

# **RETAIL PHARMACY NETWORK SALES TRENDS OF OVER-THE-COUNTER CODEINE CONTAINING MEDICINES IN GAUTENG, WESTERN CAPE AND KWAZULU NATAL**

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the degree of Master of Science in Medicine in Pharmaceutical  
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## **DECLARATION**

I Fortunate Fakudze, student number 0416482N declare that this Research Report is my own, unaided work. It is being submitted for the Master of Science in Medicine in Pharmaceutical Affairs at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signature: \_\_\_\_\_

Date: 17<sup>th</sup> March 2017

## **Dedication**

I would like to dedicate this research report to my family which has been my pillar of strength throughout the writing of this report. They have supported and encouraged me; they allowed me time to work on my project and for that I appreciate them. Special thanks go to my two children Mhlengi and Angella for their understanding and support and to my parents for their encouragements.

## **Abstract**

In the Republic of South Africa codeine containing medicines are either sold as prescription only medicines or over the counter depending on the strength of codeine contained in the medicine. The analgesic properties of codeine are thought to be derived from the conversion of codeine to morphine. Codeine is often combined with nonsteroidal anti-inflammatory drugs (NSAIDs). Codeine is a relatively weak opioid analgesic that has seemingly addictive properties; the misuse of codeine-containing-medicines can cause morbidity in patients with known codeine addiction. The Regulation of codeine has been reviewed in a number of countries to try and curb the misuse of the product. This involves the reduction in the strength of codeine, reduction in the package size and duration of treatment of over-the-counter (OTC) codeine containing products and in some countries the OTC codeine containing products have been rescheduled into prescription only medicines.

The study aims to monitor and describe trends in the sales of OTC codeine-containing medicines from Pick n Pay retail pharmacies in Gauteng, Western Cape and KwaZulu Natal provinces of South Africa from July 2011 to June 2014. Secondary data on the sales of OTC codeine-containing medicines from Pick n Pay Pharmacies database was obtained, which described the (1) pharmacy name, (2) the trade name of the medicine items sold, (3) the quantities of the medicines sold, (4) the purchase date of medicine, (5) the cost of the medicine, (6) the age of the purchaser, (7) the gender of the purchaser and (8) the mode of payment used when purchasing for the study period. A statistical software system, SPSS® version 20 was used to analyse the data.

The study findings indicate a steady increase in the sales of the OTC codeine containing medicine over the years. Females were found to be the main purchasers of these products and the age group which purchased most of the products is the 40 to 45 years age group. The top three selling brands of the OTC codeine containing medicines were found to be Genpayne Capsules (30%), Myprodol Capsules (27%) and Mybuline Tablets (14%) of all the sales of these products in the three provinces combined. The mode of payment used for these purchases was mainly cash payment which accounted for sixty-five percent of the payments. There is a need to review the Codeine Car Initiative to monitor and audit the sales of these products so as to make an informed decision on their appropriate regulation.

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## Table of Contents

Declaration.....	2
Dedication.....	3
Abstract.....	4
Acknowledgement.....	5
Chapter 1: Introduction and Background Information.....	10
1.1 Rationale.....	16
1.2 Research Question.....	17
1.3 Purpose of the study.....	17
1.4 Specific Objectives.....	17
Chapter 2: Study Methodology.....	18
2.1 Study Design.....	18
2.2 Study Population and data source.....	18
2.3 Sample Size.....	19
2.4 Data Collection Tools and Techniques.....	19
2.5 Data Analysis.....	20
Chapter 3: Results.....	21
3.1 General Demographic Information.....	21
3.2 Retail Pharmacy Sales.....	24
3.3 Mode of Payment of Purchasers.....	26
3.4 Costs of Medicines.....	26
Chapter 4: Provincial Analysis.....	28
4.1 Gauteng Province.....	28
4.2 Western Cape Province.....	29
4.3 Kwa-Zulu Natal Province.....	31
Chapter 5: Discussion.....	33
5.1 Limitations of the study.....	36
5.2 Conclusion and Recommendation.....	37
References.....	39

## **Table of Figures:**

### **Chapter 3**

Figure 3.1.1: Tree Diagram Indicating the Percentage Sales of Codeine-Containing Medicine by Province .....	22
Figure 3.1.2: Gender Distribution of Codeine-Containing Medicine Purchasers per Province over the Years 2011 – 2014 .....	23
Figure 3.1.3: Distribution of Purchasers by Age Groups over the Study Period, July 2011 – June 2014.....	23
Figure 3.2.1: Percentage Distribution of the Top Ten Selling Brands of Codeine-Containing Medicine in All Three Provinces, July 2011 - June 2014 .....	25
Figure 3.4.1: Total Cost to Purchasers of All Codeine-Containing Medicine over the Years.....	26
Figure 3.4.2: Total Cost of Codeine-Containing Medicine to Purchasers Forecasted up to 2016.....	27

### **Chapter 4**

Figure 4.1.1: Percentage Distribution of the Top Ten Selling Brands of Codeine-Containing Medicine in Gauteng Province – July 2011 – June 2014.....	28
Figure 4.1.2: Percentage Sales of Codeine-Containing Medicines by Mode of Payment, July 2011 - June 2014 in the Gauteng Province.....	29
Figure 4.2.1: Percentage Distribution of the Top Ten Selling Brands of Codeine-Containing Medicine in Western Cape Province – July 2011 – June 2014.....	30
Figure 4.2.2: Percentage Sales of Codeine-Containing Medicines by Mode of Payment, July 2011 - June 2014 in the Western Cape.....	30
Figure 4.3.1: Percentage Distribution of the Top Ten Selling Brands of Codeine-Containing Medicine in Kwa-Zulu Natal – July 2011 – June 2014 .....	31
Figure 4.3.2: Percentage Sales of Codeine-Containing Medicines by Mode of Payment, July 2011 - June 2014 in the Kwa-Zulu Natal.....	32

## **Table of Tables:**

### **Chapter 2**

Table 2.3.1: Pick n Pay Retail Pharmacies in the three provinces of SA that provided a sample for the study.....	19
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### **Chapter 3**

Table 3.2.1: Retail Pharmacy Sales of OTC Codeine-Containing Medicines per Province Cross .....	24
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Table 3.3.1: Mode of Payment used when Purchasing Codeine-Containing Medicine over the study period .....	26
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## **List of Acronyms**

ACMP: Access to controlled Medicines Programme

AIFA: Agenzia Italiana del Farmaco

CNS: Central Nervous System

CPS: Community Pharmacy Sector

EMA: European Medicine Agency

GDP: Gross Domestic Product

INCB: International Narcotics Control Board

MCC: Medicine Control Council

NGO: Non-Governmental Organization

NHIF: National Health Insurance Fund

NHS: National Health System

NHI: National Health Insurance

NSAID: Non-Steroidal Anti-Inflammatory Drug

OTC: Over-the-counter

PHC: Primary Health Care

PSSA: Pharmaceutical Society of South Africa

SNPs: Single Nucleotide Polymorphisms

USFDA: United States Food and Drug Authority

WHA: World Health Assembly

NDPSC: National Drugs and Poisons Schedule Committee

## Chapter 1: Introduction and Background Information

In the Republic of South Africa codeine containing medicines are either sold over-the-counter or as prescription only medicines depending on their schedule. Scheduling is a classification system for controlling how medicines and related chemicals are made available to the public. The primary consideration in scheduling a substance is its safety profile in relation to the therapeutic indication for its use. A medical substance may also be listed in more than one schedule based on its dosage form, route of administration, strength, indication, dose and treatment duration. The major determining factors in the scheduling of medicines in South Africa are the toxicity evidence of the substance, its safety in use, the proposed indication for the substance, the need for a medical diagnosis, monitoring, medical management by healthcare professionals, the abuse potential and the need for access to the substance<sup>1, 2</sup>.

Different countries have different pharmaceutical scheduling arrangements; Australia and New Zealand have four schedules which are prescription only (schedule 4), pharmacist only (schedule 3), pharmacy only (schedule 2) and general sale medicines. The United Kingdom has three schedules which are prescription only, pharmacy only and general sales medicines whilst the United States of America have two schedules which are prescription and non-prescription medicines. Canada has scheduled its medicines into four schedules at provincial level; prescription medicines (schedule 1), pharmacist assisted (schedule 2), pharmacy self-selection (schedule 3) and general sales<sup>3</sup>. South Africa has scheduled medicines into eight (8) schedules which can be broken down into four main schedules like Australia and New Zealand, and these are prescription only (schedule 3 to 8), pharmacist assisted (schedule 2), pharmacy only (schedule 1) and general sales (schedule 0). Internationally, a number of factors drive the rescheduling of medicines; in the United Kingdom, factors driving the rescheduling of medicines from prescription only to pharmacy only medicines include patient empowerment, consumerism, decreasing power of the professions, pharmacists drive to extend their role and the government's policy to contain the National Health System's medicine expenditure<sup>4</sup>. The increased public access due to the availability of non-prescription medicines which were previously prescription only has given rise to an increase in the trend of self-medication<sup>5, 6</sup>.

In South Africa codeine phosphate is a schedule six (6) medicine but it became a schedule two (2) medicine when in combination with one or more therapeutically active substance(s) containing 20mg or less per dosage unit and for liquids oral preparations containing 20mg or less per 5ml dosage unit. In February 2015, the Medicines Control Council resolved to reschedule Acetyldihydrocodeine, Codeine, Dihydrocodeine and Norcodeine. For all schedule 2 listing the maximum amount of codeine and dihydrocodeine per dosage unit was reduced from 20mg to 10mg, the maximum daily dose was limited to 80mg and the maximum treatment period was reduced to five (5) days for oral solid preparations. For oral liquid preparations the maximum amount of codeine and dihydrocodeine per 5ml dosage unit was reduced from 20mg to 10mg, the maximum daily dose was limited to 80mg and the maximum pack size was reduced to 100ml. Codeine and dihydrocodeine oral and liquid preparations exceeding the maximum quantity of active per dosage unit (of 10mg) was included in the schedule 3 listing. Acetyldihydrocodeine and norcodeine were rescheduled from schedule 2 to schedule 6<sup>7</sup>.

