracking system such as a national database, as a means of controlling codeine misuse and abuse, proves impractical for the South African healthcare system, the complete up-scheduling of codeine-containing products should be considered.

Researchers, clinicians and policy makers in South Africa need to work together to enforce stricter laws and develop appropriate and effective community-based intervention, awareness programs and strategies for the prevention and control of codeine misuse, abuse and dependence in the interest of public health.

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APPENDIX A: QUESTIONNAIRE

Codeine use in OTC pain medication: A questionnaire based on pharmacist knowledge and perception

SECTION A **The following questions relate to your perception of general pain management**				
1. What medication would you dispense when treating the following patients? (Please state your first preference)				
1.1 A 25-year-old female with menstrual cramps				
1.1 A 55-year-old male with pain and swelling in his joints				
1.3 A 45-year-old male with a migraine				
1.4 A 30-year-old male, with pain due to a sprained ankle				
1.5 A 12-year-old boy, with fever and mild to moderate aches and pains				
1.6 An asthmatic 18-year-old girl with tension headache due to exam stress				
1.6 A 35-year-old male with fever and mild to moderate aches and pains				
2 What are you most likely to base your general treatment decisions on: (You may choose more than 1 option)				
2.1 Anecdotal evidence				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree

2.2 Patient request				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
2.3 Marketing of a drug				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
2.4 Evidence-based medicine				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree

SECTION B **Questions relating to the utilisation of codeine**				
3 What dose of codeine do you think works best to enhance the analgesic effect of Non- steroidal anti- inflammatory drugs (NSAIDs)				
3.1 8 mg-10 mg				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
3.2 10 mg-20 mg				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
3.3 >20 mg				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
4 What dose of codeine do you think works best to enhance the analgesic effect of Paracetamol				
4.1 8 mg- 10 mg				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
4.2 10 mg-20 mg				

Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
4.3 >20 mg				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
5 Side effects of codeine include				
5.1 Nausea				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
5.2 Diarrhoea				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
5.3 Respiratory Depression				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
5.4 Increased Heart Rate				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
5.5 Indigestion				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
5.6 Dizziness				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
5.7 Pruritus				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
5.8 Miosis				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree

6 The benefits of codeine outweigh its side effects when providing symptomatic relief				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
7 On average, how many codeine-containing combination products do you dispense a day?				
7.1 <20 packs				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
7.2 20- 30 packs				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
7.3 30- 40 packs				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
7.4 >40 packs				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
8 To your knowledge, which of the following products contain codeine?				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
8.1 Genpayne				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
8.2 Nurofen				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
8.3 Empacod				

Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
8.4 Broncleer cough syrup				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
8.5 Sinutab C				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
8.6 Allergex				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
9 Patients visiting your pharmacy, are more likely to insist for codeine-containing preparations for:				
9.1 The self- treatment of pain				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
9.2 Treatment of cough				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
9.3 Sleep or anxiety problems				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
9.4 Sinus				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
9.5 Common Cold				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
9.6 Other:				
10 Our pharmacy keeps an OTC register that records the sale of codeine.				

Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
11 The register is a useful tool in monitoring the use and abuse of codeine.				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
12 Codeine dependence is a significant problem in the community.				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree

13.1 Codeine misuse is a significant problem in the community.				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
13.2 Codeine abuse is a significant problem in the community.				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
13.2 How would you counsel a patient you suspect of misusing or abusing codeine?				
a. Refuse to dispense the product.				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
b. Warn the patient by limiting their use at your pharmacy for a specific time period.				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
c. Referral to a doctor.				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
d. Referral to a rehab facility				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree

14 In order to prevent codeine misuse and abuse, the Medicines Control council have proposed to reduce the maximum quantity of codeine per dosage unit, in schedule 2 preparations, from 20mg to 10mg (MCC,2014).				
a. The proposal above, is in the best interest of all patients				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
b. The proposal above will have a positive impact on the Health Care system and should be implemented				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
c. The proposal above will have a negative impact on the Health Care System and should not be implemented.				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree
d. There should be an alternative strategy to prevent OTC abuse in South Africa.				
Strongly Agree	Agree	Not Sure	Disagree	Strongly disagree

Thank you for your participation.

APPENDIX B: INTERVIEW GUIDE

ANALYSING CODEINE USE IN OVER-THE-COUNTER (OTC) PAIN MEDICATION: A STUDY OF PHARMACIST KNOWLEDGE AND PERCEPTION

Background

1. For how long have you been practicing as a community pharmacist?

2. How long have you worked in this specific pharmacy for?

3. May I ask, what is your highest post-graduate qualification?

Treatment decisions

4. I'm going to give you a couple of scenarios: walk me through your thought process when selecting an appropriate treatment for them:
    - A 55-year-old male, with pain due to swelling in his joints
    - A 25-year-old female with menstrual cramps
    - A 30-year old male with pain due to a sprained ankle.

