Opioid prescribing patterns in the South African private health sector

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ABSTRACT

This study aimed to determine the prescribing patterns of opioid analgesics in the South African private healthcare sector over the 1 January 2011 to 31 December 2017 period. To achieve this aim, two specific objectives were set for the study: 1) to determine the changes in prescribing patterns of opioid treatment for chronic pain by repeated cross-sectional estimates for each year (1 January 2011 to 31 December 2017), stratified into two treatment groups (i.e., cancer-related and chronic non-cancer pain (CNCP) treatment); and 2) to determine the association between depression (ICD-10 codes F30-F39) and treatment duration, with treatment duration divided into short-term (defined as total days of medicine supply < 90 days) and long-term treatment duration (defined as total days of medicine supply ≥ 90 days).

A retrospective, quantitative, observational approach was adopted for this study. To obtain objective one, a repeated cross-sectional design was utilised. For objective two, the period between 1 January 2011 and 31 December 2017 was regarded as one continuum.

The study population for objective one, which consisted of prescriptions for patients who had received at least one prescribed opioid (claimed from chronic, oncology or prescribed minimum benefits) during the study period, totalled 2 499 patients in 2011; 3 079 patients in 2012; 2 954 patients in 2013; 3 951 patients in 2014; 3 871 patients in 2015; 3 998 patients in 2016; and 5 636 patients in 2017. Although the male-to-female ratio per year remained stagnant over the seven years on the central database, the results showed that the number of female patients decreased marginally from 53.7% (*N* = 2 499) in 2011 to 53.2% (*N* = 5 636) in 2017, corresponding to the increase in male patients from 46.3% in 2011 to 46.8% in 2017. The number of patients 57 years and younger and those between the ages of 58 and 66 years with at least one prescription for opioid analgesics decreased from 27.1% and 26.1% in 2011 (*N* = 2 499) to 26.2% and 21.0% in 2017 (*N* = 5 636) respectively. In contrast, the number of patients older than 66 years with at least one prescription for opioid analgesics increased over the study period.

Most patients who received at least one opioid analgesic received this for cancer-related pain, reimbursed from oncology benefits. The number of patients who received at least one opioid for cancer-related pain increased progressively from 90.0% (*N* = 2 499) in 2011 to 98.2% (*N* = 5 636) by 2017.

The combination opioid product containing tramadol and paracetamol was the most prescribed product over the study period. Prescriptions for morphine-containing opioids decreased over the study period, whereas those for oxycodone- and buprenorphine-containing products increased. In terms of dose, as measured by the DDD/1 000 inhabitants/day, however, an increase in morphine prescribed in milligrammes was observed. Furthermore, a joinpoint analysis showed

that, although the number of medicine items containing buprenorphine increased over the study period, the prescribed doses peaked in 2015 and then declined. The average annual percentage change (AAPC) of buprenorphine was 51.5 (95% CI: 27.5, 80.0) ($p < 0.001$). The prescribing of fentanyl, dihydrocodeine and tramadol decreased from 2011 to 2017 with AAPCs -7.6; (95% CI: -10.7, -4.4) ($p = 0.002$), -9.4; (95% CI: -24.6, 8.9) ($p = 0.226$), and -3.8 (95% CI: -9.4, 2.0) ($p = 0.150$) respectively.

For objective two, 23 910 treatment episodes were identified. Most treatment episodes were of short-term duration (85.5%, $N = 23\ 910$). Overall, the study failed to establish a practically significant association between treatment duration and depression ($p < 0.0001$, Cramér's $V < 0.5$). Stratification by age showed that among the patients receiving short-term treatment, most were in the age group ≤ 57 years, at 44.9% ($N = 20\ 448$). The majority of short-term duration treatment episodes (77.6%, $N = 20\ 448$) were for patients without depression. A statistically and practically significant association ($p < 0.0001$, Cramér's $V = 0.6$) between short-term treatment duration and depression by age group were found. However, no association between short-term treatment duration and depression by gender ($p < 0.0001$, Cramér's $V < 0.5$) were identified. There was also no association between long-term treatment duration and depression by gender ($p < 0.2661$, Cramér's $V < 0.5$) or age group ($p = 0.3242$, Cramér's $V < 0.5$).

In conclusion, the results revealed that patients who received at least one opioid analgesic for chronic pain increased marginally from 2011 to 2017. The increase was mainly due to patients receiving opioids for cancer-related pain. Although most patients receiving opioid treatment did not experience depression, an association between depression and short-term opioid analgesic treatment duration in adults below the age of 57 years was found.

Key terms: opioids, chronic pain, cancer-related pain, chronic non-cancer pain (CNCP), medicine claims data, prescribing patterns, private healthcare sector, depression, DDD/1 000 inhabitants/year.

LIST OF ABBREVIATIONS

APA	American Psychological Association
API	Active pharmaceutical ingredient
ASIPP	American Society of Interventional Pain Physicians
CNCP	Chronic non-cancer pain
DDD	Defined daily dose
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
HICs	High-income countries
IASP	International Association for the Study of Pain
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
INS	International Neuromodulation Society
JCAHO	Joint Commission on the Accreditation of Healthcare Organizations
LMICs	Low- and middle-income countries
MIMS	Monthly Index of Medical Specialities
MUSA	Medicine Usage in South Africa
NAPPI	National Pharmaceutical Product Interface
NCPC	Non-cancer pain conditions
NOUGG	National Opioid Use Guideline Group. Canada.
OTC	Over-the-counter
PBM	Pharmaceutical Benefit Management Company
PMB	Prescribed minimum benefits

SAHPRA	South African Health Products Regulatory Authority
UMCs	Upper-middle income countries
USA	United States Of America
WMA	World Medical Association
WHO	World Health Organization

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CHAPTER 1 INTRODUCTION AND RESEARCH METHODOLOGY

1.1 Background

The International Association for the Study of Pain (IASP) (Raja *et al.,* 2020:1976) defines pain as an "*unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*". According to Isa and Chetty (2021:266), this definition emphasises that "pain results from a complex interaction of sensory, emotional, physical, cognitive, social, psychological and spiritual components that can be influenced by age, sex, environmental conditions and experiences". Acute pain is described as a defence mechanism with important adaptive roles by Isa and Chetty (2021:266). It serves as a crucial early warning system by signalling the presence of a stimulus that could be detrimental to the human body (Świeboda *et al*., 2013:2). Pain triggers withdrawal reactions to stop the damage from worsening, localises unpleasant stimuli, and reduces mobility, all of which aid in recovery. Yet when acute pain loses its adaptive value, it becomes a burden (Milligan & Watkins, 2009:35). Any pain that lasts longer than the time it takes for normal tissue to recover, which is typically three months, is classified as chronic pain (Ho *et al.,* 2013:139).

According to estimates by the World Health Organization (WHO, 2008b), by 2030, chronic pain will be one of the four main concomitant causes of the global burden of illness. Most population-based surveys, which have been conducted by non-governmental research programmes, have indicated that, currently, 20% of adult patients in the world experience chronic pain (Ho & Nair, 2018:173). The prevalence of chronic pain conditions has been estimated at 41.1% in developed countries and 37.3% in developing countries (De Villiers *et al.*, 2015:97; Tsang *et al*., 2008:889). France and the United States of America (USA) have the highest chronic pain prevalence rates in developed countries (Ho & Nair, 2018:172-173). According to Kamerman *et al.* (2020:1630), in 2016, approximately one in five (18.3%) South Africans 15 years and older suffered from chronic pain.

Pain might start at an early age, affecting children and adolescents; however, it is more prevalent among elderly people 65 years of age and above and results in poor quality of life (Aguiar *et al.,* 2017:366; Edwards *et al.,* 2016:T70). About 38% of patients in institutions (nursing homes) and 27% at home experience pain regularly (NOUGG, 2017). Chronic pain affects about one-third higher among female patients than among their male counterparts (Andrew *et al.,* 2014:81; NOUGG, 2017; Raff *et al.*, 2014:78).

Chronic pain affects patients' general health and psychological and socioeconomic wellbeing (Butow & Sharpe, 2013:S101). For instance, about 30–60% of patients suffering from pain also report having comorbid depression, and about 50-60% of chronic pain patients suffer from

anxiety, particularly generalised anxiety disorder (Feingold *et al.,* 2017:1; Goesling *et al.,* 2013:421; Hooten, 2016:958). Headaches often occur twice as often in individuals suffering from depression or anxiety disorders as among patients without neuropsychiatric disorders (Bruffaerts *et al.,* 2015:43). Additionally, people with comorbid depression and chronic pain might experience a poor quality of life, ineffective therapy, substance addiction and a higher risk of suicide (Feingold *et al.,* 2018:294; Robinson *et al.,* 2017:620). The aetiological hypotheses for the coexistence of depression and physical pain are based on the dysfunction of serotonergic and noradrenergic pathways in depression, which explains mood symptoms and a lack of inhibitory control of ascending pain messages. This is typically controlled in the spinal cord by descending serotonergic and noradrenergic projections (Fasick *et al.,* 2015:140; Rajmohan & Kumar, 2013:146; Viguier *et al*., 2013:9). According to Fasick *et al*. (2015:140), as the pain gets worse, the chance of depression rises (e.g., severity, frequency, duration and number of symptoms). Moreover, those who have various pain syndromes are three to five times more likely to experience depression than those who do not (Gambassi, 2009:104; Goesling *et al.,* 2013:421; Goldenberg, 2010:17-19). Conversely, moderate to severe pain is linked to severe depression outcomes, including lower quality of life, reduced work performance and a higher need for medical attention, as well as increased depressive symptoms (Feingold *et al.,* 2018:293).