In Australia the National Drugs and Poisons Schedule Committee (NDPSC) in June 2008 formed a Codeine Working Party to review the availability of all over-the-counter (OTC) combination analgesics containing codeine following concerns on the abuse of codeine-ibuprofen combination analgesic products. In February 2009 the NDPSC; based on the report from the Codeine Working Party decided not to reschedule all OTC codeine from Schedule 2 to Schedule 3 but decided to limit the maximum daily dose to 100mg codeine, limit the pack size to a five (5) days' supply, restrict preparations to 12mg of codeine per dosage unit and restrict undivided preparations to 0.25% codeine. In June 2009 the NDPSC agreed on the scheduling of OTC codeine combinations for coughs and cold to remain as they are and to reschedule all OTC combination analgesics containing codeine from schedule 2 to schedule 3 with the February 2009 limits. This decision was to be implemented on the 1<sup>st</sup> of May 2010<sup>8</sup>.

The rescheduling of codeine to schedule 3 in Australia failed to achieve the required reduction in harm to affected individuals. Further studies indicated no reduction in the risk associated with codeine since the rescheduling in the year 2010. Codeine is increasingly a drug of abuse in Australia with some individuals developing severe adverse effects from the high doses of paracetamol and ibuprofen that accompany the use of large numbers of tablets in codeine-dependent persons. An interim decision was made by the Australian Advisory Committee on Medicines Scheduling to be implemented on the 1<sup>st</sup> of June 2016 to delete the

schedule 3 entry for codeine and reschedule all current schedule 3 codeine to schedule 4 (prescription only) as a result of issues of morbidity, toxicity and dependence<sup>8</sup>. In Europe, codeine is not an OTC medicine; codeine is a prescription only medicine in thirteen (13) countries in Europe namely; Austria, Belgium, Croatia, Czech Republic, Finland, Germany, Greece, Italy, Luxembourg, Portugal, Slovakia, Spain and Sweden. Codeine is also a prescription only medicine in the USA, Hong Kong, Iceland, India, Japan, Maldives, Romania, Russia and the United Arab Emirates<sup>8</sup>,

Codeine and dihydrocodeine are contained in many medicines sold over-the-counter in the United Kingdom pharmacies. In July 2005, a voluntary agreement was reached with manufacturers to restrict the pack sizes of OTC medicines containing codeine or dihydrocodeine to 32 tablets. In January 2009 the All-Party Parliamentary Drug Misuse Group (APPDMG) published a report with evidence received from the Royal Pharmaceutical Society of Great Britain, the self-help group over-count and the Medicines and Healthcare products Regulatory Agency (MHRA) on physical dependence and addiction to prescription and OTC medicines. The APPDMG made recommendations to reduce the risk of misuse of medicines in particular OTC medicines containing codeine or dihydrocodeine on the basis of the information from the report, the new sales data and information from the self-help group. The recommendations stated that all indications relating to colds, influenza, coughs and sore throat and reference to minor pain conditions should be removed from product information; the patient information leaflets and labels should state that the products are for short-term use only; all pack sizes greater than 32 tablets of solid dose codeine or dihydrocodeine-containing OTC medicines including effervescent formulations will only be available on prescription only and advertisements should be updated to reflect the new indications and warnings without making reference to the painkilling power and strength and the advert should include the statement, “can cause addiction and for three days use only”<sup>9</sup>.

Addiction has traditionally been associated with illicit substance abuse. However, an increasing number of cases are being associated with the intake of codeine, although considered a weak opioid, codeine, like all opioids is associated with tolerance and dependence with long term use. In clinical use, codeine is mainly used as an analgesic, an antidiarrheal and or a cough suppressant agent<sup>10</sup>. However, there is no evidence suggesting that codeine shortens the duration or reduces the severity of paediatric coughs<sup>11</sup>. The analgesic properties of codeine are thought to be derived from the conversion of codeine to

morphine. Codeine, also known as 3-methylmorphine is a pro-drug and as such it has to be converted to morphine for it to be active and this is achieved through the removal of a methyl group by the cytochrome P450 2D6 enzyme<sup>12</sup>. The known analgesic efficacy of codeine is influenced by the polymorphisms of the cytochrome P450 enzymes<sup>13</sup>. There is significant inter-individual variability in the activity of this enzyme and the genetic variations affect the rate at which people convert the prodrug to morphine.

An *in-vitro* DNA sequence variation at a single location in the genome resulting in two allelic variants is called a single nucleotide polymorphism (SNP) occurring commonly within a population. This occurrence implies that the distributions among populations of the variant forms can differ but overall, they are consistent with a population. The CYP2D6 (a Cytochrome P450 2D6 enzyme in humans) has an important role in the metabolism of about twenty-five (25) percent of currently used medicines; these include many agents used to treat pain. Therefore, the presence of an allelic variant in a particular CYP isoform will result in one of four drug-metabolizing phenotypes namely; poor metabolizers, intermediate metabolizers, extensive metabolizers or ultra-rapid metabolizers<sup>14,15</sup>.

So far, only about ten per cent (10%) of the codeine dose is converted to morphine and other metabolites such as norcodeine, normorphine and hydrocodone. Codeine and its metabolites are excreted by the kidney as conjugates with glucuronic acid<sup>16</sup>. Common adverse effects associated with the use of codeine are drowsiness and constipation, less common adverse effects include itching, nausea, vomiting, dry mouth, miosis, orthostatic hypotension, urinary retention, depression, and coughing. Rare adverse effects include anaphylaxis, seizure, acute pancreatitis and respiratory depression<sup>17</sup>. Individuals with poor metabolizer phenotype tend to have virtually undetectable levels of morphine as a result codeine lacks efficacy in this group<sup>18</sup>. However, ultra-rapid metabolizers' phenotypes individuals will extensively metabolize codeine to morphine increasing the risk of respiratory depression at regular doses of codeine<sup>19</sup>. This is exacerbated by higher and or repeated doses of codeine.

Pharmacogenetic variants of codeine have been identified which can influence the rate at which codeine is metabolised to morphine and its subsequent effects. The global distribution of ultrafast metabolising variant of CYP2D6 varies geographically (40% in North Africa, 26% in Oceania, 12% in the Middle East, 8% in North America and 3% in Europe), and this

results in the production of high levels of morphine after codeine intake<sup>20</sup>. Pharmacogenetics is the study of inherited genetic differences in medicine metabolic pathways affecting the individual's therapeutic response and adverse effects to medicines<sup>21</sup>. The pharmacokinetics of codeine is unpredictable. Codeine has been used for over two hundred (200) years; but it has not been subjected to the mandatory vigorous safety studies applied to new chemical entities.

Limited research has been done on the extent and the nature of the over-the-counter (OTC) medicine misuse in South Africa. The findings from the specialist treatment centres in Cape Town indicated that Benzodiazepines are the most misused products followed by analgesics. The study indicated that of the misused analgesics the codeine-containing OTC medicines were the ones mostly misused. The study highlighted that patients using OTC medicines as their primary drug of misuse are more likely to be females aged over forty (40) years whilst males over the age of forty (40) use OTC medicines as an additional drug of misuse<sup>22</sup>. Deaths and serious morbidity such as liver toxicity and gastric haemorrhage have been reported. Codeine dependence and abuse have been reported to occur in people who have used OTC products for pain conditions initially.

Over-the-counter medicines are generally medicines of acceptable safety margin, low misuse and abuse potential. They are medicines where a medical practitioner is not needed for the safe and effective use of the product since they are easy to recognize and use<sup>23</sup>. The availability of medicines without a prescription from a medical practitioner has offered benefits in terms of improved access, choice of medicines, the involvement of individuals in their health and in the decision making process thus reducing healthcare costs<sup>24</sup>. It has been suggested that the low price of codeine containing medicines, their ease of availability over-the-counter and the tendency of the public to perceive OTC medicines to be safer than the prescription medicines contribute a lot to their rapidly increasing potential as drugs of abuse<sup>25, 26, 27, 28</sup>.

Similarly, codeine can be used as a recreational drug and the potential of codeine abuse is lower than that of heroin or morphine. However, the ingestion of large doses of codeine produce euphoric effects, thus illicit opioid users turn to these non-prescription products in the absence of their usual opioid supplies<sup>29</sup>. A heroin addict may use codeine to ward off the the unpleasant physical reaction that accompanies the process of ceasing to take an addictive drug such as heroin. The misuse of codeine-containing-medicines can cause morbidity in

patients with known codeine addiction<sup>30,31</sup>. According to Matthew F. *et al* study findings, 96% of the patients in the study reporting prolonged use of high doses of OTC medicines containing codeine and ibuprofen exhibited non-steroidal anti-inflammatory drug (NSAID) toxicity which included gastrointestinal diseases, renal failure, anaemia and severe hypokalaemia.

Analgesics with anti-inflammatory properties as a group of pharmaceuticals record the highest sales among OTC medicines<sup>32</sup>. A large proportion of OTC analgesics contain NSAIDs in combination with other agents such as codeine and paracetamol<sup>33</sup> in varying concentrations. There is limited evidence to suggest the analgesic benefits caused by the synergy obtained from the incorporation of low-dose codeine into combination analgesics<sup>34</sup>. There are disadvantages however, in combining relatively safe analgesics like ibuprofen and paracetamol with small doses of opioids that may bring about minimal therapeutic benefits but increase the risk profile of the medicines in terms of abuse, addiction and adverse effects<sup>35</sup>. If high doses of combination analgesics are ingested in a bid to experience the opioid effects, there is an increased likelihood of the occurrence of non-opioid toxicity as a result of the other combination analgesic such as ibuprofen, aspirin or paracetamol in the preparation<sup>36</sup>. The misuse of these products may indicate that patients lack knowledge on the potential side effects associated with their medication especially OTC medicines.

The combinations of codeine with ibuprofen and combinations of codeine with paracetamol have been observed to be problematic largely because ibuprofen has been said to cause perforated gastric ulcers and hypokalaemia secondary to renal acidosis<sup>37, 38, 39, 40, 41</sup>. Although paracetamol does not cause gastrointestinal problems like ibuprofen, it can cause liver damage when large doses are ingested per given time. Paracetamol is metabolized in the liver and if the liver glutathione is depleted, hepatotoxicity may occur.