Codeine use

5. Tell me about codeine use in the area.

6. Please can you describe different ways that you know of codeine being used?

7. How do you feel about codeine being used for pain?

8. What dose of codeine, do you think works best to enhance the analgesic effect of other types of analgesics for example NSAIDS/and or Paracetamol?
    - Could you tell me why you think so?
9. How do you feel about codeine being available over-the-counter?

Codeine misuse and abuse

10. What do you understand by codeine abuse?
11. What do you understand by codeine misuse?
12. If at all, how often do you encounter patients that you suspect of having a codeine abuse or dependence problem?
    - Could you give me an example of how you've recently counselled a patient you suspected of either problem?

Wrap-up

13. Is there anything else that we haven't talked about, that you would like to address regarding this matter?

14. May I just look through my guide and make sure I've covered everything?

Thank you and greeting.

APPENDIX C: CONSENT FORM AND PARTICIPANT INFORMATION SHEET FOR QUESTIONNAIRE

INFORMED CONSENT

Study Title: Codeine use in over-the-counter (OTC) pain medication: A study of pharmacist knowledge and perception.

Dear Pharmacist

My name is Nasrene Khan. I am a student at Wits University. I am conducting a study to determine pharmacist knowledge and perception on the use of codeine in over-the-counter (OTC) pain medication.

Codeine misuse an abuse is becoming a major concern in our society. Globally, the demand for codeine has also risen. Codeine is readily available in Over-the-Counter combination pain therapy, cold and flu preparations as well as cough-syrups. The widespread availability of codeine in South Africa, matched to it large abuse potential has piqued my interest in this field, and I would like to gain a deeper understanding of pharmacists' current perception, by administering questionnaires to pharmacists based in Gauteng, regarding the following matters:

- General OTC pain management
- Codeine for OTC pain management
- Opioid misuse and abuse
- Current and proposed regulations for the prevention of codeine misuse and abuse

The questionnaire designed, is divided into two sections. Section A which contains both open and close-ended questions and section B which will contain close- ended questions. I will then use these questionnaires to collect data. Data analysed will not disclose your identity or any such personal information of you or your pharmacy.

I would like you to consider participating in this study. It is completely voluntary and non-completion will not result in any consequences. Should you require any further information, please feel free to contact the study researcher or supervisors.

	Name	Email Address	Contact no.
Researcher	Nasrene Khan	nasrene.khan93@gmail.com	0767946393
Project Supervisors	Dr Neil Butkow	neil.butkow@wits.ac.za	+27 11 717 2371
	Ms Neelaveni Padayachee	neelaveni.padayachee@wits.ac.za	+27 11 717 2269

If you require any additional information regarding your rights as a research participant, or if you have any complaints regarding this research study, you may contact the Chairperson of the Human Research Ethics Committee, University of the Witwatersrand:

Prof. Cleaton Jones	011 717 2100

INTRODUCTION

You are invited to consider participating in a research study. Your participation in this study is entirely voluntary.

1. Before agreeing to participate, it is important to read and understand the following regarding the purpose of the study, the procedures, and your right to withdraw from the study at any time.
   This information leaflet will help you decide if you would like to participate. You should fully understand what is involved before you agree to take part in this study.
2. You should not agree to take part unless you are satisfied about all the procedures involved.
3. If you decide to take part in this study, you will be asked to sign an informed consent letter, which confirms that you understand the study and are participating voluntarily.

Some of the most frequently asked questions you may have are answered below:

WHAT IS THE PURPOSE OF THE STUDY?

To investigate the utilisation of codeine-containing analgesic OTC preparations in the private healthcare market and to elucidate the practices around these products.

WHAT IS INVOLVED IN THE STUDY?

The Study involves administering questionnaires, as well as conducting in-depth-interviews with pharmacists around Gauteng in order to investigate their perception of codeine as an analgesic agent, its side effect profile and abuse potential, as well as to investigate pharmacists' treatment decision making relating to pain.

WHO IS INVOLVED IN THE STUDY?

The questionnaire will be open to pharmacists on duty in pharmacies around Gauteng who are interested in participating. The questionnaire responses will be seen only by the researchers involved.

WHAT DO I HAVE TO DO?

You will be required to complete the questionnaire by answering the questions based on pharmacist perception.

DO I HAVE TO TAKE PART?

- Your participation in this study is entirely voluntary and you can decline to participate, or stop at any time, without stating any reason.
- Non-participation or withdrawal will not result in any consequences.

ARE THERE ANY BENEFITS IF I TAKE PART?

No

ARE THERE ANY DISADVANTAGES TO TAKING PART?

No

WHO HAS REVIEWED AND GIVEN ETHICAL APPROVAL FOR THE STUDY?

- This study protocol has been submitted to the University of the Witwatersrand, **Medical Human Research Ethics Committee (HREC)**

HOW WILL MY PARTICIPATION IN THE STUDY AND QUESTIONAIRE RESPONSES BE KEPT CONFIDENTIAL?