Depending on whether the underlying disease compromises the somatosensory nerve system's integrity, chronic pain is either nociceptive or neuropathic (Scholz, 2014:O15). Nociceptive pain is caused by pain impulses being conveyed from the place of origin to the brain. In comparison, neuropathic pain is caused by a lesion or disease of the somatosensory nervous system (Isa & Chetty, 2021:266; Lehne, 2010:287). Nociceptive pain originates from injury to tissues, whereas neuropathic pain originates from damage to peripheral nerves (Hansen & Malcangio, 2013:121; Lehne, 2010:287; Mann & Carr, 2006:22). Nociceptive pain has two forms, namely somatic and visceral pain (Giordano, 2006:1-2; Lehne, 2010; Mann & Carr, 2006:9). Somatic pain is caused by injury to the somatic tissues, such as bone joints and muscles (Ward & Linden, 2013:121). Visceral pain is caused by injury to the visceral organs, such as the small intestines (Lehne, 2010:287), experienced with traction or stretching of the associated peritoneum (Zakka *et al.,* 2013:311). Somatic and visceral pain both respond well to opioid analgesics and might respond, to a lesser extent, to anti-inflammatory medicines (Giordano, 2006:1-2; Lehne, 2010; Mann & Carr, 2006:9). There are three degrees of pain: acute, chronic and malignant (Craven & Hirnle, 2009:1189). Acute pain occurs immediately after injury or disease and might also be associated with anxiety and/or fear. It is possible to locate the pain sensation on the skin or mucous membrane (Świeboda *et al*., 2013:4), which increases during wound care (Craven & Hirnle, 2009:1189). Chronic pain lasts for an extended period, is continuous and persists beyond the normal healing period for an acute injury or disease (Craven & Hirnle, 2009:1189). Malignant pain is recurrent pain that presents as acute pain episodes or continuous chronic pain, or both, and is

associated with a progressive malignant-type process that is resistant to cure (Craven & Hirnle, 2009:1189). The focus of this study is chronic pain.

Opioids are considered the gold standard for treating moderate to severe pain arising in various clinical settings, such as chronic pain due to cancer and postoperative pain (Gálvez & Pérez, 2012:33; Size *et al*., 2007:39; Wiffen *et al.,* 2013). Guidelines have been established in developed and developing countries to assist in a comprehensive pain management strategy that includes long-term opioid analgesics (Raff *et al.*, 2014:78-89; Thieme *et al.,* 2017:747-756; Trescot, 2016:S52-65). For example, the WHO analgesic ladder (Anekar & Cascella, 2022) was a component of a large health initiative known as the WHO Cancer Pain and Palliative Care Program, the aim of which was to improve methods for managing cancer pain through educational campaigns, the development of shared strategies and the creation of a global support network. This analgesic path has developed over time and is now used to treat acute and chronic non-cancer pain (CNCP), degenerative illnesses, musculoskeletal conditions, neuropathic pain disorders and other types of chronic pain (Anekar & Cascella, 2022; Yang *et al*., 2020:411). The treatment guideline is outlined as follows on the WHO analgesic ladder:

- "First step. Mild pain: non-opioid analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen with or without adjuvants;
- Second step. Moderate pain: weak opioids (hydrocodone, codeine, tramadol) with or without non-opioid analgesics and with or without adjuvants;
- Third step. Severe and persistent pain: potent opioids (morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone, oxymorphone) with or without non-opioid analgesics, and with or without adjuvants".

Several researchers around the world have reported high use of opioids in the long-term treatment of CNCP conditions (Fischer *et al.,* 2016:331; Fredheim *et al.,* 2014:1213; Roxburgh *et al.,* 2011:280; Richards *et al.,* 2013:1231; Schaefer *et al.,* 2017:32; Scherrer *et al.,* 2014:491; Zin *et al.,* 2014:1343). About 90–95% of long-term opioid therapy is prescribed for CNCP conditions, including back pain, joint pain, headaches, fibromyalgia and neuropathic pain (Aktaş & Karabulut, 2017:33). Because chronic pain frequently coexists with depression, opioid analgesics are also often prescribed to these patients (Bruffaerts *et al.,* 2015:43).

A literature search in PubMed® and Google Scholar to assess publications on the prevalence of opioid prescribing for chronic pain over the past five years (2018–2022; see Annexure A) revealed no South African studies *per se*. A study by Richards *et al*. (2022:239) investigating national sales and expenditure trends of over-the-counter (OTC) codeine-containing products purchased in 31 countries, South Africa included), however, showed that from April 2013 to March 2019, OTC products containing codeine increased in overall sales and spending, with 90% of all sales data

originating from South Africa (34%), France (20%), Japan (16.5%), the UK (14.5%) and Poland (5%). In an earlier study by Truter (2016a:209), who examined the prescription of meprobamate-containing combination analgesics in South Africa in 2011, it was shown that, out of 31 854 patients, 30.7% (*n* = 9 793) received a prescription for one or more opioids. Truter (2016b:A598) showed that in 2013, South African pharmacies dispensed 212 527 opioids to 105 118 patients. Tramadol, combined with paracetamol, accounted for the majority of the products (71.9%), followed by tramadol alone (22.7% of products). Oxycodone (2%) and fentanyl (1.1%) were the only opioids that accounted for more than 1% of the total number of opioids dispensed (Truter, 2016b:A598). Codeine is frequently used in South Africa for the management of pain; however, the dosage of codeine above 10 mg of active ingredient is closely monitored and can only be given under the supervision of a pharmacist (De Beer & Cordier, 2022; Firfirey *et al*., 2022).

Opioid analgesic prescribing pattern studies show that the global opioid consumption volume and patterns vary greatly by country and region (Gomes *et al*., 2022:783; Jayawardana *et al*., 2021:4; Ju *et al*., 2022:e335; Nissen *et al.,* 2019:157; Rosner *et al*., 2019; Zin, 2020:S846-847). The USA has the highest consumption of opioids among the developed countries, with consumption levels being 43 879 defined daily doses (DDD) per million inhabitants per day in the year 2011 to 2013, followed by Canada with 23 352 defined daily doses (DDD) per million inhabitants per day and Germany, with 22 941 defined daily doses (DDD) per million inhabitants per day in the same years which are the second and third highest consumers, respectively ((Bedard *et al.,* 2017:3676; Jayawardana *et al.*, 2021:3; Organization for Economic Co-operation and Development (OECD), 2019)), however, indicated a 30% decrease in global opioid consumption from 2009 to 2019. Opioid consumption rates in upper-middle-income and low-to-middle-income nations, on the other hand, were significantly lower and increased slightly between 2009 and 2019.

1.2 Problem statement and research questions

Chronic pain is a common problem among people of all ages worldwide. Opioid analgesics are potent medications utilised for chronic pain treatment. The literature has shown a high prevalence of opioid prescribing in high-income countries, decreasing over the last few years, in contrast to an increase in consumption in low-to-middle-income countries. There is limited data on the prescribing trends of opioids for the treatment of chronic pain in South Africa *per se*. Secondly, there is limited data on the prevalence of depression in patients who are prescribed opioid analgesics.

In light of the above, the following research questions were formulated for this study:

- How prevalent is chronic pain, internationally and in South Africa?
- How is chronic pain treated?

- What is the role of opioid analgesics in chronic pain treatment?
- Is there an association between the regular use of prescribed opioids and psychiatric conditions? If so, why?
- What are the current prescribing trends and patterns of opioid analgesics associated with chronic pain in the South African private health sector?

1.3 Research aims and objectives

1.3.1 Research aim

The primary aim of this study was to determine the prescribing patterns of opioid analgesics in the South African private health sector from 1 January 2011 to 31 December 2017.

1.3.2 Specific research objectives

The research objectives for this study were divided into two main sections, namely those that could be achieved by means of a literature review and empirical research. The specific objectives for the literature review were to:

- Describe what chronic pain entails.
- Describe the role of opioid analgesics in chronic pain treatment.
- Review opioids as a pharmacological group of pain medication, their indications for use, side effects, drug-drug interactions and special precautions.
- Describe the policies and guidelines that govern opioid prescribing worldwide.
- Determine opioid prescribing patterns internationally and locally.
- Determine the association between the regular use of prescribed opioids in patients and psychiatric conditions.

The specific objectives for the empirical study were to:

- Determine the changes in the prescribing patterns[1] of opioid analgesics for chronic pain by repeated cross-sectional estimates for each year (1 January 2011 to 31 December

[1] The drug-prescribing indicators that will be investigated in this study include the annual number of patients and the number of medicine items (stratified by age, gender and geographic location), active pharmaceutical ingredients, and the defined daily dose per 1 000 inhabitants per day (in milligramme) for buprenorphine, codeine, dihydrocodeine, fentanyl, tramadol and morphine.

2017), stratified into two treatment groups (i.e., cancer-related treatment and CNCP-related treatment).

- Determine the association between depression (ICD-10 codes F30-F39) and opioid analgesic treatment duration (stratified into two groups, i.e., short-term use[2] and long-term use[3] of prescribed opioids).

1.4 Research methodology overview

An empirical investigation was conducted after an assessment of the available literature.

1.4.1 The literature review

Several books, articles, journals, and websites were used to gain knowledge and understanding to achieve the literature objectives for the study. Databases and search engines that were used included the following: Google Scholar®, PubMed®, Scopus®, EBSCOHost®, Science Direct®, and SAePublications®. The following search terms separately and in combination: “analgesics”, “chronic pain” and/or “chronic non-cancer pain” and “prevalence”, “treatment guidelines” or “drugs” and “chronic pain” and/or “chronic non-cancer pain”, “opioids”, “chronic non-cancer pain” and “psychiatric conditions” or “depression”, “chronic pain” and “prescribing patterns”, “chronic pain” and “South Africa”.

1.4.2 The empirical investigation

To identify opioid prescribing trends and patterns in the South African private health sector and to ascertain the relationship between prescribed opioids and depression in patients, a retrospective, quantitative drug utilisation study was conducted using medicine claims data on prescriptions for opioid-containing analgesics for patients dispensed from the 1 January 2011 to 31 December 2017.

According to the WHO (2008a), drug utilisation refers to drug marketing, distribution, prescription and use in society. It also emphasises the medical, social and economic results. Drug utilisation research is, thus, described as “*a diverse collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes*” (Wettermark *et al*., 2016:1-12).