The United States Food and Drug Authority (US-FDA), European Medicine Agency (EMA) and the Agenzia Italiana del Farmaco (AIFA) confirmed a ban on the use of codeine in children undergoing surgery for tonsillectomy and adenoidectomy for obstructive sleep apnea. EMA and AIFA extended this ban on the use of codeine used for pain control in children under twelve (12) years<sup>42</sup>. Codeine has a high potential for abuse and addiction, but the US-FDA panel was more worried about children suffering dangerous side effects than children becoming addicted. The US-FDA has been updating codeine's warnings for almost a

decade. In 2007, the agency added a statement about a risk of respiratory depression in infants and nursing mothers to the label of drugs containing codeine. In 2012, the agency announced it had received reports of children dying after taking codeine following a tonsillectomy or an adenoidectomy. Then in 2013, the agency issued a black-box warning, its strongest warning, about the risk of death in children who receive codeine after a tonsillectomy or adenoidectomy<sup>43</sup>. In South Africa, patients are required to supply key personal details such as name, date of birth and address, when purchasing a range of popular OTC medicines containing codeine as of January 2014 however, this only happens in limited retail pharmacies.

## **1.1 Rationale**

South Africa's total expenditure on health as a percentage of GDP is 8.5 and the total expenditure on health per capita is 942; yet the country has poor health status indicators compared to other middle-income countries, despite such high expenditure on healthcare. Health Care in South Africa is generally financed through a combination of mechanisms. In 2005, allocations from general tax accounted for about forty percent (40%), whereas private medical schemes accounted for forty-five percent (45%), and out-of-pocket payments about fourteen percent (14%) of total health care financing<sup>44; 45</sup>.

A number of countries including the United Kingdom have seen an increase in codeine related mortality<sup>46</sup> and in the United States of America<sup>47</sup>, the United Kingdom and Australia<sup>48</sup> case series of codeine deaths have been reported. A potential driver of the deaths in Australia may have been the introduction of OTC products containing larger amounts of codeine including codeine combined with ibuprofen. The stakeholders in both the South African Pharmaceutical Manufacturing Industry and the South African retail pharmacy have expressed concerns that the move to up-schedule codeine containing OTC products would put these medicines out of reach of many poor and economically disadvantaged South Africans.

Instead, both the South African Pharmaceutical Manufacturing Industry and Retail Pharmacy Associations feel that effective self-regulation will help preserve the OTC sales of these medicines that would continue benefiting the patients. This argument resulted in the initiation of the Codeine Care Initiative by the Community Pharmacist Sector (CPS) and



Pharmaceutical Society of South Africa (PSSA) to monitor and audit the sale and supply of codeine-containing medicines<sup>49</sup>. This initiative utilises the computerised system for monitoring sales of codeine-containing medicines. However, there were challenges with this initiative which included the fact that consumers had a choice of whether to participate or not, also it was voluntary for pharmacies to sign up to use this initiative to access and share their database and many pharmacies lacked the required software. This resulted in few retail pharmacies taking part in the initiative.

The purpose of the research study is to establish the extent of the sales of OTC codeine-containing medicines in retail pharmacies in South Africa. The study utilized the Pick n Pay Retail Chain Pharmacies database of the sales of OTC codeine-containing medicines within the Gauteng, Western Cape and KwaZulu Natal province as a proxy for retail pharmacies in South Africa. The information may be used to inform decision-making with regards to the regulation and control of the sale of OTC codeine-containing products in South Africa. Ascertaining the trends of the sales of OTC codeine containing medicines within these pharmacies will also provide a basis for future studies.

## **1.2 Research Question**

What were the trends in the sale of the OTC codeine-containing medicines in South Africa over the period of July 2011 to June 2014?

## **1.3 Purpose of the study**

The purpose of the study is to monitor and describe trends in the sales of OTC codeine-containing medicines from Pick n Pay retail pharmacies in the Gauteng Province, Western Cape Province and the Kwa-Zulu Natal Province over the period of July 2011 to June 2014.

## **1.4 Specific Objectives**

The study aims to:

- i) Describe the sales trends of OTC codeine-containing medicines; and

ii) Determine the demographics of the populations purchasing OTC codeine-containing medicines over the study period.

## **Chapter 2: Study Methodology**

### **2.1 Study Design**

This is a retrospective, descriptive study of the sales of OTC codeine-containing medicines using secondary data from the Pick n Pay Retail Chain Pharmacies in the Gauteng Province, Western Cape Province and the Kwa-Zulu Natal Province over the period of July 2011 to June 2014 as a proxy for retail pharmacies in South Africa. The study was a record review and consent from patients was not required. The Pick n Pay Retail Pharmacies were chosen because they are one of the retail chain pharmacies that adopted the Codeine Care Initiative to monitor and audit the sales and supply of codeine-containing medicines. They utilise the computerised system for monitoring sales of codeine-containing medicines which stand-alone owned pharmacies did not voluntarily sign up to use because they lacked the required software. The three provinces were included in the study because they have high populations compared to the other provinces in South Africa, together they account for more than 50% of the total population; the Gauteng Province has the most population followed by the Kwa-Zulu Natal Province and lastly the Western Cape Provinces according to the 2011 census. Western Cape was chosen because it had more Pick n Pay pharmacies compared to the Eastern Cape which happens to have a high population compared to it.

### **2.2 Study Population and Data Source**

Data on the sale of OTC codeine-containing medicines from eighteen (18) Pick n Pay retail pharmacies was extracted from twenty-five (25) Pick n Pay retail pharmacies in the three (3) provinces of South Africa namely; the Gauteng Province, Western Cape Province and Kwa-Zulu Natal Province data base. The three provinces were included in the study because they have the highest population compared to the other provinces in South Africa.

## 2.3 Sample Size

The data of the OTC codeine-containing medicines from the eighteen (18) Pick n Pay Retail Pharmacies in Gauteng, Western Cape and Kwa-Zulu Natal were used from the total of twenty-five (25) Pick n Pay retail pharmacies in the three provinces due to data availability. The Pick n Pay Retail Pharmacy outlets studied are shown in Table 2.3.1 below.

**Table 2.3.1: Pick n Pay Retail Pharmacies in the three provinces of SA that provided a sample for the study**

Site Identified	Number of Pick n Pay Retail Pharmacies Studied	% Retail Pharmacies	Population Size (2011 Census)
Gauteng Province	10	55.5	12272263
Western Cape Province	5	27.8	5822734
Kwa-Zulu Natal	3	16.7	10267306
<b>TOTAL</b>	<b>18</b>	<b>100</b>	<b>28362303</b>

## 2.4 Data Collection Tools and Techniques

The data was collated using Microsoft Excel spreadsheet as a data abstraction form.

### Variables in the Study:

The variables in this research study consisted of the following demographic characteristics:

- i). the pharmacy name,
- ii). the trade name of the medicine items sold,
- iii). the quantities of the medicines sold,
- iv). the purchase date of medicine,
- v). the cost of the medicine,
- vi). the age of the purchaser,
- vii). the gender of the purchaser and

- viii). the mode of payment used when purchasing (cash or medical aid) for the period July 2011 to June 2014.

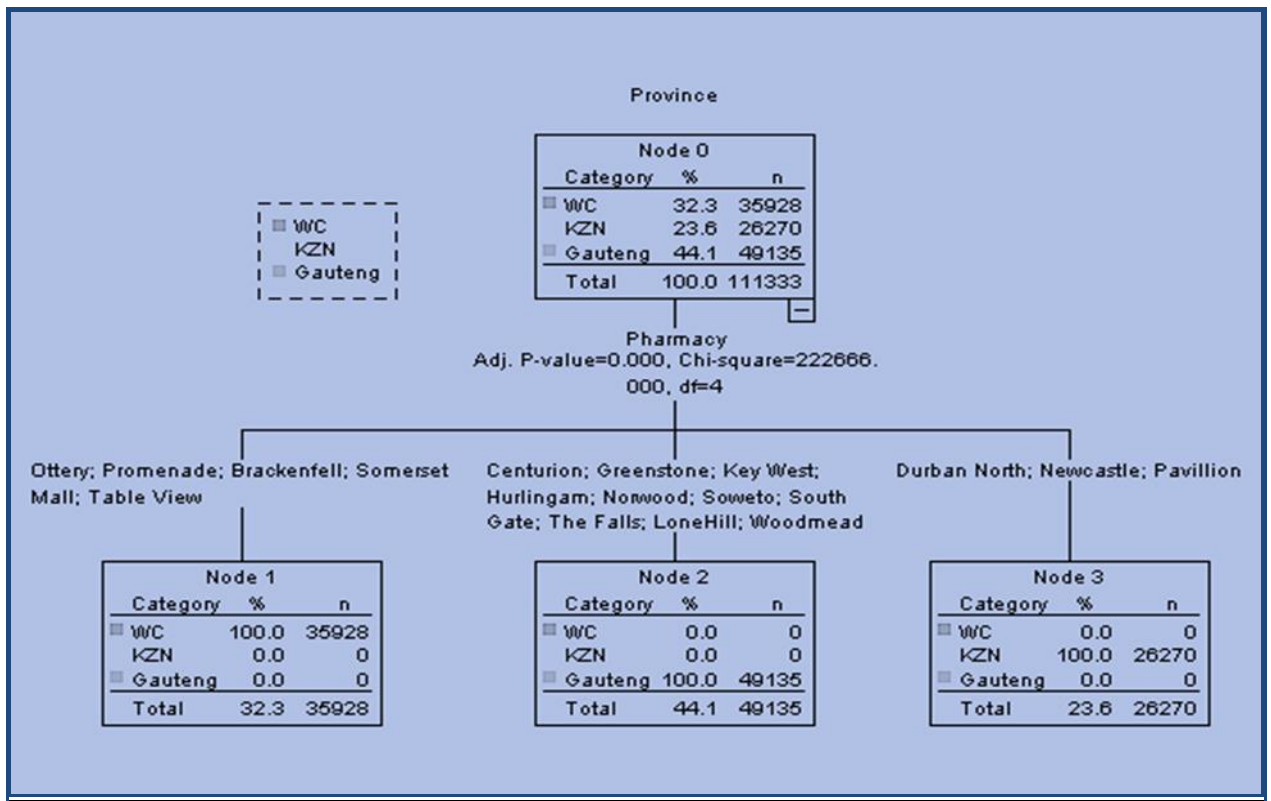
## **2.5 Data Analysis**

A statistical software system, SPSS version 20 was used to analyse the data. Descriptive statistics were used to show the study results per variable and frequency distribution analyses were drawn. For visual presentation of results, Microsoft Excel 2010 was used to create charts and graphs. Data was analysed and disaggregated by province as well as by the year in which sale of OTC codeine-containing medicines were made in order to see the sales trends. Further disaggregation of results was made in terms of other demographic variables included in the study such as gender, age and mode of payment. To measure the significant changes noted in the sampling procedure the Chi-Square Test was applied to the relevant variables.