- No information regarding your participation or responses will be used for any purpose other than to determine your perception of pain treatment as well as the use and abuse of codeine.
- At no point in the study will you be asked to disclose any personal or identifiable information.

WHO WILL HAVE ACCESS TO THE RESULTS OF THE STUDY?

- The researcher and supervisors
- Results may be published in a peer- reviewed journal

APPENDIX D: CONSENT FORM AND PARTICIPANT INFORMATION SHEET FOR IN-DEPTH-INTERVIEW

INFORMED CONSENT

Study Title: Codeine use in over-the-counter (OTC) pain medication: A study of pharmacist knowledge and perception.

Dear Pharmacist

My name is Nasrene Khan. I am a student at Wits University. I am conducting a study to determine pharmacist knowledge and perception on the use of codeine in over-the-counter (OTC) pain medication.

Codeine misuse an abuse is becoming a major concern in our society. Globally, the demand for codeine has also risen. Codeine is readily available in Over-the-Counter combination pain therapy, cold and flu preparations as well as cough-syrups. The widespread availability of codeine in South Africa, matched to it large abuse potential has piqued my interest in this field, and I would like to gain a deeper understanding of pharmacists' current perception, by conducting in-depth interviews regarding the following matters:

- General OTC pain management
- Codeine for OTC pain management
- Opioid misuse and abuse
- Current and proposed regulations for the prevention of codeine misuse and abuse

The interview consists of approximately twelve questions and should take no longer than half an hour. Information gathered from the interview will not disclose your identity or any such personal information of you or your pharmacy.

I would like you to consider participating in this study. It is completely voluntary and non-completion will not result in any consequences. Should you require any further information, please feel free to contact the study researcher or supervisors.

	Name	Email Address	Contact no.
Researcher	Nasrene Khan	nasrene.khan93@gmail.com	0767946393
Project Supervisors	Dr Neil Butkow	neil.butkow@wits.ac.za	+27 11 717 2371
	Ms Neelaveni Padayachee	neelaveni.padayachee@wits.ac.za	+27 11 717 2269

If you require any additional information regarding your rights as a research participant, or if you have any complaints regarding this research study, you may contact the Chairperson of the Human Research Ethics Committee, University of the Witwatersrand:

Prof. Cleaton Jones	011 717 2100

PARTICIPANT INFORMATION SHEET

INTRODUCTION

You are invited to consider participating in a research study. Your participation in this study is entirely voluntary.

4. Before agreeing to participate, it is important to read and understand the following regarding the purpose of the study, the procedures, and your right to withdraw from the study at any time.
   This information leaflet will help you decide if you would like to participate. You should fully understand what is involved before you agree to take part in this study.
5. You should not agree to take part unless you are satisfied about all the procedures involved.
6. If you decide to take part in this study, you will be asked to sign an informed consent letter, which confirms that you understand the study and are participating voluntarily.

Some of the most frequently asked questions you may have are answered below:

WHAT IS THE PURPOSE OF THE STUDY?

To investigate the utilisation of codeine-containing analgesic OTC preparations in the private healthcare market and to elucidate the practices around these products.

WHAT IS INVOLVED IN THE STUDY?

The Study involves administering questionnaires, as well as conducting in-depth-interviews with pharmacists around Gauteng in order to investigate their perception of codeine as an analgesic agent, its side effect profile and abuse potential, as well as to investigate the rationale behind pharmacist decision-making relating to pain.

The study will also involve, upon consent, the audio recording of the interview.

WHO IS INVOLVED IN THE STUDY?

The questionnaire will be open to community pharmacists on duty in pharmacies around Gauteng who are interested in participating. The questionnaire responses will be seen only by the researchers involved.

Interviews will also involve community pharmacists in the Gauteng region who are willing to be interviewed.

WHAT DO I HAVE TO DO?

You will be required to answer questions regarding your perception of general over-the-counter pain management, codeine use, as well as codeine used specifically for pain management. This will take place during a one-on-one interview process involving the researcher.

DO I HAVE TO TAKE PART?

- Your participation in this study is entirely voluntary and you can decline to participate, or stop at any time, without stating any reason.
- Non-participation or withdrawal will not result in any consequences.

ARE THERE ANY BENEFITS IF I TAKE PART?

No

ARE THERE ANY DISADVANTAGES TO TAKING PART?

No

WHO HAS REVIEWED AND GIVEN ETHICAL APPROVAL FOR THE STUDY?

- This study protocol has been submitted to the University of the Witwatersrand, **Medical Human Research Ethics Committee (HREC)**

HOW WILL MY PARTICIPATION IN THE STUDY BE KEPT CONFIDENTIAL?

- No information regarding your participation or responses will be used for any purpose other than to determine your perception of general OTC pain management as well as the use and abuse of codeine.
- Any personal or identifiable information included in the audio recording or transcripts will not be used in presentations or in written products resulting from the study and will only be known to the researcher.