A detailed discussion of the empirical investigation methodology follows in section 1.5.

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[2] Short-term treatment duration is defined as total days of medicine supply < 90 days.
[3] Long-term treatment duration is defined as total days of medicine supply ≥ 90 days.

1.5 Empirical investigation methodology overview

1.5.1 Study design

A quantitative approach was suitable for this study because it involved quantifying the measurable aspects of human behaviour, unlike a qualitative study, which involves utilising a variety of empirical materials, such as case studies, personal experiences, introspectives, life stories, interviews, and observational, historical, interactional and visual texts that describe routine and problematic moments and the meanings ascribed to them by individuals (Aspers & Corte, 2019:142). Quantitative research begins with preconceived notions about how the concepts are related, and the focus is mostly on a small set of concepts. Objectivity is emphasised when collecting and analysing information (Brink *et al.,* 2012:38-39). The researcher analyses numerical information by means of statistical procedures. An observational study produces data that indicates the occurrence of a particular phenomenon and tests the causes of any problems (Waning & Montagne, 2001:44).

A cross-sectional study design was utilised in this research. In cross-sectional studies, data for a sample is collected for each wave (survey period) to represent the population for that period (Setie, 2016:262). To obtain objective one (i.e., to determine the changes in prescribing patterns), a repeated cross-sectional design was utilised. In repeated cross-sectional studies, a sample is defined and information about parameters of interest is collected. This collection is repeated at defined intervals but not necessarily with the same sample (Butler *et al*., 2022:597). For objective two of the study, the period between 1 January 2011 and 31 December 2017 was treated as one continuum.

1.5.2 Data source and data fields

According to Zeni and Kogan (2007:21), databases provide researchers with an opportunity to access a large representative sample instead of a convenience sample. Data for this study came from a South African PBM company's database of medication claims.

More than 52 medical assistance schemes and capitation provider clients, served by 16 distinct healthcare administrators' plans in South Africa, receive medicine management services from the PBM which is connected to all pharmacies and 98% of all dispensing doctors in South Africa. The database has records of longitudinal patient medicine claims data for more than 2.1 million beneficiaries of medical schemes.

The data fields extracted from the database included:

- prescription numbers;
- encrypted patient member and dependants' numbers;

- the patients' genders;
- the patients' dates of birth;
- the quantity of the medicine items prescribed (i.e., number of tablets/capsules);
- the number of days for which the medicine was supplied;
- the drug's trade name and strength;
- the active substance;
- the National Pharmaceutical Product Interface (NAPPI)-code[4];
- the date the prescription was filled;
- the diagnosis (ICD-10 code);
- the geographical area of the prescriber (province); and
- the final log status (whether the claim was paid from the patient's acute, OTC, chronic, oncology or PMB benefits).

1.5.3 Target and study population

"The target population is the specific, conceptually bounded group of potential participants to whom the researcher may have access that represents the nature of the population of interest." (Casteel & Bridier, 2021:344) Effective participant selection is essential for obtaining a sample of participants representing the target population (Neuman, 2014:252). The target population for this study comprised all patients using opioid-containing analgesic therapy in the private healthcare sector in South Africa. The study population consisted of all prescriptions on the database from 1 January 2011 to 31 December 2017 containing at least one opioid-containing analgesic (active pharmaceutical ingredient (API)) as listed in the Monthly Index of Medical Specialities (MIMS) classification system (Snyman, 2016:54), that was reimbursed from chronic, PMB or oncology benefits (refer to Table 1-1).

Table 1-1: Inclusion and exclusion criteria for the study population

Inclusion criteria	Exclusion criteria
Study period: 1 January 2011–31 December 2017 **Active pharmaceutical ingredient:** Narcotic analgesics (classified according to active ingredients) and combinations thereof (classified according to active ingredients) based on the MIMS classification system (Snyman, 2015): fentanyl; tramadol, morphine; dihydrocodeine; hydromorphone; codeine phosphate; oxycodone; pentazocine; pethidine; buprenorphine; codeine combinations; morphine combinations and tramadol combinations	**Final log status:** claims reimbursed for acute and OTC medications were excluded. **Dosage form:** all injections and suppositories.

[4] "NAPPI codes are unique, nine-digit product codes implemented with electronic transactions in mind – product name, pack size, strength, manufacturer plus exclusions, etc., are incorporated" (Snyman, 2015)

1.5.4 Data analysis

Data analysis refers to the variables, techniques and statistical analyses utilised in the study.

1.5.4.1 Variables

A description of the variables used in the study is provided in Table 1-2.

Table 1-2: Description of the study variables

Variable	Description
Gender	Only patients whose gender (i.e., male or female as recorded on the dataset) was known were included in this study.
Age	The patient's age on the treatment date was calculated from the patient's birth date and the date of treatment (i.e., when the prescription was filled). Patients were divided into age quartiles based on descriptive statistics.
Geographical location/province	The prescriber's postal code was used as a proxy for the patients' geographical location.
Active pharmaceutical ingredient	Active pharmaceutical ingredients of medicinal products were identified using the data fields "drug's trade name" and/or the NAPPI codes, as specified in the MIMS (Snyman, 2015).
Drug prescribing indicators	The drug-prescribing indicators used in the study included the following: • The total number of patients per year; • The total number of medicine items per year; • Active pharmaceutical ingredient; and • The defined daily dose (DDD) per 1000 inhabitants per day in milligrammes for buprenorphine, codeine, dihydrocodeine, fentanyl, tramadol and morphine.
Quantity	The number of tablets/capsules claimed for a specific medicine item (active substance) on a prescription.
Number of days' supply	The total number of days for which a medicine item (active substance) on a prescription was provided.
Prescribed daily dosage	The average dosage of a medicine item (active substance) prescribed per day (WHO, 2013:31). This was calculated from the strength of a product (indicated by the products' trade name), the quantity and the number of days' supply. The following formula was used: (strength in milligramme x quantity)/days' supply) (WHO, 2013). The Prescribed daily dose (PDD) was used to calculate the number of DDDs/1000 inhabitants per day.
Diagnosis (ICD-10 code)	The ICD-10 diagnosis code for depression (F30–F39) was used to identify patients with depression (WHO, 2016).
Study/period	For objective one, a repeated cross-sectional design was utilised (refer to paragraph 1.4.2.1). For this analysis, the study/time period had annual intervals (i.e., 2011, 2012, 2013, 2014, 2015, 2016 and 2017). For objective two, the period between 1 January 2011 and 31 December 2017 was regarded as a continuum.
Days of treatment	Because a patient could receive more than one opioid analgesic during the study period or the same API in different strengths, the total days of treatment for each tradename product the patient received, was determined using the first and last treatment date with the specific product.

Variable	Description
Treatment episode	Unique sets of mutually exclusive “days of treatment” were determined for each patient per tradename product received over the study period.
Treatment duration groups	Treatment episodes where stratified into two treatment duration groups based on the number of days of treatment: short-term treatment duration (defined as the total days of treatment < 90 days) and “long-term treatment duration” (defined as the total days of treatment of ≥ 90 days).
Chronic pain treatment groups	The final log status (data field) indicates the medical benefits for which the medicines were reimbursed, such as claims reimbursed for oncology, chronic, or prescribed minimum benefits. This data field was used to stratify patients into two chronic pain treatment groups: CNCP treatment (claims reimbursed from chronic or PMB benefits) and cancer-related treatment (claims reimbursed from oncology benefits).

1.5.4.2 Statistical analysis

The data were analysed using the Statistical Analysis System®, SAS 9.4 software (SAS Institute Inc., 2002-2012) and the Joinpoint Regression Program Version 4.9.1.0 (2022). The statistical methods that were used are described in the following paragraphs.

1.5.4.2.1 Descriptive statistics

According to Brink *et al.* (2012:241), a descriptive analysis is performed to organise the data, summarise the findings and make it possible to exhibit the evidence, describe how the data are dispersed and investigate links between different areas of the data.

The techniques that were followed to describe the study sample in this study were as follows: frequencies/counts (*n*), percentages (%), means, standard deviations and 95% confidence intervals (Cl), medians, and interquartile ranges (Brink *et al.*, 2012:189; Neuman, 2014:297).

1.5.4.2.2 Inferential statistics and effect sizes

With inferential statistics, a researcher can extrapolate results from a sample to a sizeable population and calculate the population’s characteristics (Brink *et al*., 2012:190).

Differences in independent group means (e.g., the mean number of items per prescription between male and female patients) were determined using the independent *t*-test. Cohen’s *d* was used to determine practical significance as a standardised effect size for measuring the size of the difference between two group means. Cohen’s *d* was calculated as follows:

$$d = \frac{\bar{x}_1 - \bar{x}_2}{SD_{max}}$$

Where:

d = effect size

$\bar{x}_1$ and $\bar{x}_2$ = means of the two groups

SD_{max} = standard deviation of either group (Cohen, 1988:20).

A *d*-value of 0.2 is a small effect size, 0.5 is medium, and 0.8 is large (Sullivan & Feinn, 2012:280). In this study, effect sizes ≥ 0.8 were regarded as practically significant. Changes in the prescribing patterns (i.e., drug prescribing indicators) (see Table 1-2) were determined using a generalised estimating equations (GEE) approach by using the PROC GENMOD command (SAS, 2008a). Repeated continuous responses linear mixed models were fitted to analyse the trend over time using PROC MIXED GENMOD (SAS, 2008b). This procedure allows for correlated data.