## Chapter 3: Results

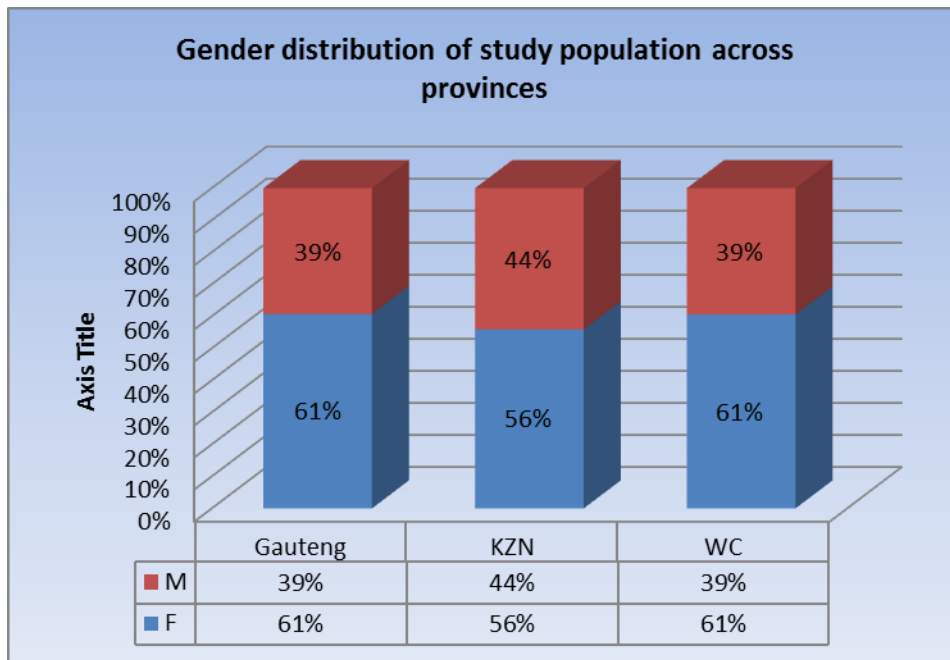
### 3.1 General Demographic Information

The results of the tree diagram indicates that a majority (44.1%) of the purchases of OTC codeine-containing medicines were made in the Gauteng Province, followed by the Western Cape at 32.3 % and Kwa-Zulu Natal Province accounting for 23.6% of the purchases made. This is in-line with the number of retail pharmacies sampled from the respective provinces however; it is not in line with the population sizes of the three provinces. The Gauteng Province has the most population followed by the Kwa-Zulu Natal Province and lastly the Western Cape Provinces according to the 2011 census. In order to measure if these different sample sizes included in the study caused any significant variations in the analysis, the Chi-Square ( $X^2$ ) Test statistic was applied. Since the *P*-value is less than 0.05, the results of the Chi-Square show that there are significant differences noted across the provinces. The higher the number of pharmacies sampled in a province, the higher the number of sales irrespective of the population size which might have been expected to have an influence in the observed sales trends.

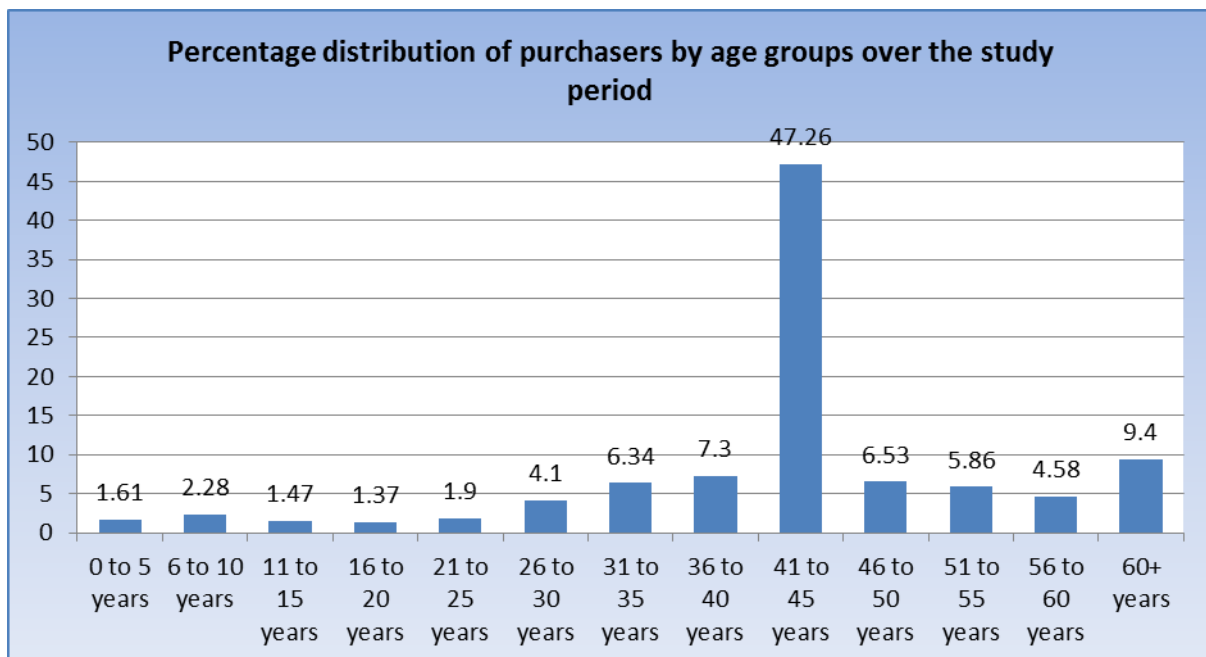


**Figure 3.1.1: Tree Diagram Indicating the Percentage Sales of Codeine-Containing Medicine by Province**

The gender distribution of the purchasers of the codeine-containing medicines during the study period July 2011 to June 2014 indicates that the more purchasers of these medicines are females which accounts for fifty-nine (59) percent of all the purchasers in all the three provinces combined. The breakdown of the gender distribution over the years indicates that the pattern remains the same over the years with the females carrying out the most purchases over the provinces and over the years July 2011 to June 2014.



**Figure 3.1.2: Gender Distribution of Codeine-Containing Medicine Purchasers per Province over the Years 2011 – 2014**



**Figure 3.1.3: Distribution of Purchasers by Age Groups over the Study Period, July 2011 – June 2014**

Figure 3.1.3 indicates the age groups distribution of the purchasers of the codeine-containing medicines over the study period of July 2011 to June 2014; the age group 41 to 45 years recorded 47.26 % of all the purchases followed by the age group of 60 plus years which

recorde 9.4% of all the purchase. The age group to record the least purchases over the study period was the age group 16 to 20 years which accounted for 1.37% of all the purchases.

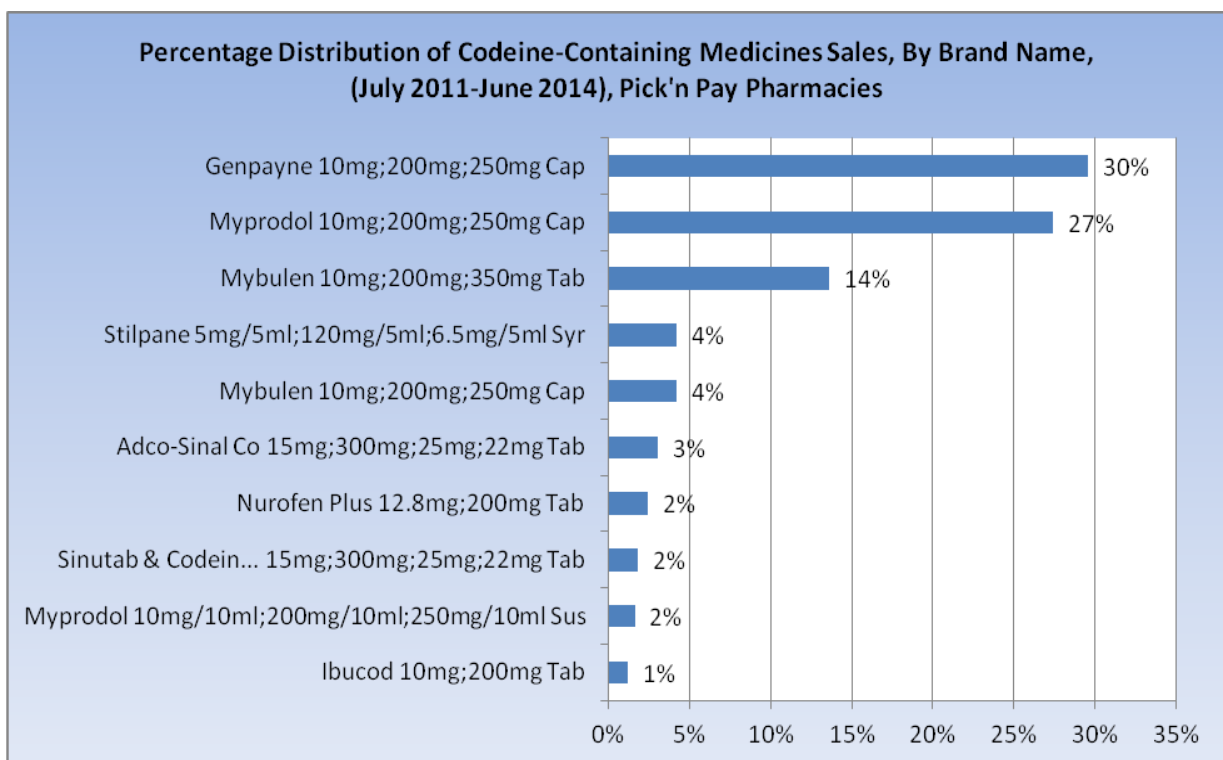
### 3.2 Retail Pharmacy Sales

**Table 3.2.1: Retail Pharmacy Sales of OTC Codeine-Containing Medicines per Province Cross**

Retail Pharmacy Name	# of OTC codeine containing medicine sales			Total # of OTC codeine containing medicine sales	Percentage of Sales per retail pharmacy
	Western Cape	KZN	Gauteng		
Brackenfell	9361	-	-	9361	8%
Ottery	10062	-	-	10062	9%
Promenade	6952	-	-	6952	6%
Somerset Mall	6005	-	-	6005	5%
Tablet View	3548	-	-	3548	3%
Durban North	-	22020	-	22020	20%
Newcastle	-	2656	-	2656	2%
Pavilion	-	1594	-	1594	1%
Centurion	-	-	6249	6249	6%
Hurlingham	-	-	6582	6582	6%
Greenstone	-	-	5614	5614	5%
Lone Hill	-	-	2689	2689	2%
Norwood	-	-	8226	8226	7%
South Gate	-	-	4215	4215	4%
The Falls	-	-	3602	3602	3%
Woodmead	-	-	2913	2913	3%
Key West	-	-	2560	2560	2%
Soweto	-	-	6485	6485	6%
<b>Total # of Sales</b>	<b>35928</b>	<b>26270</b>	<b>49135</b>	<b>111333</b>	