WHO WILL HAVE ACCESS TO THE RESULTS OF THE STUDY?

- The researcher and supervisors
- Results may be published in a peer- reviewed journal

APPENDIX E: RECORDING CONSENT FORM

Study Title:

Codeine use in over-the-counter (OTC) pain medication: A study of pharmacist knowledge and perception.

Researcher:

Nasrene Khan

Wits University

Department of Pharmacy and Pharmacology

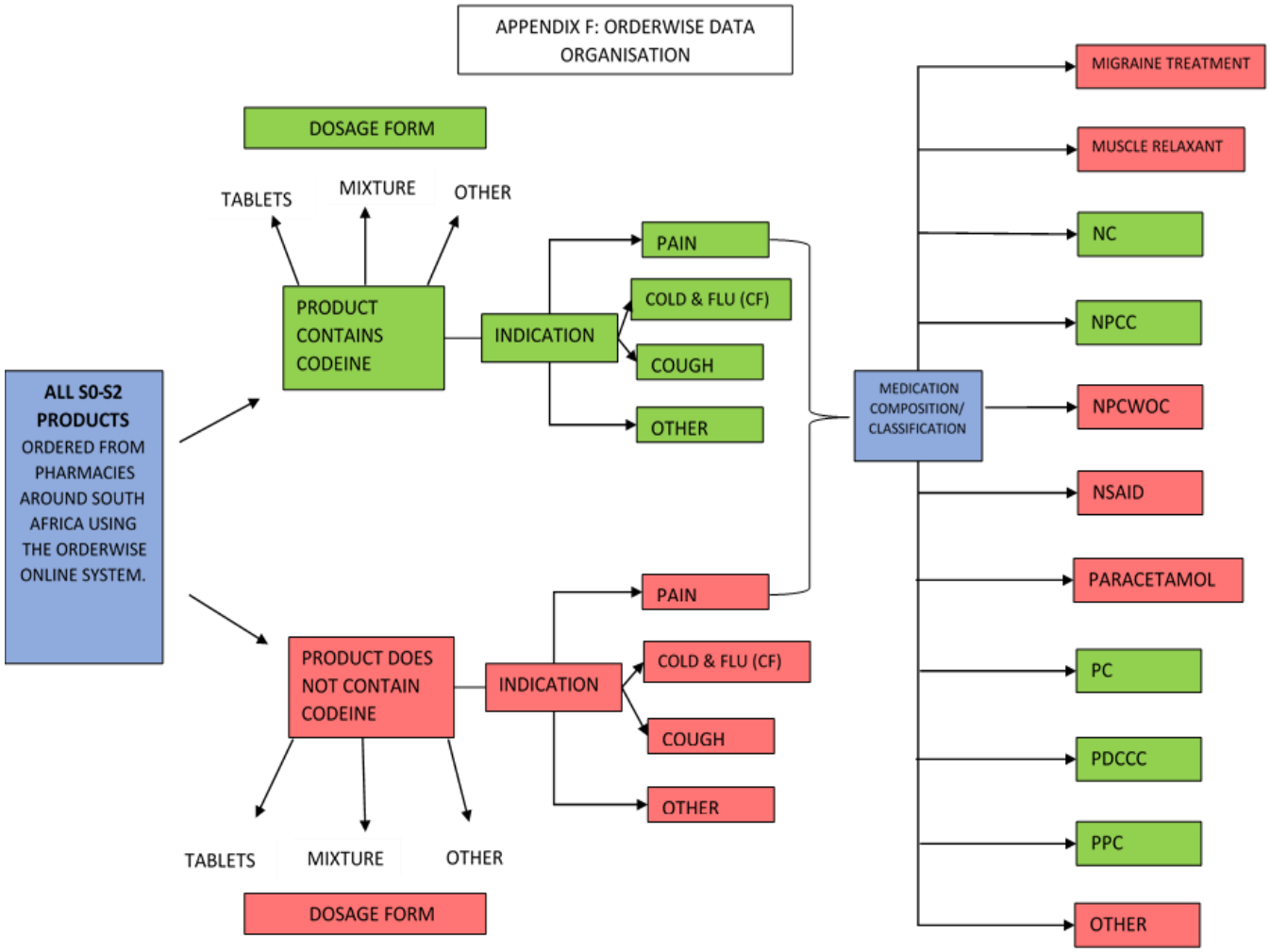
This study involves the audio or video recording of your interview with the researcher. Neither your name nor any other identifying information will be associated with the recording or the transcript. Only the researcher, supervisors and ethics board (if necessary) may listen to the recordings.

The tapes will be transcribed by the researcher and erased after the retention time frame (stipulated by the ethics committee) expires. Transcripts of your interview may be reproduced in whole or in part for use in presentations or written products that result from this study. Neither your name nor any other identifying information will be used in presentations or in written products resulting from the study.