The most frequent measuring unit used in drug consumption research is the DDD, which is used to assess drug intake or prescribing (WHO, 2007). The DDD/1 000 inhabitants/day on prescription data offers an approximation of the percentage of the populace within a specified area treated daily with a particular medicine (WHO, 2013:34). The formula for the calculation of the DDD/1000 inhabitants per day (WHO, 2013) is given as:

$$\text{DDD/1000 inhabitants/day} = \frac{Amount\ of\ drug\ (mg)\ dispensed\ in\ 1\ year}{DDD\ (mg) * 365 * number\ of\ inhabitants} * 1\ 000$$

Where

DDD = Defined daily dose assigned by the WHO

Inhabitants = the number of patients captured in the central dataset for each year

Changes in the DDD/1000 inhabitants/day in milligrammes for six active pharmaceutical ingredients, namely buprenorphine, codeine, dihydrocodeine, fentanyl, tramadol and morphine, were investigated using joinpoint regression analysis. Joinpoint regression involves determining the time point(s) at which an observed trend changes, also referred to as the "joinpoint(s)", and estimating the regression function of the detected joinpoints (Liu *et al*., 2022:5). The formula for the joinpoint regression model for the observations in aggregate data $(x_1,y_1),\ldots,(x_n,y_n)$, where $x_1<x_2<\ldots<x_n$ denotes the time variable, and y_i (i = 1,…, n) represents the response variable, is given as:

$$E[\gamma|x] = \beta_0 + \beta_1 x + \delta_1(x - \tau_1)^+ + \cdots + \delta_k(x - \tau_k)^+$$

Where:

τ_k = the unknown joinpoints

Temporal trends were reported as annual percentage changes (APCs) and average annual percentage changes (AAPCs).

Cross-tabulation with chi-squared statistics was used to assess the association between depression and treatment duration by age group and gender. Cramér's *V* statistics, a measure of the strength of an association between two nominal variables, gives a value between 0 and +1. A value of 0.5 is practically significant (Pietersen & Maree, 2016:234).

1.6 Ethical considerations

The contract between the research entity Medicine Usage in South Africa (MUSA) and the PBM, as well as the approval of the Health Research Ethics Committee of the North-West University (Ethics certificate number NWU-00179-14-A1) and the PBM's board of directors (refer to Annexure B), allowed for this study to be conducted. There was no contact or interaction with any patient; therefore, no discomfort or other risk of harm could occur. The benefits of this study outweighed the risks. This study falls under the category of low risk. The North-West University's insurance covered the researcher and project. The researcher and study leaders reported no conflict of interest.

1.7 Chapter summary

This chapter briefly discussed the problem by providing background. The literature in this chapter established that chronic pain burdens society in both developed and developing countries and affects patients' general health and psychological and socio-economic well-being. Prescribing patterns may be useful in determining how chronic pain can be managed. The following chapter discusses chronic pain, the use of opioid analgesics, their mechanism of action, indications, drug-drug interactions, side effects and recommended daily doses of opioid analgesics.

CHAPTER 2 LITERATURE CHAPTER

2.1 Introduction

This chapter comprises a review of the literature on chronic pain and the use of opioid analgesics in the treatment thereof. The mechanism of action, indications, drug-drug interactions, side effects and recommended daily doses of opioid analgesics are described. An overview of opioid prescribing patterns worldwide is provided. The chapter concludes with a comment on the association between the regular use of prescribed opioids in patients with chronic pain and psychiatric conditions, particularly depression.

2.2 Definitions, terminology and pain classification

The Kyoto Protocol of the IASP defines pain as "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*". This definition caters for the fact that pain is subjective and could be psychological (Loeser & Treed, 2008:473-477). Pain is also described as the occurrence of damaged or inflamed tissues in a localised area of the body and is perceived as a sign and symptom of a disease (Kasper *et al*., 2015:87). Chronic pain is defined as *"pain that persists beyond normal tissue healing time, which is assumed to be three months"* (Ho *et al.*, 2013:139).

According to the IASP (2018) criteria, pain can be categorised according to its physiology, intensity, temporal features, the type of tissue affected, and syndrome as follows:

- Pain physiology (nociceptive, neuropathic, inflammatory);
- Intensity (mild-moderate-severe; 0–10 numeric pain rating scale);
- Type of tissue involved/location (skin, muscles, viscera, joints, tendons, bones);
- Syndromes (cancer, fibromyalgia, migraine, others);
- Special considerations (psychological state, age, gender, culture); and
- Time course (acute, chronic).

The schematic diagramme in Figure 2-1 (adapted from Xiao and Zhang, 2018:207) indicates the definition and classification of pain as detailed by the IASP (2018).

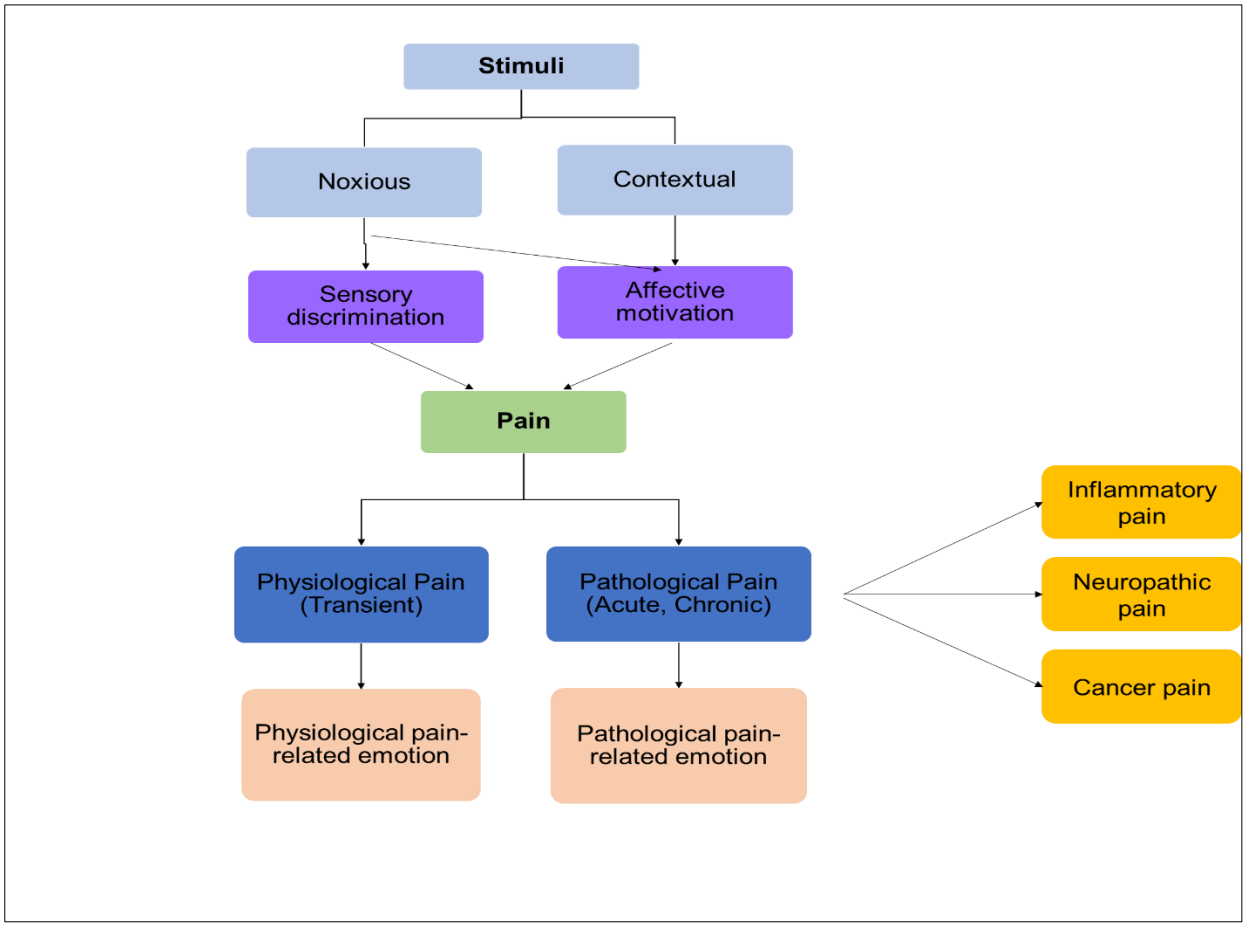

Figure 2-1: The description of pain pathways

The classification of pain based on pain physiology, intensity, type of tissue involved/location, syndromes and time course/duration of pain is described in the following section.

2.2.1 Classification based on pain physiology

Pain is classified as peripheral nociceptive, neuropathic or central and can be of an inflammatory or structural nature or both (Ablin & Buskila, 2015:113). All the classifications can be acute or chronic (Ward & Linden, 2013:121).

When the somatosensory nerve system, which includes the bones, joints and muscles, is damaged or afflicted by disease, it produces neuropathic pain (Giordano, 2006:1-2; Lehne, 2010:287; Mann & Carr, 2006:9). Neuropathic, functional and nociceptive pain are all forms of chronic pain that continue for more than three to six months (Fornasari, 2012:46). Neuropathic pain, which is intermittent and linked to peripheral nervous system damage or pathological alterations, develops in the central nervous system (CNS) (Fornasari, 2012:46). The skin, muscles and visceral organs all receive signals from the somatosensory nervous system (Treede *et al*., 2015:1005).

Nociceptive pain is generated by tissue damage that activates particular pain receptors called “nociceptors”, which are sensitive to noxious stimuli. Depending on where the activated nociceptors are located, this form of pain is further divided into somatic and visceral pain (WHO, 2012).

Somatic pain that originates from the piercing of the skin, for example, with a needle (Ward & Linden, 2013:121), is called “superficial pain” and can be either a fast or slow pain (Guyton & Hall, 2006:598). Fast pain is sharp, pricking, acute or electric and occurs within 0.1 seconds after stimuli are applied (Guyton & Hall, 2006:599). Slow pain, also referred to as searing, aching, throbbing or queasy pain, and persistent pain, begins one second or longer after the application of stimuli (Guyton & Hall, 2006:599).

The activation of nociceptors in the viscera (the body‘s internal organs enclosed within a cavity, such as thoracic and abdominal organs) is the source of visceral pain. Infection, fluid or gas emboli, stretching or compression and, most commonly, solid tumours can all cause pain (WHO, 2012).