The breakdown of sales over the study years by pharmacy indicates that most sales of OTC codeine-containing medicines were recorded by the Durban North Pharmacy in the Kwa-Zulu Natal Province which recorded twenty (20) percent of the total sales of all eighteen (18) retail pharmacies studied. This was followed by the Ottery Pharmacy in the Western Cape Province which recorder nine (9) percent of the sales and Brackenfell Pharmacy also in the Western Cape Province which recorder eight (8) percent of the sales. The pharmacy with the least sales of codeine-containing medicines was the Pavilion Pharmacy in the Kwa-Zulu Natal Province.



**Figure 3.2.1: Percentage Distribution of the Top Ten Selling Brands of Codeine-Containing Medicine in All Three Provinces, July 2011 - June 2014**

Figure 3.2.1 indicates that over the study period July 2011 to June 2014 the most sales by brand name of the OTC codeine containing medicines in all the three provinces combined were those of Genpayne Capsules which recorded 30% of all the sales followed by Myprodol Capsules which recorded 27% of all the sales and Mybulen Tablets with fourteen (14%) of all the sales. The top three selling brands alone accounted for 71% of all the OTC codeine-containing medicine sales over the study period.

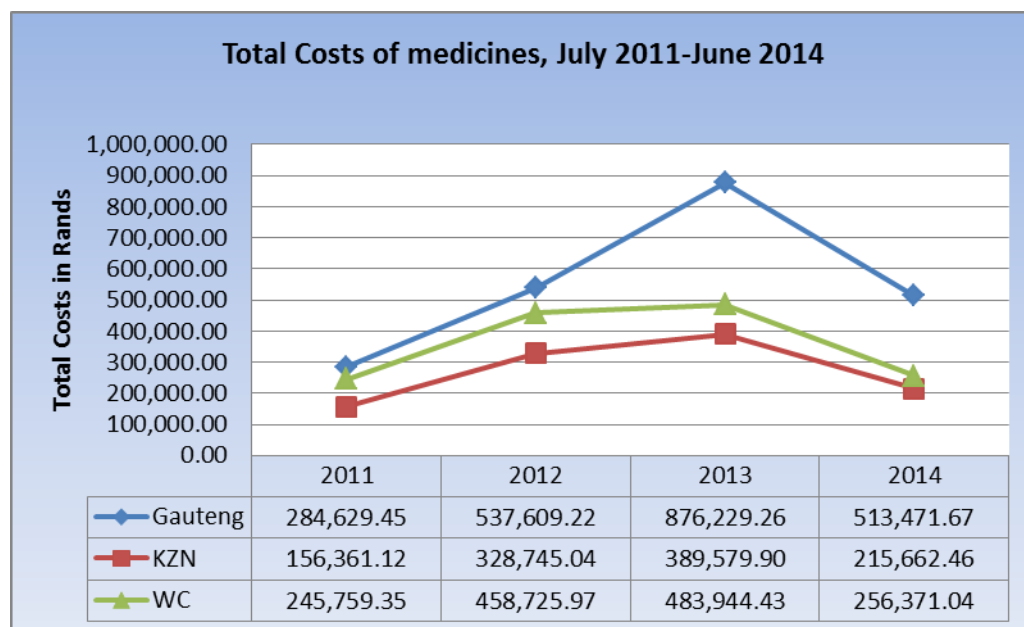
### 3.3 Mode of Payment of Purchasers

**Table 3.3.1: Mode of Payment used when Purchasing Codeine-Containing Medicine over the study period**

	Frequency	Percentage	Valid Percentage	Cumulative Percentage
<b>Medical Aid</b>	39511	35.49	35%	35
<b>Cash</b>	71822	64.51	65%	100.0
<b>Total</b>	<b>111333</b>	<b>100.0</b>	<b>100%</b>	

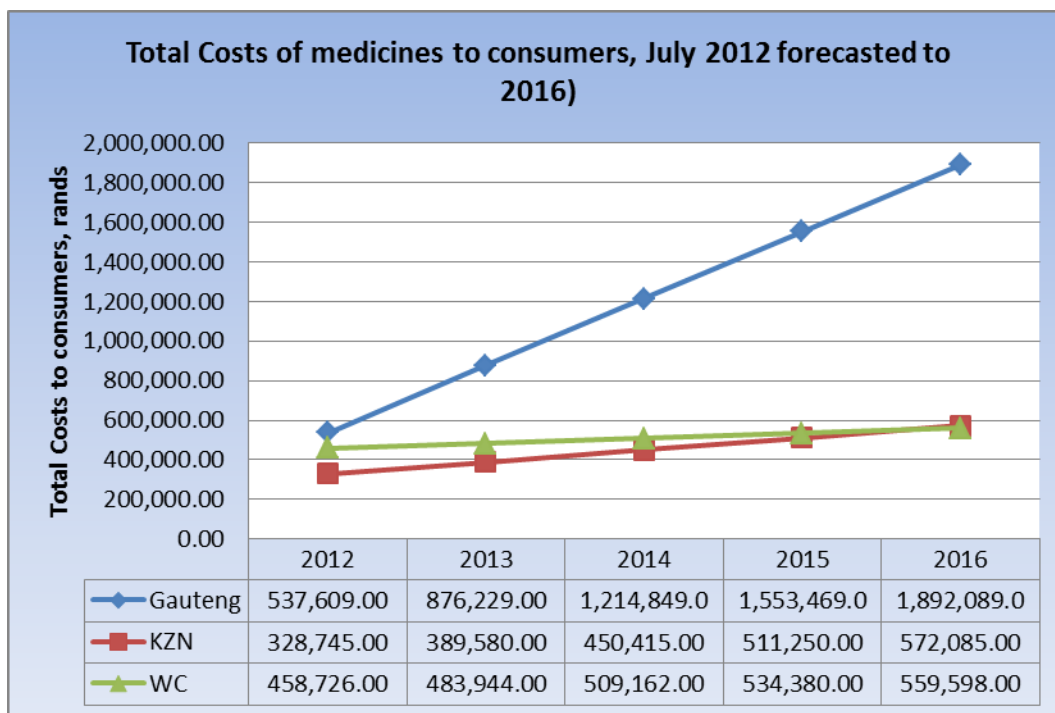
A majority of codeine-containing medicines purchasers (65%) use cash to pay for their medicines, as shown in table 3.3.1 above. The remaining 35% of the purchasers in the study use medical aid to pay for their medicines.

### 3.4 Costs of Medicines



**Figure 3.4.1: Total Cost to Purchasers of All Codeine-Containing Medicine over the Years**

Figure 3.4.1 indicates that the total cost of all the codeine containing medicines purchased over the study period July 2011 to June 2014 was R4, 747,088.91.



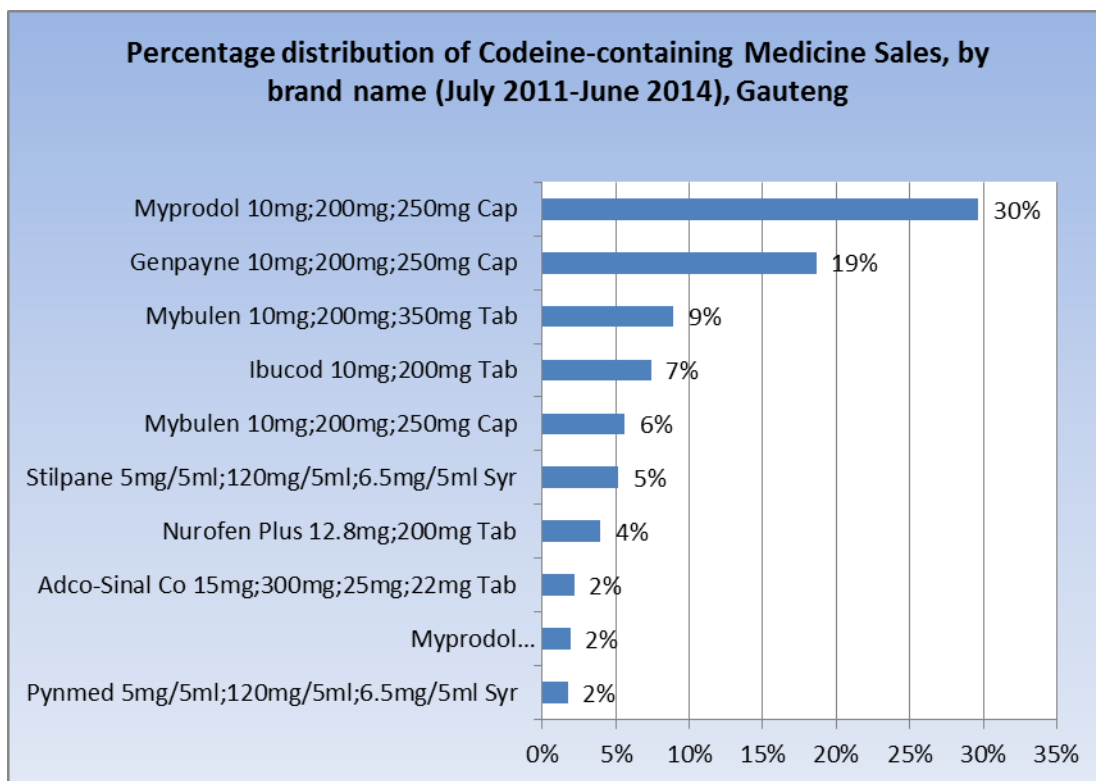
**Figure 3.4.2: Total Cost of Codeine-Containing Medicine to Purchasers Forecasted up to 2016**

Figure 3.4.2 above attempts to show the trends in the cost of these medicines in the event that the full years are represented using an extrapolation. This indicates an increase in the total cost spent by purchasers on the codeine containing medicines over the years in all three provinces.