By signing this form, I am allowing the researcher to record the interview as part of this research.

Participant	**Researcher**
Name: _____	Nasrene Khan
Signature: _____	Signature: _____
Date: _____	Date: _____

APPENDIX F: *ORDERWISE* DATA ORGANISATION TREE



APPENDIX G: PAIN MEDICATION CLASSIFICATION SYSTEM

Table G.1: Medication organisation and classification system

Product Classification	Description	Examples® (Brand Names)
PDCCC	Paracetamol, doxylamine, codeine and caffeine.	Adco-dol, Syndol, Tensopyn, Acurate
PPC	Paracetamol. Promethazine and codeine	Stilpane syrup, Go Pain
NPCC	NSAID, paracetamol and codeine combination	Genpayne, Myprodol, Mybulen, Ibupain forte
NPCWOC	NSAID and paracetamol without codeine	Ibupain, Mypaid
PC	Paracetamol and codeine combination	Dolorol forte, Painamol plus
NC	NSAID and codeine combination	Ibucod, Nurofen Plus
ECC	Ergotamine, cyclizine and caffeine (used for open-ended responses to questionnaire only)	Migril
NSAID	Only active ingredient is an NSAID	Nurofen, Brufen, Aleve, K-fenak
Paracetamol	Only active ingredient is paracetamol	Panado, Clicks Paracetamol, Painamol
Migraine treatment	(used for *Orderwise* data only) any product indicated for the treatment of migraine	Migril, Menograine
Muscle Relaxant	Any product indicated as a muscle relaxant (may be in combination with paracetamol)	Norflex, Spasmend, Uniflex

APPENDIX H: NATIONAL CODEINE PRODUCT UTILISATION TRENDS

Figure H.1: Percent distribution of CCPM and NCCPM product types available on the *Orderwise* system.

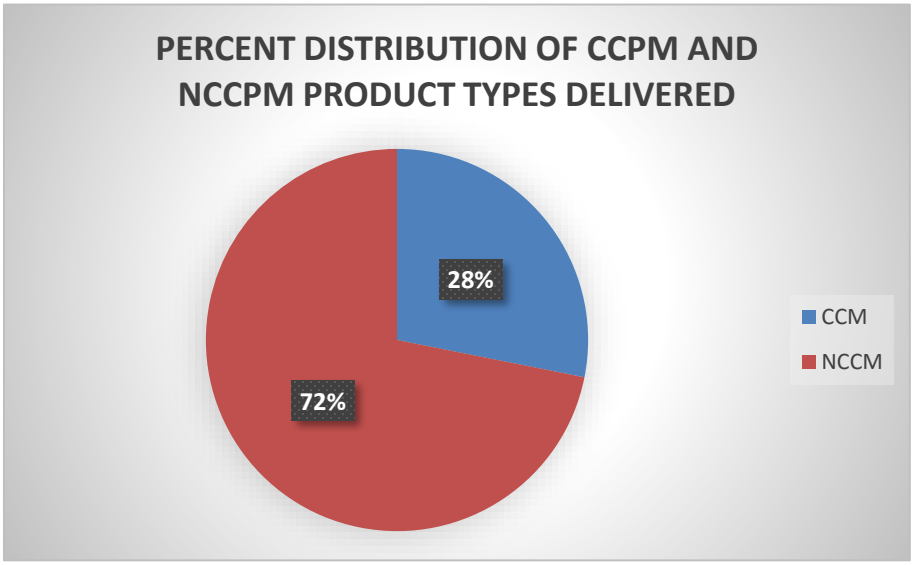


Figure H.2: The percent distribution of the total OTC products delivered per treatment indication from 1 January 2016- 30 June 2016