2.2.2 Classification of pain based on intensity (mild-moderate-severe; 0–10 numeric pain rating scale)

The intensity of pain differs from one patient to the next over time, depending on the individual. Patients can describe pain that is due to some pathological condition differently (e.g., on a scale of 0 to 10, where 0 signifies no pain and 10 is the worst pain). Non-cancer pain ranges from mild to moderate to severe (Thienhaus & Cole, 2002:32).

2.2.3 Type of tissue involved/location (skin, muscles, viscera, joints, tendons, bones)

When nerves are compressed, or pain signals are processed improperly, neuropathic pain affects the brain and spinal cord. The peripheral CNS and any process that damages nerves, such as metabolic, traumatic, infectious, ischemic, toxic or immune-mediated pathological diseases, might be affected by neuropathic pain (WHO, 2012). Visceral pain, often referred to as “deep somatic pain”, affects internal organs such as the liver, pancreas, pleura and peritoneum. In contrast, nociceptive pain, also known as “deep somatic pain”, affects the bones, joints, muscles and connective tissue (WHO, 2012).

2.2.4 Syndromes (cancer, fibromyalgia, migraine, others)

Cancer patients might experience neuropathic pain due to tumour-associated neural compression, directly or indirectly, as a result of cancer treatment, such as surgery or chemotherapy, or concurrently with non-cancer-related neuropathic pain (Reis-Pina *et al.,*

2018:298). The pain associated with fibromyalgia syndrome includes afferent enhancement of peripheral stimuli, particularly of the nociceptive variety, as well as other neuropathic symptoms such as exhaustion and changes in cognition and mood (Smith & Barkin, 2011:248-249). Migraine is the most common chronic headache. It occurs mainly during middle age and is less reported in the teenage group and patients older than 60 years of age. It is caused by psychosocial stress, depression, anxiety, inadequate or too much sleep, strong smells, atmospheric pressure and humoral factors such abnormal blood glucose and gonadotrophic hormones (Bartleson & Cutrer, 2012:38; Khalili *et al*., 2017:136-137).

2.2.5 Classification of pain based on time course/duration

Acute pain follows injury and does not last long, typically for less than 30 days (Thienhaus & Cole, 2002:32; WHO, 2012). Chronic pain can start as acute pain and endure for a long time or recur due to the persistence of noxious stimuli or the recurring worsening of an injury. Chronic pain is continuous or recurrent and lasts for the normal healing period of an acute injury or disease, that is, beyond three months (Ho *et al*., 2013:139). Most studies describe "chronic pain" as "CNCP", which includes back pain, joint pain or osteoarthritis, fibromyalgia and headaches (Ambrose & Golightly, 2015:122; Chang, S.C., *et al.,* 2015:93; Jo *et al.,* 2016:106).

The WHO (2012) categorises chronic pain, according to the new International Classification of Diseases (ICD), as follows: (1) "chronic primary pain, (2) chronic cancer pain, (3) chronic posttraumatic and postsurgical pain, (4) chronic neuropathic pain, (5) chronic headache and orofacial pain, (6) chronic visceral pain and (7) chronic musculoskeletal pain." Table 2-1, compiled from the International Classification of Diseases 11th Revision (WHO, 2012), shows the classification.

Table 2-1: International Classification of Diseases 11th Revision for chronic pain disease

Classification of chronic pain disease	ICD-codes
Chronic primary pain	MJ40.1
Chronic cancer pain	MJ40.2
Chronic posttraumatic and postsurgical pain	MJ40.3
Chronic neuropathic pain	MJ40.6
Chronic headache and orofacial pain	MJ40.7
Chronic visceral pain	MJ60.5
Chronic musculoskeletal pain	MJ60.4

Chronic primary pain occurs in one or more anatomical parts of the body for longer than three months. It is linked to mental distress that interferes with daily life and social interactions (WHO, 2012). Lower back pain is caused by the natural degeneration of the intervertebral disk in the spine, which is called “degenerative disk disease” (Abi-Hanna *et al.*, 2018:188). There are two back pain conditions, lumbar and cervical back pain, mainly co-occurring (Angst *et al.,* 2017:605). Lower back pain is a chronic pain that commonly affects the elderly population from the age of 60 years and above and affects their quality of life by limiting their activities and requiring daily care to manage their lives (Aguiar *et al.*, 2017:366; Aktaş & Karabulut, 2017:33; Harrisson *et al.*, 2017:1296). Dancing, a rigorous physical activity, is linked to chronic lower back pain in both male and female children (Swain *et al.*, 2018:8). Chronic lower back pain is also common in patients with Parkinson’s disease (Ozturk & Kocer, 2018:191). According to Da Silva *et al*. (2015:928), weak back muscles caused by a shift in the number of type II muscle fibres and reciprocal lumbar muscular atrophy can lead to chronic lower back pain.

Chronic posttraumatic and postsurgical pain occurs three months after surgery or tissue injury, including tissue trauma or burns (WHO, 2012).

Chronic neuropathic pain, such as that related to diabetic neuropathy, stroke or nerve trauma, is brought on by a disorder of the somatosensory nervous system, which transmits information about the body, including the skin, musculoskeletal system and visceral organs (WHO, 2012). Fibromyalgia is a chronic musculoskeletal pain condition (Gonzalez-Roldan *et al.*, 2016:39; Sluka & Clauw, 2016:114) with presenting symptoms of fatigue and cognitive impairment, and these symptoms can be triggered by chronic pain or auto-immune diseases (Alev *et al.*, 2017:200; Garrido *et al.*, 2017:116; Marques *et al.*, 2017:357). Fibromyalgia is induced by physical or emotional stress such as traumatic accidents, surgery or posttraumatic stress disorder (Di Tella *et al.*, 2017:87; White & Robinson, 2015:245). It is associated with localised tenderness affecting 19 parts of the body, with physical findings of 11–18 tender points on examination (Alev *et al*., 2017:200; Ratter *et al.*, 2014:144).

Chronic headache and orofacial pain occur on most days during a period of three months (Treede *et al.,* 2015:1005; WHO, 2012). Temporomandibular disorders are the most common chronic orofacial pain in the definition of chronic pain and present as primary headaches (Wang *et al.*, 2017:56; WHO, 2012). A long-lasting headache consistent for at least 4 hours per day and persisting for days is also described as chronic pain. Migraine and tension-type headaches are common chronic headache syndromes (Khalili *et al.*, 2017:136; McAbee, 2015:137; Przekop *et al.*, 2016:716). Headaches can also be caused by concussions due to sports-related injuries ~~in schools~~ and lead to tension-type headaches or migraine (Bramley *et al*., 2015:493). Chronic headaches continue for at least four hours per day and could occur for about 15 days in a month; this type of headache starts as a migraine or occasional tension-type headache, referred to as

“chronic tension-type headaches” (Przekop *et al.*, 2016:716) and continue as daily headaches (Gladstein & Rothner, 2010:88). Children might also experience headaches that are of short duration lasting for less than an hour (McAbee, 2015:137).

Constant or recurrent pain originating from the internal organs in the head and neck region and the abdominal, thoracic and pelvic cavities are referred to as “chronic visceral pain” (WHO, 2012).

Chronic musculoskeletal pain is a persistent or recurrent pain that develops due to a disease process affecting one or more of the following: muscles, joints, bones or associated soft tissues (WHO, 2012). “Arthritis” is a broad term that defines rheumatic diseases (Abella *et al.*, 2016:140) or any form of degenerative, inflammatory or autoimmune conditions affecting the joints. Rheumatic diseases are osteoarthritis or inflammatory arthritis, such as rheumatoid arthritis or psoriatic arthritis (Apfelbacher *et al*., 2017:49).

Osteoarthritis is a chronic musculoskeletal progressive disease affecting the joints, most commonly the knee joints (Dias, J.M., *et al.*, 2017:450; Kooner *et al.*, 2017:309; Nielen *et al.*, 2017:202). Three main biological processes cause the effects on joint tissues in the body: decreased sex hormones, genetic alterations and ageing (Herrero-Beaumont *et al.*, 2017:55). Osteoarthritis affects the quality of life of the elderly population. Most risk factors associated with osteoarthritis are age and obesity, bone density, muscle weakness, joint laxity, previous knee trauma and physically-demanding activities (Calvet *et al.*, 2018:276-277; Laires *et al.*, 2017:230; Trouvin & Perrot, 2017:429-430). Osteoarthritis has been associated with peripheral pain mechanisms involving primary nociceptors activation in somatic tissues, such as joints, bones and muscles (French *et al.*, 2017:1). Additionally, osteoarthritis has a neuropathic component, in which pain is brought on by actual harm to the peripheral nerve system (McDougall et al., 2017:926). Most elderly patients are affected by hip osteoarthritis, resulting in physical disability (Iidaka *et al.*, 2017:2072; Kaukinen *et al.*, 2017:1830; O’Connell *et al.*, 2016:40).

Rheumatoid arthritis is a common autoimmune rheumatic disease affecting the synovium, resulting in joint destruction (Gioxari *et al*., 2018:114). Rheumatism causes muscle stiffness and pain and also affects joints (Ablin & Buskila, 2013:112). Psoriatic arthritis is defined as chronic inflammation affecting the joints, with negative test results for rheumatism and cutaneous psoriasis (Ouédraogo & Meyer, 2012:17).

2.3 The mechanism of chronic pain

According to Isa and Chetty (2022:11), in the presence of pain chronification[5], pain processing and pathways undergo several structural and functional changes, resulting in the sensitisation of the peripheral or central nervous system. Two categories of events are responsible for the changes in peripheral and central sensitisation, namely post-translational modification[6] and altered gene expression[7].