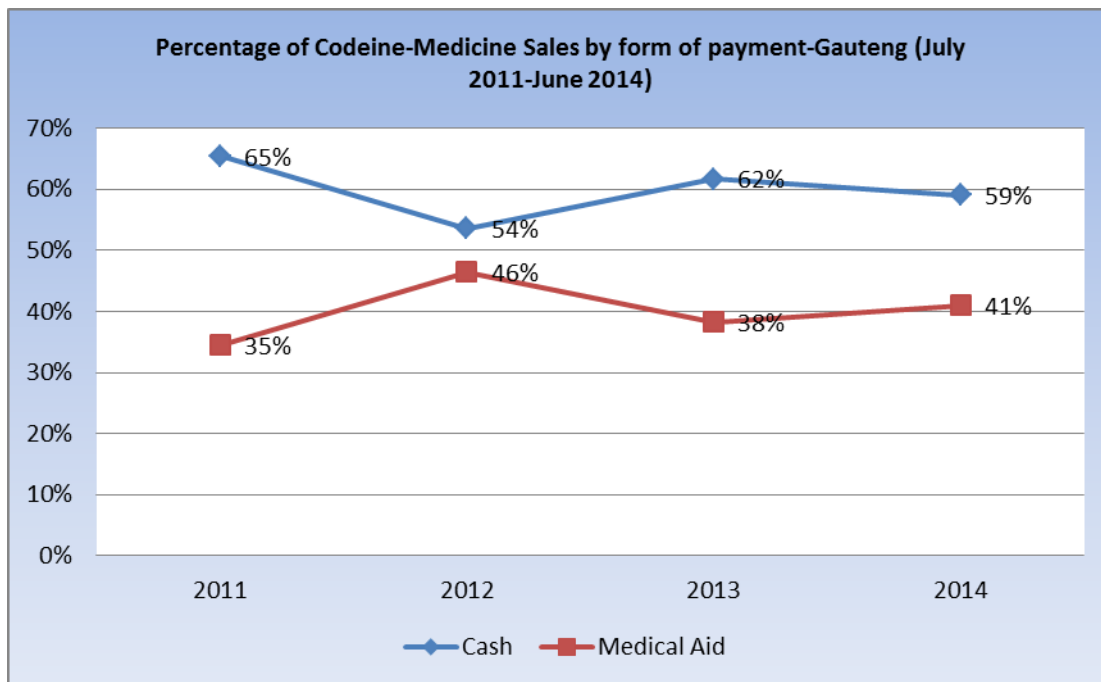
## Chapter 4: Provincial Analysis

### 4.1 Gauteng Province

In the Gauteng Province the top three selling OTC codeine-containing medicinal products by brand name are Myprodol Capsules accounting for 30% of all the sales followed by Genpayne Capsules accounting for 19% and lastly Mybulen Tablets accounting for 9% of all the sales. The top three selling brands alone accounted for 58% of all the OTC codeine-containing medicine sales whilst the top ten selling brands accounted for 85% of all the sales of OTC codeine containing medicines sold in the Gauteng Province over the study period.



**Figure 4.1.1: Percentage Distribution of the Top Ten Selling Brands of Codeine-Containing Medicine in Gauteng Province – July 2011 – June 2014**

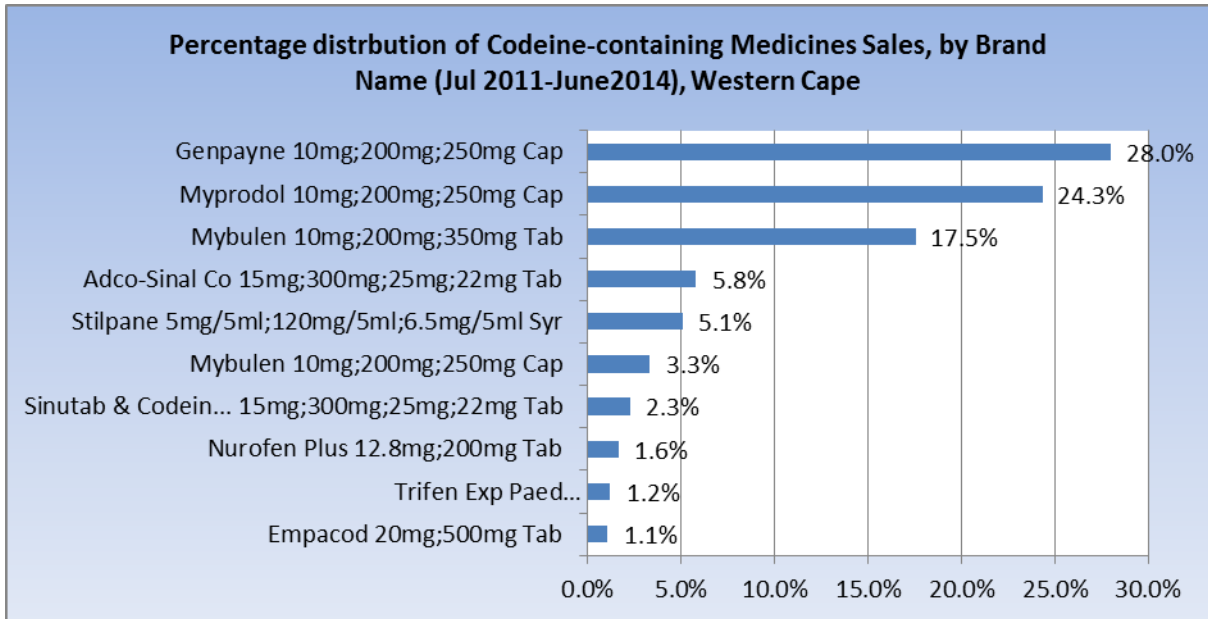


**Figure 4.1.2: Percentage Sales of Codeine-Containing Medicines by Mode of Payment, July 2011 - June 2014 in the Gauteng Province**

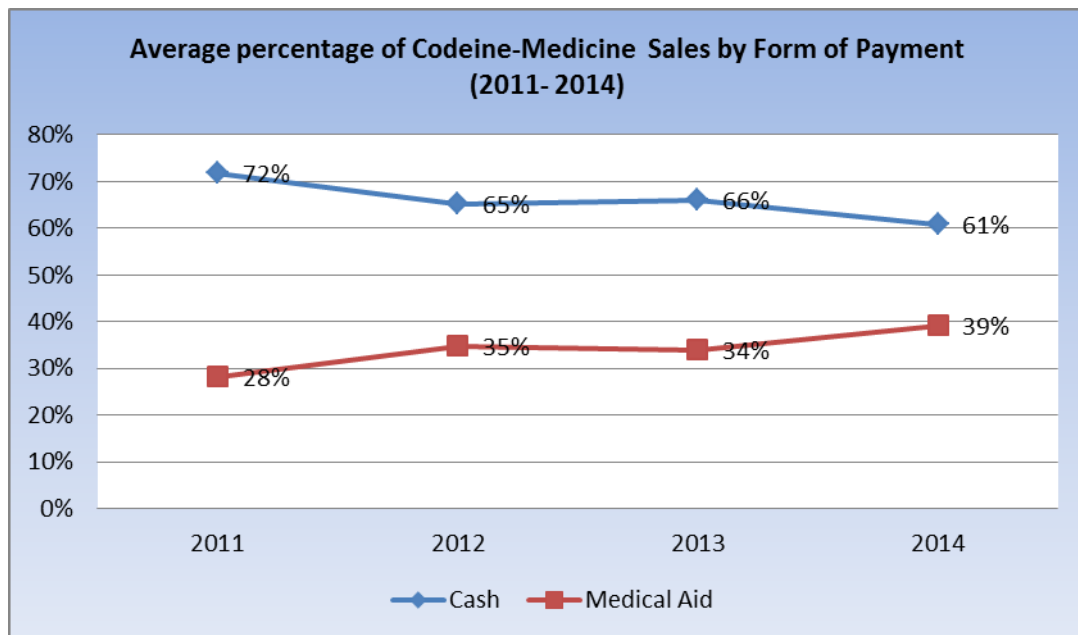
Most of the purchases of codeine containing medicines were paid for using cash in the Gauteng Province over the study period as indicated by Figure 4.1.2. This figure indicates a slight decline in the cash payments and a corresponding increase in the medical Aid payments.

## 4.2 Western Cape Province

In the Western Cape Province the top three selling OTC codeine-containing medicinal products by brand name are Genpayne Capsules accounting for 28% of all the sales followed by Myprodol Capsules accounting for 24% and lastly Mybulen Tablets accounting for 17.5% of all the sales. The top three selling brands alone accounted for 70% of all the OTC codeine-containing medicine sales whilst the top ten selling brands accounted for 90% of all the sales of OTC codeine containing medicines sold in the Western Province over the study period.