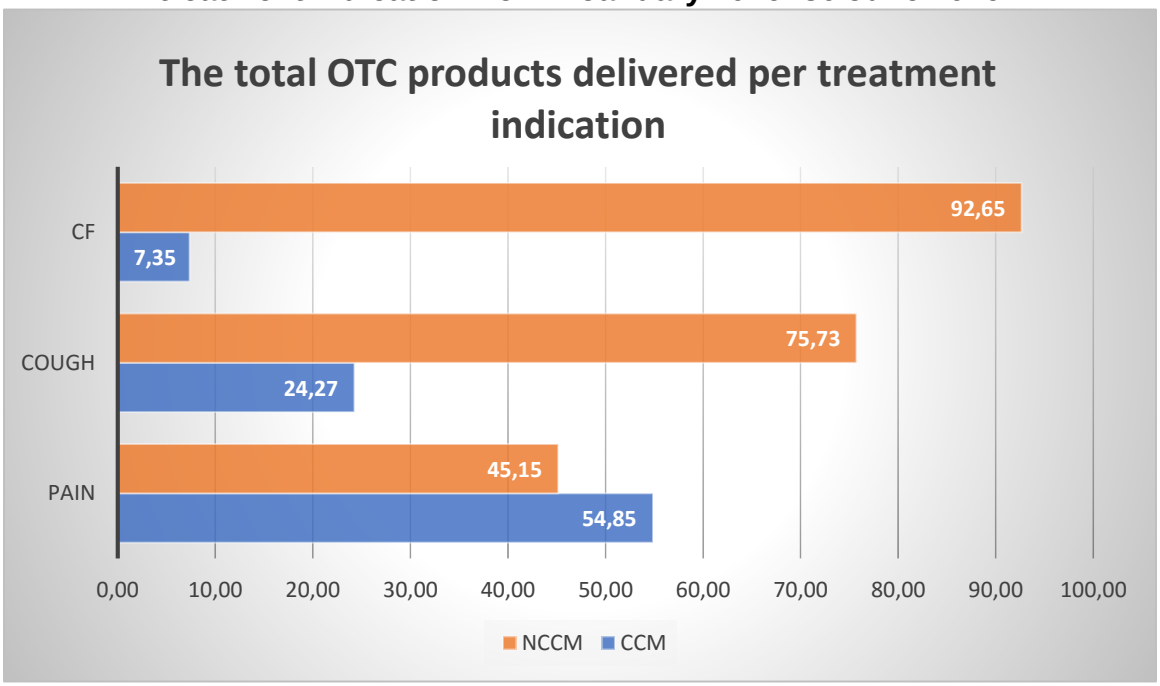


Table H.1: Codeine products per indication delivered nationally from 1 January 2016 – 30 June 2016.

Treatment Indication	CCM delivered frequency (n)	Percentage
PAIN	2215591	71.39%
COUGH	674966	21.75%
CF	212941	6.86%
TOTAL	3103498	100.00%

APPENDIX I: TREATMENT PREFERENCES FOR OTC PAIN SCENARIOS PER PHARMACY ROLE

Table I.1: Drug treatment preference per pharmacy role type for a 25-year-old female with menstrual cramps.

A 25-year-old female with menstrual cramps.						
Pharmacy Role	**Total**	**% NSAIDs**	**%NPCWOC**	**%paracetamol**	**Other***	**%NPCC**
Intern Pharmacist	24	83.33	4.17	4.17	8.33	0.00
Locum Pharmacist	55	85.45	9.09	1.82	1.82	1.82
QPBPA	39	82.05	10.26	0.00	7.69	0.00
PEP	50	94.00	2.00	2.00	0.00	2.00
Pharmacy manager	42	97.62	0.00	0.00	2.38	0.00
Pharmacy owner	5	100.00	0.00	0.00	0.00	0.00
Total respondents	215	89.30	5.12	1.40	3.26	0.93

**Other: any antispasmodic, products from ECC class, herbal supplements.*

Table I.2: Drug treatment preference per pharmacy role type for a 55-year-old male with pain and swelling in his joints.

A 55-year-old male with pain and swelling in his joints.						
Pharmacy Role	**Total**	**% NSAIDs**	**%NPCWOC**	**%paracetamol**	**Other***	**%NPCC**
Intern Pharmacist	24.00	87.50	8.33	0.00	4.17	0.00
Locum Pharmacist	51.00	82.35	3.92	0.00	5.88	7.84
QPBPA	40.00	87.50	7.50	2.50	2.50	0.00
PEP	47.00	82.98	10.64	0.00	4.26	2.13
Pharmacy manager	42.00	78.57	7.14	2.38	9.52	2.38
Pharmacy owner	5.00	80.00	0.00	0.00	0.00	20.00
Total respondents	209.00	83.25	7.18	0.96	5.26	3.35

**Other: muscle relaxant, colchicine, herbal supplements.*

Table I.3: Treatment preference per pharmacy role type for a 45-year-old male with a migraine.

A 45-year-old male with a migraine.										
Pharmacy Role	**Total**	**%NSAIDs**	**%NPCWOC**	**%Paracetamol**	**%NPCC**	**%ECC**	**%PDCCC**	**%PC**	**%NC**	**%Other**
Intern Pharmacist	24.00	16.67	8.33	8.33	8.33	45.83	8.33	0.00	0.00	4.17
Locum Pharmacist	49.00	8.16	8.16	2.04	12.24	51.02	10.20	0.00	0.00	8.16
QPBPA	39.00	2.56	2.56	2.56	5.13	74.36	0.00	0.00	5.13	7.69
PEP	49.00	16.33	6.12	4.08	6.12	55.10	2.04	2.04	0.00	8.16
Pharmacy Manager	42.00	2.38	11.90	4.76	2.38	61.90	14.29	0.00	0.00	2.38
owner	5.00	20.00	20.00	0.00	0.00	60.00	0.00	0.00	0.00	0.00
Total respondents	208.00	9.13	7.69	3.85	6.73	58.17	6.73	0.48	0.96	6.25

**Other: muscle relaxant, clonidine, triptan.*

Table I.4: Treatment preference per pharmacy role type for a 30-year-old male with pain due to a sprained ankle.