Peripheral sensitisation is the process whereby the peripheral nerves become more sensitive to pain signals (IASP, 2021). This can occur due to inflammation, injury, or other factors that activate the peripheral nervous system's nociceptors. As a result, even mild stimuli can cause pain. The inflammatory mediators cause neuroplastic alterations in the nociceptors that innervate the injured tissue via the release of a host of endogenous inflammatory mediators, including serotonin, bradykinin, substance P, histamine, adenosine triphosphate (ATP), prostaglandins (PGE2), thromboxanes, leukotrienes, endocannabinoids, nerve growth factor (NGF), cytokines (IL6, IL1β, TNFα), chemokines and calcitonin gene-related peptide (CGRP). As a defence mechanism, peripheral sensitisation is limited to nociceptors located in the inflammatory environment and will go away when tissues repair and the inflammation subsides (Courtney *et al.,* 2017:119-120). These inflammatory mediators stimulate and sensitise nociceptors, causing either short-term post-translational modifications in proteins or long-term alterations in protein gene expression (Isa & Chetty, 2022:11), such as alterations in ion channels, ectopic discharges in injured fibres, abnormal activity in axons not directly affected by lesions and neuro-immune interactions (Isa & Chetty, 2022:11-12).

Central sensitisation: This process involves changes in the CNS that lead to “increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input” (IASP, 2021). This can occur due to repetitive or persistent pain signals from the periphery. It can also be caused by changes in the structure and function of neurons in the spinal cord and brain that process pain signals. As a result, the brain may perceive even non-painful stimuli as painful (Courtney *et al*., 2017:119). Central sensitisation and the

[5] “Pain chronification describes the process of transient pain progressing into persistent pain.” (Morlion *et al*., 2018:1170)

[6] Post-translational modification: alterations that emerge from modifying proteins after messenger RNA (mRNA) has been translated into proteins, such as phosphorylation of protein kinase A and C, increased expression of calcium and sodium channels, and downregulation of potassium ion channels. The activity and functionality of the proteins are impacted by these alterations (Isa & Chetty, 2022:11).

[7] Alteration in gene expression: Changes to proteins change their functions; for instance, an increase in transient potential vanilloid-1 (TRPV1) gene expression would result in the overexpression of TRPV1 receptors, which will increase pain signals (Isa & Chetty, 2022:11).

development of pain chronicity can furthermore be the results of hyperexcitability of neurons, neuronal loss, disinhibitory mechanisms and structural reorganisation (Isa & Chetty, 2022:12).

Psychological and social factors can also play a role in chronic pain. Stress, anxiety, depression, and other mental health issues can increase pain perception. Social factors, such as social isolation and poor support networks, can also contribute to chronic pain.

2.4 Prevalence of chronic pain

2.4.1 Global prevalence

Chronic pain is among the most prevalent physical conditions, affecting 8–22% of the population annually in developed countries (Feingold *et al.,* 2018:293). Worldwide, the data indicates that low- and middle-income groups in developing countries have a high prevalence of chronic pain compared to those in developed countries (Brennan-Olsen *et al.,* 2017:271; Turner *et al.,* 2017:2111). African-American and Caucasian populations have been shown to have a similar prevalence of chronic pain (Hooten *et al.,* 2012:1500).

Around 85% of people globally are predicted to have lower back discomfort at some point (Henschke *et al.,* 2016:1038). Lower back pain is caused by physiological changes in the body, such as muscle weakness, decreased physical capabilities and degeneration of the tissues (Ferreira & de Luca, 2017:193; Leopoldino *et al.,* 2016:259). Lower back pain affects about two-thirds of the population of the USA (Edward *et al.,* 2017:2). There is a high prevalence of lower back pain in the French population, which is about 57% in a one-year period (Gourmelen *et al.,* 2007:640). Personnel in the nursing profession have a higher prevalence of lower back pain than the industrial workforce (Van Hoof *et al.,* 2018:222-231). Lower back pain is more common among pregnant women than non-pregnant women (Sencan *et al.,* 2017:33-34).

Fibromyalgia has an estimated prevalence of 0.5–5% in the general population worldwide (Aguglia *et al.,* 2011:262; Branco *et al.,* 2010:449). The prevalence of fibromyalgia in the adult population of the USA is estimated at 2%. Similar prevalence rates have been reported in other countries, such as Canada at 3.3%, Germany at 3%, Spain at 2.4%, Italy at 2.2%, and Sweden at 2.5%. In contrast, the prevalence of fibromyalgia has been found to be low in Finland and Denmark at 0.8% and 0.7% respectively (Branco *et al.*, 2010:449). Fibromyalgia is more prevalent among obese than normal weight patients (Dias, D.N.G., *et al.,* 2017:426).

Patients with advanced or complicated diabetes mellitus experience pain called “painful diabetic neuropathy”, which happens directly due to abnormalities in the somatosensory system. It occurs most commonly among patients with type 1 and 2 diabetes (Lewis & Kriukelyte, 2016:571; Roe & Sehgal, 2016:549-550).

The *Global Burden Disease* study conducted in 2010 showed that migraine conditions in Africa were ranked as the 13th most common disabling condition (Woldeamanuel *et al.,* 2014:2). Rheumatoid arthritis has an estimated prevalence of 0.5%–1% in the global population, with an estimated prevalence of 0.33% in southern Europe, 0.5% in northern European countries and 0.35% in developing countries. The estimated prevalence of rheumatoid arthritis in the urban areas of South Africa is 2.5% and 0.07% in rural areas (Brunier *et al.,* 2017:455-456; Gioxari *et al.,* 2018:114).

2.4.2 Prevalence based on age group and gender

Patients 65 years of age and older are most affected by chronic pain, and women are more likely than men to have it (Kudrina *et al*., 2015:157; Robinson *et al*., 2017:620). In the adult population, chronic pain is believed to be present in 25% of people worldwide (Smith *et al*., 2015:72). Adult populations suffer from chronic headaches for 15 days or more each month. Headaches are among the highest disabling conditions worldwide (Bruffaerts *et al.,* 2015:43; Schytz *et al.,* 2017:71). In one study, symptomatic headaches were reported to be prevalent in 50% of the adults in the sample within the year of assessment (Mihalov *et al.,* 2017:446).

Headaches and migraines are more prevalent in women than among their male counterparts worldwide (Andersen *et al.,* 2017:38; Khalili *et al.,* 2017:136; Seyed Forootan *et al.,* 2017:153). Rheumatoid arthritis is the most common inflammatory disease in adults and most prevalent in women between the ages of 30 and 50 years (Gomes *et al.,* 2017:413). Fibromyalgia is more prevalent in women than men (Aguglia *et al.,* 2011:262; Marques *et al.,* 2017:357). Lower back pain is highly prevalent in the ageing population, from 60 to 65 years of age (Ferreira & de Luca, 2017:193; Leopoldino *et al.,* 2016:259). Lower back pain affects about 80% of the working-class population in their physically active years, which is up to 45 years old and is the leading cause of absenteeism in the working environment (Buchbinder *et al.*, 2013:576; Hoy *et al.,* 2010:769; Mody & Brooks, 2012:239; Stubbs *et al.,* 2016:64).

2.5 Management of chronic pain

There are generally six main kinds of treatment for chronic pain: pharmacological, physical medicinal, behavioural, neuromodulational, interventional and surgical. Multiple strategies coordinated by a multidisciplinary team lead to the best patient outcomes (Rosenquist *et al*., 2017). Primary care collaborative care models can enhance patient outcomes and pain management.

2.5.1 Physical medicine

According to the Merriam-Webster online dictionary (Merriam-Webster Inc., 2018), physical medicine is defined as "*a medical speciality concerned with preventing, diagnosing and treating disabling diseases, disorders and injuries by physical means (such as by the use of electrotherapy, therapeutic exercise or pharmaceutical pain control)*". Physical medicine, also referred to as "physiatry" or "rehabilitation", is a valuable treatment for chronic pain, physical functions affecting the brain, spinal cord, nerves, bones, joints, ligaments, muscles and tendons, sleep, cognitive function, and overall health and disease risk reduction. It also improves physical activity and affects daily activities, quality of life, emotional impacts, overall physical function and independence (Ambrose & Golightly, 2015:122; Tedesco *et al.,* 2017; WHO, 2012).

Conditions often treated with physical medicine include headaches (including migraines), lower back pain and fibromyalgia. For example, according to De Goffau *et al.* (2017:615) and Toldo *et al.* (2017:509), headaches can be treated using stress management, relaxation, exercises and a healthy diet. Lower back pain can be treated by therapeutic exercise, thermotherapy and education (Adnan *et al.,* 2017:659; Krath *et al.,* 2017:410), whereas fibromyalgia can be treated with aerobic exercise, massage, physical therapy and cognitive behavioural therapy (Ablin & Buskila, 2013:336; Boehm *et al.,* 2014:732; Kas *et al.,* 2016:775-776; Yuan *et al.,* 2015:258).

2.5.2 Behavioural therapy

Cognitive-behavioural therapy is a non-pharmacological method used to manage pain. The focus of this method is on the environment, behaviour and understanding (Ehde *et al.*, 2014:155). During behavioural therapy, patients undergo about 10–20 sessions that help them with problem-solving and teach them how their thoughts contribute to the symptoms of their disorder (Graham *et al.,* 2016:47; Veehof *et al.*, 2011:533). Patients are then taught how to modify these thoughts. The most helpful exercises are relaxation and controlled-breathing exercises, which are easy to learn (Rosenquist *et al.,* 2017).

2.5.3 Neuromodulation

Neuromodulation is an advanced method used in chronic pain management therapy. "Neuromodulation" refers to a technique that directly activates nerves by applying electrical or chemical stimuli to a target area, blocking pain signalling at the stimulation site and preventing pain signals from travelling to the brain (American Society of Interventional Pain Physicians (ASIPP), 2010; International Neuromodulation Society(INS), 2010). Neuromodulation therapy is classified into four categories: external peripheral, internal peripheral, spinal and supraspinal (Rosenquist *et al*., 2017). External peripheral systems can be further subdivided into surface and percutaneous systems.

Surface external peripheral neuromodulation, known as “transcutaneous nerve stimulation”, is the most commonly used method (Rosenquist *et al.,* 2017; Rothemeyer & Enslin, 2016:859). It involves applying electrical currents, employing surface electrodes to apply a low-voltage electrical current to the skin from a portable battery-operated device. It is a safe, non-invasive treatment, and patients can apply it independently (Rosenquist *et al*., 2017).