**Figure 4.2.1: Percentage Distribution of the Top Ten Selling Brands of Codeine-Containing Medicine in Western Cape Province – July 2011 – June 2014**



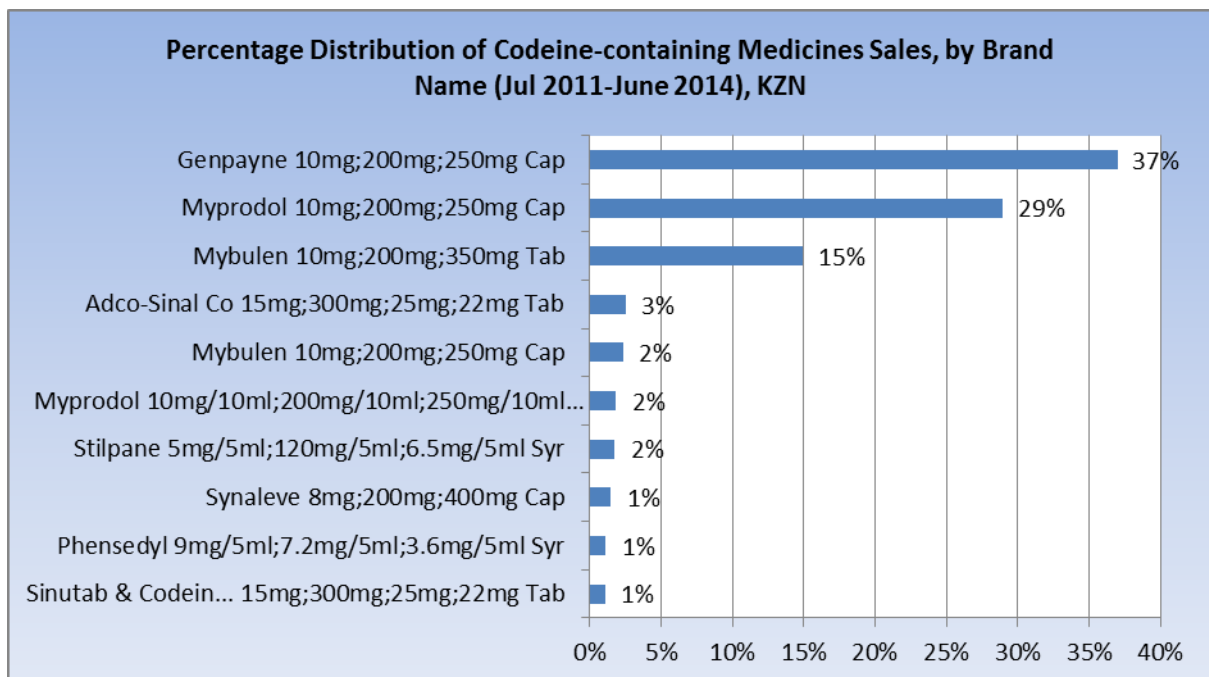
**Figure 4.2.2: Percentage Sales of Codeine-Containing Medicines by Mode of Payment, July 2011 - June 2014 in the Western Cape Province**

Most of the purchases of the codeine containing medicines were paid for using cash in the Western Cape Province over the study period as indicated by Figure 4.2.2. However, this

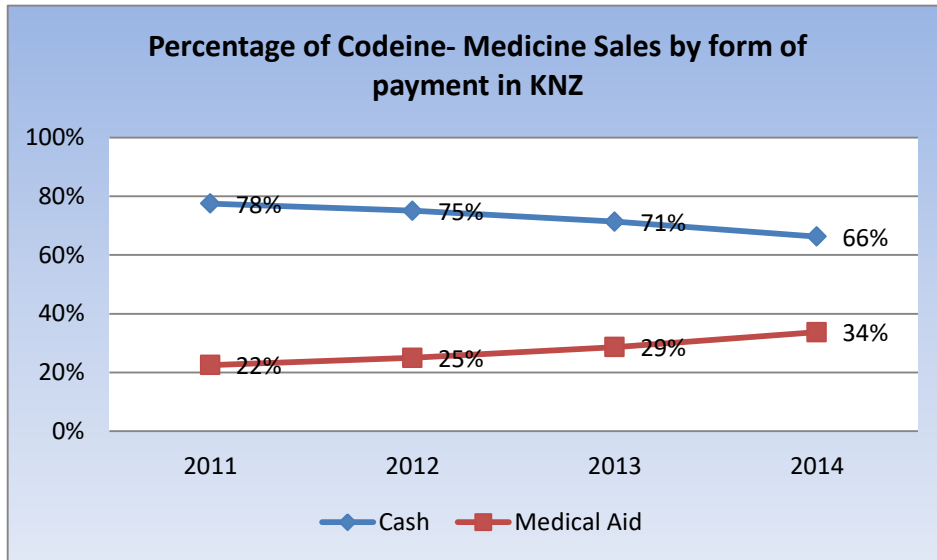
figure indicates a slight decline in the cash payments and a corresponding increase in the medical aid payments.

### 4.3 Kwa-Zulu Natal Province

In the Kwa-Zulu Natal Province the top three selling OTC codeine-containing medicinal products by brand name are Genpayne Capsules accounting for 37% of all the sales followed by Myprodol Capsules accounting for 29% and lastly Mybulen Tablets accounting for 15% of all the sales. The top three selling brands alone accounted for 81% of all the OTC codeine-containing medicine sales whilst the top ten selling brands accounted for 93% of all the sales of OTC codeine containing medicines sold in the Kwa-Zulu Natal Province over the study period.



**Figure 4.3.1: Percentage Distribution of the Top Ten Selling Brands of Codeine-Containing Medicine in Kwa-Zulu Natal – July 2011 – June 2014**



**Figure 4.3.2: Percentage Sales of Codeine-Containing Medicines by Mode of Payment, July 2011 - June 2014 in Kwa-Zulu Natal**

Most of the purchases of codeine containing medicines were paid for using cash in Kwa-Zulu Natal Province over the study period as indicated by Figure 4.3.2. However, this figure indicates a decline in the cash payments and a corresponding increase in the medical aid payments.



## Chapter 5: Discussion

There is a tendency for more products to be made available without prescriptions in countries that have schedules with pharmacy involvement like South Africa, Australia, New Zealand, Canada, France and the United Kingdom and a tendency for preparations to be held under prescription only schedules in the United States of America where pharmacy involvement or pharmacy-only schedules do not exist<sup>3</sup>. According to the International Narcotics Control Board Report of 2010 on the availability of internationally controlled drugs, South Africa is ranked number one in Africa and number 49 in the world (of 193 countries) in terms of average consumption of defined daily doses of narcotic drugs<sup>50</sup>. South Africa is a signatory to three major conventions and the International Narcotics Control Board (INCB) calls upon all governments to be vigilant for problems involving the abuse of pharmaceutical preparations not requiring prescriptions and adopt measures to effectively prevent the abuse of these preparations.

The study used the Pick n Pay retail pharmacies sales from Gauteng Province, Kwa-Zulu Natal Province and the Western Cape Province as a proxy for retail pharmacies in South Africa. The total sales of OTC codeine containing medicines within the eighteen pharmacies studied during the study period accounted for four million seven hundred and forty seven thousand and eighty-eight Rands ninety-one cents (R4, 747,088.91). Sixty-five (65%) percent of the purchases were paid for using cash payment and the medical aid payments accounted for thirty-five (35%) percent. This means that three million and eighty five thousand six hundred and seven Rands seventy-nine cents (R3,085,607.79) accounted for cash payments for these OTC codeine containing medicines purchases which translates to out of pocket expenditure. Another study has shown that the main cost drivers of medical schemes expenditure are private hospitals, specialists and medicines<sup>51</sup>. Once an individual has exhausted the fund allocated to medicines within their medical aid or purchases any medicines not covered by the medical aid then they have to pay for their medicines out of pocket<sup>52</sup>.

The cash payments for the purchases of codeine containing medicine per province accounted for fifty-nine (59%) percent of payments in the Gauteng Province, sixty-one (61%) percent of all the payments in the Western Cape Province and sixty-six (66%) percent of all the

payments in the Kwa-Zulu Natal Province. The results indicate that Gauteng Province had most medical aid payments compared to the Western Cape and Kwa-Zulu Natal Province accounted for the least medical aid payments. According to the South African Demographics and Socio-Economic Status Report employment is a key economic indicator sensitive to economic growth. The majority of employed people are employed in the formal economic sectors with 9% and 11 % respectively of populations employed in the information sector in Gauteng and the Western Cape, Kwa-Zulu Natal has more. This explains the mode of payment trends observed in this study in that the economic status of people in Gauteng is higher than that of people from the Western Cape which is also high that that of Kwa-Zulu Natal. Gauteng and the Western Cape according to this report are projected to continue to be more economically attractive Provinces for people from other provinces.

The distribution of sales by gender indicates that females account for 59% of all the purchasers whilst males accounted for 41%. This is in line with the findings from the specialist treatment centre's study in Cape Town which indicated that of the misused analgesics, the codeine-containing OTC medicines were the ones mostly misused and that patients using OTC medicines as their primary drug of misuse are more likely to be females aged over forty (40) years whilst males over the age of forty (40) use OTC medicines as an additional drug of misuse<sup>22</sup>. The distribution of the sales of these products by age in all the three provinces over the study period indicates that most purchasers of the over-the-counter codeine containing medicines belonged to the age group forty-one (41) to forty-five (45) years. The age group accounted for forty-seven (47%) percent of all the purchaser of the over-the-counter codeine containing medicine. Findings from an Australian and New Zealand study suggest that the misuse and harm from combination codeine analgesics may be a growing problem in countries where they are available OTC and that the average age of clients addicted to OTC codeine products is 44 years in New Zealand<sup>34</sup>. This is a mature and financially stable age group which is likely to be in the formal employment sector or self-employed and can afford to finance their health needs through medical aid schemes and or out of pocket payment. The age group of 60 years and above accounted for 9.4% of the purchasers. These are the retired age group which tend to be on chronic medication use as well.

The sales trend of the OTC codeine-containing-medicines indicates a steady increase in the sale of these products over all three provinces over the study period. When considering the

top three OTC codeine-containing medicines with most sales in all three provinces combined (Genpayne Capsules, Myprodol Capsules and Mybulen Tablets) they account for seventy-one (71%) percent of all the sales of the OTC codeine-containing medicines sold. The two major brands that dominate the three provinces' market for over-the-counter codeine containing medicines are Genpayne and Myprodol Capsules, they both contain Codeine Phosphate 10mg, Ibuprofen 200mg and Paracetamol 250mg and they cost R37.38 and R62.79 per pack of 30 tablets respectively. Aspen Pharmacare's Mybulen Tablets contain Codeine Phosphate 10mg, Ibuprofen 200mg and Paracetamol 350mg and it cost R42.77 per pack of 30 tablets whilst their Mybulen Capsules contain Codeine Phosphate 10mg, Ibuprofen 200mg and Paracetamol 250mg and cost R37.38 per pack of 30 tablets.

Genpayne and Myprodol are both Adcock Ingram's products which have managed to maintain their brand equity in the market over the years. Myprodol is the well-known red and green capsule that has maintained its leadership in the analgesic market due to their continuing growth in sales. Sales force commitment, strong branding and creative advertising strategies have contributed to the two brands maintaining their market leadership position in the total pharmaceutical market rankings despite the fact that Myprodol is more costly compared to Genpayne per pack of 30's. In all the respective retail pharmacies, the prices of these products remain constant because these are Pick n Pay chain stores thus the prices of similar medicines are the same. Also, the country regulates the prices of medicines using the single exit price system to ensure that medicines are affordable to the general population.