A 30-year-old male with pain due to a sprained ankle.								
Pharmacy Role	**n**	**% NSAIDs**	**%NPCWOC**	**%Paracetamol**	**%NPCC**	**%PDCCC**	**%NC**	**Other**
Intern Pharmacist	23	47.83	13.04	0.00	17.39	4.35	0.00	0.17
Locum Pharmacist	51	52.94	11.33	0.00	13.73	3.92	0.00	0.18
QPBPA	38	28.95	6.91	2.63	13.16	2.63	2.63	0.45
PEP	44	59.09	1.69	0.00	13.64	0.00	0.00	0.25
Pharmacy manager	43	53.49	11.22	0.00	6.98	2.33	0.00	0.23
Pharmacy owner	5	40.00	5.00	0.00	0.00	0.00	0.00	0.20
Total respondents	204	49.02	40.80	0.49	12.25	2.45	0.49	0.25

**Other: muscle relaxant, topical treatment.*

Table I.5: Treatment preference per pharmacy role type for a 12-year-old boy with fever and mild to moderate aches and pains.

A 12-year-old boy with fever and mild to moderate aches and pains.						
Pharmacy role	**n**	**% NSAIDs**	**%NPCWOC**	**%paracetamol**	**%PDCCC**	**%NPCC**
Intern Pharmacist	23.00	34.78	0.00	60.87	0.00	4.35
Locum Pharmacist	50.00	28.00	34.00	32.00	0.00	6.00
QPBPA	37.00	37.84	24.32	29.73	2.70	5.41
PEP	49.00	20.41	36.73	38.78	0.00	4.08
Pharmacy manager	42.00	54.76	21.43	23.81	0.00	0.00
Pharmacy owner	5.00	0.00	100.00	0.00	0.00	0.00
Total respondents	206.00	33.50	28.16	33.98	0.49	3.88

Table I.6: Treatment preference per pharmacy role type for an asthmatic 18-year-old girl with tension headache due to exam stress.

An asthmatic 18-year-old girl with tension headache due to exam stress.							
Pharmacy role	**Total**	**% NSAIDs**	**%NPCWOC**	**%paracetamol**	**%NPCC**	**%PDCCC**	**%PC**
Intern Pharmacist	24.00	12.50	4.17	33.33	0.00	16.67	4.17
Locum Pharmacist	46.00	8.70	4.35	19.57	0.00	28.26	15.22
QPBPA	37.00	5.41	2.70	40.54	0.00	13.51	10.81
PEP	47.00	12.77	2.13	29.79	0.00	17.02	12.77
Pharmacy manager	40.00	2.50	7.50	15.00	7.50	30.00	7.50
Pharmacy owner	5.00	0.00	0.00	0.00	0.00	40.00	0.00
Total respondents	199.00	8.04	4.02	26.13	1.51	22.11	10.55

Table I.7: Treatment preference per pharmacy role type for a 35-year-old male with fever and mild to moderate aches and pains.

A 35-year-old male with fever and mild to moderate aches and pains.									
	n	**% NSAIDs**	**%NPCWOC**	**%paracetamol**	**%NPCC**	**%PDCCC**	**%PC**	**%NC**	**% other**
Intern Pharmacist	22	18.18	22.73	27.27	22.73	4.55	0.00	4.55	0.00
Locum Pharmacist	48	16.67	39.58	10.42	25.00	6.25	0.00	0.00	2.08
QPBPA	36	19.44	41.67	5.56	16.67	11.11	2.78	0.00	2.78
PEP	45	26.67	31.11	8.89	28.89	0.00	4.44	0.00	0.00
Pharmacy manager	40	10.00	52.50	12.50	15.00	10.00	0.00	0.00	0.00
Pharmacy owner	5	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00
Total respondents	196	17.86	40.31	11.22	21.43	6.12	1.53	0.51	1.02

**Other: muscle relaxant, herbal supplement.*

APPENDIX J: APPROVAL OF TITLE

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

05 January 2018
Person No: 604744
PAG

Miss N Khan
P O Box 1611
Mondeor
Johannesburg
2110
South Africa

Dear Miss Khan

Master of Pharmacy: Approval of Title

We have pleasure in advising that your proposal entitled *Codeine use in over-the-counter (OTC) pain medication: A study of pharmacist knowledge and perception* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX K: ETHICAL CLEARANCE

R14/49 Miss Nasrene Khan

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160317

NAME: (Principal Investigator)	Miss Nasrene Khan
DEPARTMENT:	Pharmacy and Pharmacology
PROJECT TITLE:	Analysing the Use of Codeine in Over-the-Counter Pain Medication: A Study of Pharmacist Knowledge and Perception
DATE CONSIDERED:	01/04/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Neil Butkow

APPROVED BY: Professor P Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 18/04/2016

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in March and will therefore be due in the month of March each year.