Spinal cord stimulation is a spinal neuromodulation analgesic method for chronic neuropathic pain caused by nerve or nervous system injury (ASIPP, 2010; Deer *et al.*, 2014:678; Rosenquist *et al.,* 2017). Acupuncture and spinal manipulative therapy also treat lower back pain (Kizhakkeveettil *et al.,* 2017:202; Van Dillen *et al.,* 2016:53).

Deep brain stimulation is called “neuromodulation of the brain”. It is used for neuropathic pain and is most effective for post-stroke and facial pain and should be performed only by well-experienced technicians (INS, 2010; Rosenquist *et al.,* 2017; Rothemeyer & Enslin, 2016:859).

2.5.4 Interventional treatment

Interventional treatment methods complement other pain management strategies by targeting the site of pain (Overton *et al.,* 2008:S61-S64; Rosenquist *et al.*, 2017). The most frequent interventional procedures involve percutaneous injections, in which a pharmacologic substance, such as a glucocorticoid and/or local anaesthetic, is administered after a small-bore needle is inserted through the skin and directed to the suspected site of pain using an imaging technique (Rosenquist *et al.,* 2017). With a questionable prognosis, this technique is a final resort for patients experiencing excruciating cancer pain. The technique could offer brief analgesia for certain individuals to enable physical therapy (Rosenquist *et al.,* 2017).

2.5.5 Surgical approaches

Lower back pain caused by degenerative disk disease can be treated by one of the two major surgical treatments, namely lumbar fusion or total disk replacement (LTDR), known as “lumbar disk arthroplasty” (Abi-Hanna *et al.,* 2018:188; Rainville *et al.,* 2009:257). Lumbar or spinal fusion is the most common procedure: two or more vertebral bodies are joined to restrict spinal motion and relieve pain caused by the degenerated disc (Rosenquist *et al*., 2017).

2.5.6 Pharmacological treatment

When necessary, medication should be combined with other treatment modalities to achieve treatment goals rather than serving as the only focus of therapy (Rosenquist *et al.,* 2017). Chronic pain can be treated by differing classes of medication, namely NSAIDs, antidepressants, anti-epileptics and opioids (Fornasari, 2012:46; Zhang *et al.,* 2015:94). The role of NSAIDs,

antidepressants and anti-epileptics in the management of CNCP is addressed in subsequent paragraphs, whereas that of opioids follows in section 2.6.

2.5.6.1 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory medications are used to treat both acute and chronic pain, especially in the case of inflammatory diseases such as fibromyalgia (Boehm *et al.,* 2014:1329; Jensen *et al.,* 2014:1329) and rheumatoid arthritis (Nikolaus & Zeyfang, 2004:23). These medications block the synthesis of pro-inflammatory prostaglandins by inhibiting cyclo-oxygenase (COX), which converts arachidonic acid into prostaglandins, thereby resulting in a reduction of the inflammatory effects of prostaglandins and pain thresholds (Nikolaus & Zeyfang, 2004:23; Roe & Sehgal, 2016). The NSAIDs also permeate cell membranes and have an impact on several intracellular functions. L-selectin inside neutrophils is interfered with during the process. Since L-selectin is a molecule involved in the neutrophil's inflammatory response, inflammation causes pain sensitisation (Chapman & Vierck, 2017:359.e10; Nikolaus & Zeyfang, 2004:23).

There are two forms of COX isoenzymes: COX isoenzyme 1 and 2. The inhibition of COX isoenzyme-1 results in gastrointestinal side effects, whereas the inhibition of COX isoenzyme-2 results in an analgesic effect. Diseases such as renal or cardiovascular diseases and gastrointestinal disturbances might develop when NSAIDS are used, therefore, careful consideration should be taken regarding the dose and duration of COX-2 treatment (Gu *et al.,* 2017:1247). Precautions should be considered during concurrent treatment in individuals with cardiac risk factors such as smoking, diabetes, elevated cholesterol or hypertension. Patients with vascular problems in the heart, brain or renal system might not benefit from using NSAIDs due to the increased risk of myocardial infarction and other thrombotic events in patients with vascular diseases (Roe & Sehgal, 2016:549). However, there is no additional benefit to utilising COX-2 selective NSAIDs versus non-selective NSAIDs when treating persistent lower back pain with NSAIDs (Roe & Sehgal, 2016:549). Headaches are treated with paracetamol, NSAIDs, including aspirin and ibuprofen and triptans are used as a second choice of treatment, especially for the treatment of migraine and tension-type headaches. Non-pharmacological methods such as relaxation techniques are also used as preventive method to treat headaches (De Goffau *et al.,* 2017:615; Toldo *et al.,* 2017:509).

The NSAIDs, in particular, ibuprofen and naproxen, are used in the treatment of osteoarthritis patients and to improve the mobility of the joints (Gu *et al.,* 2017:1247). More than half of osteoarthritis patients use NSAIDs regularly (Goulet *et al.,* 2017:1-2).

2.5.6.2 Antidepressants

Antidepressants are used in conjunction with other treatments to treat chronic pain, particularly neuropathic pain. They work by inhibiting the release of the neurotransmitters serotonin and norepinephrine and muscarinic and histamine H1 receptors (Gaskell *et al.,* 2014:38-39; Nikolaus & Zeyfang, 2004:31).

In the management of chronic pain, antidepressants such as tricyclic antidepressants (TCAs), selective serotonin uptake inhibitors (SSRIs) and serotonin noradrenergic reuptake inhibitors (SNRIs) are crucial. According to Gaskell *et al.* (2014:383), Kraychete *et al.* (2016:508) and Roe and Sehgal (2016:549-550), TCAs and SNRIs are more effective at treating neuropathic pain than selective SSRIs. Serotonin noradrenergic reuptake inhibitors such as venlafaxine and duloxetine, which are used to treat depression, can also be used for the treatment of severe diabetic neuropathy and fibromyalgia (Ablin & Buskila, 2013:337; Ambrose & Golightly, 2015:122; Boehm *et al.,* 2014:1329; Jensen *et al.,* 2014:1329; Roe & Sehgal, 2016:549). When treating knee osteoarthritis, duloxetine has an analgesic effect comparable to NSAIDs (Roe & Sehgal, 2016:549).

Amitriptyline and nortriptyline are two examples of tricyclic antidepressants frequently prescribed for post-herpetic neuralgia, severe diabetic neuropathy and fibromyalgia (Roe & Sehgal, 2016:550). Venlafaxine and milnacipran are effective in treating fibromyalgia (Mease *et al.,* 2010:455). According to the 2013 COMBO-DN research, in which high-dose monotherapy was compared with a combination of duloxetine or pregabalin to treat diabetic peripheral neuropathic pain, combination therapy was found to be safe and efficacious. However, it did not significantly outperform standard-dose monotherapy (Roe & Sehgal, 2016:549-550). Amitriptyline is used for chronic headaches as a preventative treatment (Przekop *et al.,* 2016:716).

2.5.6.3 Anti-epileptics

Anti-epileptic drugs, such as gabapentin and pregabalin, suppress neuropathic pain, especially post-stroke pain, diabetic neuropathy and post-herpetic or trigeminal neuralgia (Gaskell *et al.,* 2014:36-37; Nikolaus & Zeyfang, 2004:31). Patients who have not responded well or could not tolerate the first-line therapy of neuropathic pain is, therefore, given pregabalin in doses of 300–600 mg daily (Roe & Sehgal, 2016:549). Pregabalin is effective at a dose of 450 mg per day in the treatment of fibromyalgia, improving the quality of sleep, pain and fatigue levels, whereas gabapentin is effective in the treatment of fibromyalgia (Ablin & Buskila, 2013:337; Boehm *et al.,* 2014:1329; Choy *et al.,* 2011:336; Jensen *et al.,* 2014:13-28-1329).

Chronic pain is treated with anticonvulsant drugs that work by blocking calcium and sodium channels, thus interfering with the glutamatergic transmission, or by a combination of these methods (Kraychete *et al.,* 2016:508; Roe & Sehgal, 2016:549).

About 10% of people who take anti-epileptic medicine stop taking it because of side effects such as tiredness, oedema, dizziness, weight gain and gait disruption (Roe & Sehgal, 2016:549). Although carbamazepine reduces pain effectively in the short term, it can also cause adverse effects such as thrombocytopenia, leukopenia, hyponatraemia, somnolence, headaches, ataxia, nystagmus, diplopia, blurred vision and liver toxicity (Roe & Sehgal, 2016:549).

2.5.6.4 Other medicines

Intravenous metoclopramide and diphenhydramine also treat acute migraine and tension-type headaches (Friedman *et al.,* 2018:285-286).

Biological medicines that are utilised to treat rheumatic arthritis, also known as “biologic disease-modifying antirheumatic drugs” (bDMARDs), have shown positive results for patients diagnosed with rheumatic arthritis (Cappelli *et al.,* 2017:165). The triple combination of methotrexate, sulfasalazine and hydroxychloroquine is recommended in the early stages of rheumatic arthritis, and both bDMARDs and triple combinations have shown the same clinical outcomes in terms of the immediate effects. However, after two years, bDMARDs have shown improved radiological outcomes (Mazouyes *et al.,* 2017:563-564; Paul *et al.,* 2018:478).

Intra-articular injections such as corticosteroids and hyaluronic acid are used for patients who do not respond well to non-pharmacological methods and pain relief medication (Liu *et al.*, 2017:1607-1608; Repetto *et al.,* 2017:362). Hyaluronic acids, in particular, are believed to be the go-to medications for treating osteoarthritis due to their high viscoelastic properties, which result in less shear resistance, and lubricate and cushion the joint (Avenoso *et al.,* 2018:132; Von Lospichl *et al.,* 2017:477).

Sumatriptan responds well in the treatment of migraines by causing extracranial vasoconstriction blocking Substance P-mediated neurogenic inflammation and CGRP-mediated neurogenic vasodilation in the dura mater (Schytz *et al.,* 2017:72; Toldo *et al.,* 2017:509).