However, top three selling brands do not vary much over the three provinces. The top three selling products in the Gauteng Province were Myprodol Capsules thirty (30%) percent, Genpayne Capsules nineteen (19%) percent and Mybulen Tablets nine (9%) percent of all the sales in the province. In the Western Cape Province the top three sales were Genpayne Capsules twenty-eight (28%) percent, Myprodol Capsules twenty-four (24%) percent and Mybulen Tablets seventeen point five (17.5%) percent of all sales in the province. In the Kwa-Zulu Natal Province the top three selling products were Genpayne Capsules thirty-seven (37%) percent, Myprodol Capsules twenty-nine (29%) percent and Mybulen Tablets fifteen (15%) percent of all the sales in the province over the study period.

The findings from the study indicate that the top ten selling brands of OTC codeine containing medicines account for eighty-five (85%) percent of all the sales of these products

in the Gauteng Province, ninety (90%) percent of all sales of these products in the Western Cape Province and ninety-three (93%) percent of the sales of these products in the Kwa-Zulu Natal Province. It is worth noting that across all the three provinces the major sales are attributed to three main brands namely Genpayne Capsules, Myprodol Capsules and Mybulen Tablets. This further illustrates that in Gauteng Province the three products contributed to fifty-eight (58%) percent, in Western Cape Province to seventy (70%) percent and in Kwa-Zulu Natal to eighty-one (81%) percent of the total sales of these OTC codeine containing medicines. McAvoy, Dobbin and Tobin, 2011 concluded that the control of OTC codeine-containing analgesics in form of making them pharmacist-only medicines was not sufficient in limiting their non-medicinal use. An extensive literature review conducted in the United Kingdom concluded that there is not much risk when OTC codeine-containing medicines are used appropriately to treat occasional pain in the recommended doses; the problem arises with the long-term use and the use of high doses that can lead to headaches, dependence and potentially severe reactions<sup>53</sup> and morbidities. In addition, most people do not consider the misuse of these products as inappropriate in comparison to the use of illicit drugs which are believed to have a greater potential of causing harm.<sup>54</sup>

## **5.1 Limitations of the study**

The study only examined secondary sales data that was available from the Pick n Pay retail pharmacies' database system at the time of data collection. As a result, not all monthly data could be retrieved for the year 2011; only seven (7) months data was available. This was the same scenario even with the 2014 data, whereby data ended in June at the time of the data collection period. The trend analyses need to take the missing data for some months into consideration for comparison purposes. In addition, there were some missing data in the age variable due to non-availability of data and thus only available cases were included in the analysis. The stand-alone retail pharmacies could not be included in the study due to lack on sales data in these pharmacies yet they are more in numbers.

## 5.2 Conclusion and Recommendation

This study has demonstrated that there is a steady increase in the sale of over-the-counter codeine containing medicines which may be attributed to the fact that OTC codeine-containing medicines are relatively easy to purchase compared to prescription only medicines that are sold on production of a prescription and illicit drugs. Also, with the growth in the awareness of the problems of OTC codeine preparations, regulatory authorities have been examining their policies and regulations. In September 2009 the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) updated its advice on the non-prescription medicines containing codeine and dihydrocodeine. The Republic of South Africa's Medicines Control Council in February 2015 reduced the strength of codeine and dihydrocodeine in OTC codeine containing preparation from 20mg to 10mg and set the maximum treatment days to five (5) days. Preparations containing codeine and dihydrocodeine above 10mg were rescheduled from schedule 2 to schedule 3.

In Australia, the National Drugs and Poisons Schedule Committee (NDPSC) in May 2010 reschedules OTC codeine containing medicines to pharmacist-only medicines and reduced the pack sizes to thirty (30) tablets. In New Zealand, the Medical Devices Safety Authority's (MEDSAFE) Medicines Classification Committee in October 2010 also recommended that OTC codeine containing medicines be pharmacist-only medicines and the pack size was reduced to 30 tablets. In Europe, codeine is a prescription only medicine in Austria, Belgium, Croatia, Czech Republic, Finland, Germany, Greece, Italy, Luxembourg, Portugal, Slovakia, Spain and Sweden. Codeine is also a prescription only medicine in the USA, Hong Kong, Iceland, India, Japan, Maldives, Romania, Russia and the United Arab Emirates

Despite of all of these challenges with OTC codeine containing medicines there is a lot of resistance from the pharmaceutical Industry to restrict the sales of OTC codeine products. The New Zealand Self-medication Industry Association stated that it, "believes that the needs and interests of the vast majority or responsible consumers need to be balanced against the risks of harm to a very small number of individuals"<sup>37</sup>. The South African Pharmaceutical Manufacturing Industry and Retail Pharmacy Associations feel that effective self-regulation will help preserve the OTC sales of these medicines that would continue benefiting the patients thus the establishment of the Codeine Care Initiative by the Community Pharmacist

Sector (CPS) and Pharmaceutical Society of South Africa (PSSA) to monitor and audit the sale and supply of codeine-containing medicines. However, this ended up becoming voluntary and defeating the very reason for its establishment.

In view of this, there is a need for further studies to ascertain if these top three leading brands of OTC codeine-containing medicines are being misused or their sales are due to them being well marketed. Further, there is a need to ascertain the prevalence of the misuse of OTC codeine-containing medicines in South Africa and the evidence to assist in characterising the populations most at risk. This represents urgent aspects where applied research is needed to explore the extent of the misuse and the necessary regulation with regards to OTC codeine-containing medicines in South Africa. The Medical Control Council needs to review the Codeine Care Initiative by the Community Pharmacist Sector (CPS) and Pharmaceutical Society of South Africa (PSSA) to monitor and audit the sales and supply of codeine-containing medicines and consider its implementation to all retail pharmacies without an option. This will assist in coming up with the secondary data that will inform future studies into the use of OTC codeine containing medicines in South Africa. If the monitoring the sales of OTC codeine containing medicines does not have an impact on the misuse of these products , more drastic measures may need to be considered.

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**Annex 1: Gantt Chart on timelines for the execution of the Research**

PROJECT ACTIVITY	TIME (Weeks)																															
	Aug/Sept 2015				Oct/Nov 2015				Dec/Jan 2015/6				Feb/May 2016				Jun/Sept 2016				Oct 2016				Nov/Dec 2016							
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4				
Submission for Assessors Approval																																
Feedback from assessors, corrections and resubmission																																
Data Collation and Data Analysis																																
Preparation of Research Report																																
Submission of Research Report																																
Correction of Research Report																																
Final Submission of Research Report																																
Examiners Feedback																																
Final Submission for Publication																																

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**Annex 2: Estimated Budget for the Research**

<b>Activity</b>	<b>Description</b>	<b>Quantity</b>	<b>Unit Price (Rand)</b>	<b>Total (R)</b>
Stationery	Printing Paper	500 x 10	50	500.00
	Stapler	03 x 1	30	90.00
	Folders	50 x 2	10	500.00
	Paper Punch	02 x 1	30	60.00
Fuel	Unleaded Petrol (Litres) For travelling purposes	60 x 5	12	3,600.00
Communication	Email	-	100	1,500.00
	Telephone	-	1000	5,000.00
	Skype	-	100	1,500.00
Incidentals/Data Payment	-	-	-	5,000.00
<b>Grand Total</b>				<b>17,750.00</b>

### Annex 3: List of Products

List of Codeine containing over-the-counter medicines sold by Pick n Pay Retail Pharmacies over the study period (Trade Names):

	Trade Name	Manufacturer
	<b>Suspensions &amp; Syrups</b>	
1.	Actifed Dry Cough	Glaxo Smithkline Consumer
2.	Acutussive Expectorant Syrup Adult	Arrow Pharma Subs Actavis
3.	Acutussive Expectorant Syrup Pead	Arrow Pharma Subs Actavis
4.	Adco-Kiddipayne Syrup	Adcock Generics
5.	Adco-Salterpyn Syrup	Adcock Generics
6.	Adco-Tussend Syrup	Adco-OTC
7.	Ban Pain Syrup	Aspen-Pharmacare
8.	Codeine Phosphate Syrup	Medico
9.	Colcaps Syrup	Adcock OTC Tail
10.	Docsed Syrup	Aspen-Pharmacare
11.	Fludactil Co Linct Syrup	Aspen-Pharmacare
12.	Flusin Junior Co Syrup	Aspen-Pharmacare
13.	Goldgesic Syrup	Pharmachem Pharmaceuticals
14.	Lenazine Forte Syrup	Aspen-Pharmacare
15.	Lentogesic Syrup	Adcock Restan
16.	Linctifed Expectorant Adult Syrup	Glaxo Smithkline Consumer
17.	Mybulen Suspension	Aspen-Pharmacare
18.	Myprodol Suspension	Adcock Pain
19.	Painagon Syrup	Ranbaxy - Be-Tabs
20.	Phensedyl Syrup	Zentiva
21.	Pynmed Syrup	Cipla-Medpro Pharmaceuticals
22.	Stilpane Syrup	Aspen-Pharmacare
23.	Stopayne Syrup	Adcock Restan
24.	Tensopyn Syrup	Mirren
25.	Tenston Syrup	Adcock Pain
26.	Trifen Expectorate Adult Syrup	Ranbaxy - Be-Tabs
27.	Trifen Expectorate Paed Syrup	Ranbaxy - Be-Tabs
	<b>Tables &amp; Capsules</b>	
1.	Adco-Napacod Tablets	Adcock Adco
2.	Adco-Sinal Co Tablets	Adcock Adco
3.	Co-Codamol Effeference	Cipla-Medpro Pharmaceuticals
4.	Codeine Phosphate Tablets	Aspen-Pharmacare
5.	Dentopain Forte Capsules	Sandoz
6.	Dolorol Forte Tablets	Aspen-Pharmacare
7.	Empacod Tablets	Takeda (Pty) Ltd
8.	Genpayne Tablets	Adcock Generics
9.	Ibucod Tablets	Aspen-Pharmacare
10.	Ibupain Forte Capsules	Sandoz
11.	Mybucod Tablets	Aspen-Pharmacare