Principal Investigator Signature

Date 05/05/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: PV Tobias Building 3rd Floor. Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za Fax +27 (0)11-717-1265
Email: HREC-Medical.ResearchOffice@wits.ac.za

13 October 2016

Miss Khan

Pharmacy and Pharmacology

Sent by email to: nasrene.khan93@gmail.com

Dear Miss Khan

Re: **Protocol Ref no: M160317**

Protocol Title: Analysing the Use of Codeine in Over-the-Counter Pain Medication: A Study of Pharmacist Knowledge and Perception

Principal Investigator: Miss Nasrene Khan

Protocol Amendment: Addition of an in-depth interview with 8-10 pharmacists in Gauteng region

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has approved the amendments for the abovementioned protocol, as detailed in your letter.

The following documents were received:

- Summary Letter.
- Interview Guide.
- Consent Form.
- Participant Information Sheet.
- Recording Consent Form.
- Study Protocol.

Thank you for keeping us informed and updated.

Yours Sincerely,

.....

Mr Rhulani Mkansi
Administrative Officer
Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
13 OCT 2016
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

APPENDIX L: TURNITIN REPORT

Date: 8 March 2018

Note to examiners:

Please note that my student Miss Nasrene Khan, 604744, received a similarity report of 16% from Turnitin. This was due to the fact that Turnitin found an 8% similarity to a paper submitted to the University of the Witwatersrand, which is the student's (Nasrene Khan) protocol submitted to Turnitin on the 24th March 2016. Please excuse this from the report.

Sincerely

Dr Neil Butkow
Dept Pharmacy and Pharmacology
Wits Medical School

Faculty of Health Science,
University of the Witwatersrand

Masters first submission

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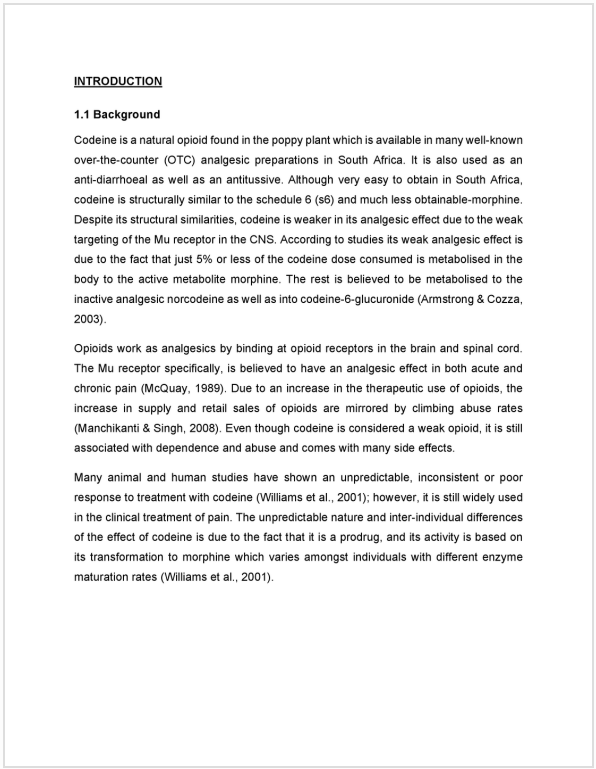

INTRODUCTION

1.1 Background

Codeine is a natural opioid found in the poppy plant which is available in many well-known over-the-counter (OTC) analgesic preparations in South Africa. It is also used as an anti-diarrhoeal as well as an antitussive. Although very easy to obtain in South Africa, codeine is structurally similar to the schedule 6 (s6) and much less obtainable-morphine. Despite its structural similarities, codeine is weaker in its analgesic effect due to the weak targeting of the Mu receptor in the CNS. According to studies its weak analgesic effect is due to the fact that just 5% or less of the codeine dose consumed is metabolised in the body to the active metabolite morphine. The rest is believed to be metabolised to the inactive analgesic norcodeine as well as into codeine-6-glucuronide (Armstrong & Cozza, 2003).

Opioids work as analgesics by binding at opioid receptors in the brain and spinal cord. The Mu receptor specifically, is believed to have an analgesic effect in both acute and chronic pain (McQuay, 1989). Due to an increase in the therapeutic use of opioids, the increase in supply and retail sales of opioids are mirrored by climbing abuse rates (Manchikanti & Singh, 2008). Even though codeine is considered a weak opioid, it is still associated with dependence and abuse and comes with many side effects.

Many animal and human studies have shown an unpredictable, inconsistent or poor response to treatment with codeine (Williams et al., 2001); however, it is still widely used in the clinical treatment of pain. The unpredictable nature and inter-individual differences of the effect of codeine is due to the fact that it is a prodrug, and its activity is based on its transformation to morphine which varies amongst individuals with different enzyme maturation rates (Williams et al., 2001).