2.6 Opioid analgesics

Opioid analgesics (and combinations) are described in this section according to the following headings: terminology, mechanism of action, indications, drug-drug interactions and recommended daily doses (RDDs).

Opioid prescriptions are a worldwide health problem affecting European countries, Australia and Canada (Kandel *et al.*, 2017:501). In the USA, patients have been prescribed opioid medicine mainly for acute postoperative pain, and women commonly receive opioid prescriptions following discharge from the hospital after giving birth by Caesarean section (Badreldin *et al.,* 2018:103e1; Bateman *et al.,* 2016:353.e1; Campbell *et al.,* 2018:31).

It is estimated that opioid prescribing in the USA increased by 300% from 1999 to 2015 (Davis *et al.,* 2019:166). The health authorities in the USA have worked with various professional organisations to issue guidelines recommending a more conservative approach to prescribing opioid analgesics in that country (Hartung *et al.,* 2018:33). In Australia, there was an almost fourfold increase in opioid prescriptions between 1990 and 2014, with codeine, oxycodone and buprenorphine being the most commonly used (Roxburgh *et al*., 2017:291). In Canada, deaths caused by overdoses of prescribed fentanyl increased from 4% in 2012 to more than 80% in 2017 and 2018, which led to the declaration of a public health emergency crisis in April 2016 (Smolina *et al.,* 2019:151).

2.6.1 Classification of opioids

Opioids are called “narcotic analgesics” which can be classified into two groups: weak opioids and strong opioid analgesics (Ward, 2015:11). Opioid analgesics are morphine-like substances that can be either natural or synthetic (Feingold *et al.,* 2017:2; Ward, 2015:11).

Various classification systems are used to classify opioids. According to McDonald and Lambert (2016:464), they are categorised into four groups, namely:

- “Endogenous opioid peptides, such as dynorphin and met-encephalin;
- Opium alkaloids, such as morphine, which is derived from a synthesis of poppy papaver somniferum;
- Semi-synthetic opioids, such as diacetylmorphine; and
- Synthetic opioids with structures unrelated to morphine (e.g., pethidine and fentanyl), methadone series (e.g., methadone and dextropropoxyphene), benzomorphan series (e.g., pentazocine) and semi-synthetic derivatives (e.g., etorphine and buprenorphine)”.

The WHO (2012) classifies opioid drugs according to the Anatomical Therapeutic Chemical (ATC) classification system in the following groups:

- Natural opium alkaloids (natural and semi-synthetic opiates), such as codeine and dihydrocodeine, in combination with other analgesics, if the content is 20 mg or more per unit dose (N02AA).
- Phenylpiperidine derivatives, such as fentanyl patches (N02AB).
- Diphenylpropylamine derivatives, such as dextropropoxyphene (N02AC).
- Benzomorphan derivatives (N02AD).
- Oripavine derivatives, such as buprenorphine (N02AE).

Katzung (2012:543–544) classifies opioid analgesics into three distinct groups; namely, i) opiates, which are derived from opium alkaloids, for example, morphine; ii) synthetic compounds that have different chemical structures from opiates but have similar effects, for example, methadone, meperidine, phenazocine and levorphanol; and iii) opioid peptides, such as ß-endorphin and enkephalins.

The South African Medicines Formulary (Rossiter, 2012:429-435) follows the same format as the WHO in its classification of opioid analgesics. Opioids, in combination with other agents, such as paracetamol and ibuprofen, are classified into various groups, as with other analgesics and antipyretics, depending on the indications (WHO, 2012).

For this study, opioid analgesics are classified according to the MIMS®-classification system, depicted in Table 2-2 (Snyman, 2015:62-77).

Table 2-2: MIMS classification of opioid analgesics

Opioid analgesics groups	Active substances
3.1 Narcotic analgesics (single active ingredients	Fentanyl Morphine Dihydrocodeine Hydromorphone Codeine phosphate Oxycodone Pentazocine Pethidine Buprenorphine
3.3 Combinations	Codeine combinations Morphine combinations Tramadol combinations

2.6.2 Mechanism of action

Opioids exert pharmacological actions through four opioid receptors: mu, delta, kappa and epsilon (Ward, 2015:11-12). A family of endogenous peptides, including encephalins, dynorphins and endorphins, generated by neurons, activate opioid receptors in the brain. Alkaloid opiates, the prototype of which is morphine, which is still the most effective analgesic in modern medicine, can also activate opioid receptors exogenously (McDonald & Lambert, 2016:465). Opioids are also divided into groups based on their mechanism of action, namely, mu-agonists, partial agonists and mixed agonist-antagonists (Ward, 2015:11). Mu-agonists bind to mu-opioid receptors, which are found in the brain stem, ventricles and medial thalamus (Trescot, 2016:45). Agonist-antagonists bind to the kappa-opioid receptors located in the limbic system, brain stem and spinal cord (Trescot, 2016:46; Ward, 2015:12).

Opioid analgesics are used to treat and manage severe or chronic pain, particularly for patients with cancer (Cheatle, 2015:S3; Galanie *et al*., 2015:1095; Mercadante *et al.,* 2009:633). Opioid analgesics relieve pain and improve the patients' quality of life (Breivik, 2005:127). Opioids can be useful when other analgesics cannot relieve pain (Enamandram *et al.,* 2015:575). Opioids and combinations (non-opioids) are used to relieve moderate to more severe pain and provide more effective pain management than monotherapy (Plosker & Lyseng-Williamson, 2012:367; Ward, 2015:13). Partial agonists have limited use as an analgesic; they are used to treat opioid addiction (Ward, 2015:12).

2.6.2.1 Codeine

Codeine is a selective agonist of the mu-opioid receptors (Lam *et al.,* 2014:50; Lotsch, 2005:S12). It is a pro-drug which provides a clinical analgesic effect after being metabolised in the liver through demethylation pathways via cytochrome P450 3A4, an enzyme responsible for the transformation of codeine to norcodeine through N-demethylation and cytochrome P450 2D6, which is, in turn, responsible for the transformation of codeine into morphine through O-demethylation (Asturias-Arribas *et al.,* 2014:315; Baber *et al.,* 2015:430; Lotsch, 2005:S12; Mercadante, 2015:74). Codeine's primary analgesic impact is mediated by the cytochrome P450, family 2, subfamily D and polypeptide 6 (CYP2D6) enzyme (CYP2D6) (Baber *et al.*, 2015:430).

2.6.2.2 Morphine

Morphine acts as a pure agonist by binding to opioid receptors (Beck *et al.,* 2014:617). Additionally, it binds to post-synaptic receptors and causes the post-synaptic neurons to hyperpolarise.

Morphine functions as an indirect antagonist of N-type calcium channels through G-protein coupling with Ca2+ channels. It reduces the conductance of pain signals in the CNS by inhibiting neurotransmitter release from peripheral nociceptive neurons to the brain (Webster, 2015:1266). Its activity begins gradually and lasts a long time (Ward, 2015:12). It is metabolised in the liver into morphine-6-glucuronide and morphine-3-glucuronide by glucuronidation in a ratio of 65:1 (Knosgaard *et al.,* 2016:117; Mercadante, 2015:75; Trescot, 2016:52).

2.6.2.3 Fentanyl

Fentanyl is highly lipid-soluble; it binds strongly to plasma proteins (Trescot, 2016:54). By way of the liver enzyme CYP3A4, fentanyl is converted into inactive, non-toxic metabolites that are subsequently eliminated through the urine. Transmucosal delivery, such as with a transdermal patch, allows for fast distribution throughout the body and passage through the blood-brain barrier to produce an analgesic effect (Mercadante *et al*., 2014:602; Mercadante, 2015:75).

With a quick start of action, fentanyl is a powerful opioid that is 50–100 times more potent than morphine (Ogawa *et al*., 2017:588); therefore, the administered dose should be titrated to provide an effective analgesic effect and reduce the unwanted effects (Mercadante *et al.,* 2016:28). Opioids with rapid onset of action are also known as “rapid-onset opioids”.

2.6.2.4 Dihydrocodeine

Dihydrocodeine is a semisynthetic weak mu-receptor agonist with a similar structure to codeine. Its analgesic effect depends on O-demethylation to hydromorphone, which binds strongly on mu receptors and is metabolised into dihydrocodone-6-glucuronide (Lotsch, 2005:S13; Trescot, 2016:51). It is 10 times more potent than codeine (Mercadante, 2015:75). The onset of action is 30 minutes (Ward, 2015:13). The analgesic potency of dihydrocodeine is comparable to that of oxycodone (Taber *et al*., 2016:23).

2.6.2.5 Hydromorphone

The hydrogenated ketone of morphine, hydromorphone, acts on mu-receptors to deliver an analgesic effect by reducing pain signals in the CNS and inducing dose dependence (Webster, 2015:1266; Yu *et al.,* 2014:835). Hydromorphone is metabolised in the liver by UGT1A3 and UGT2B7 primarily into hydromorphone-3-glucuronide (Trescot, 2016:52).

2.6.2.6 Oxycodone

Oxycodone is a semi-synthetic opioid agonist which can be used as an alternative to morphine to treat chronic pain (Mercadante, 2015:75). The onset of action is 30–60 minutes and has a three- to four-hour duration of action (Ward, 2015:13). It is metabolised by CYP3A4 and partially by

CYP2D6. Approximately 80% of oxycodone is metabolised into nor-oxycodone by means of an N-demethylation reaction catalysed by CYP3A4 and 10% is metabolised to oxymorphone after demethylation by CYP2D6 (Mercadante, 2015:75).

2.6.2.7 Buprenorphine

Buprenorphine is a highly lipophobic and long-acting partial mu-opioid receptor agonist (Daitch *et al.,* 2014:2088; Dunn *et al.,* 2018:9; Mercadante, 2015:75). It is metabolised by CYP3A4 and CYP2C8 through N-dealkylation to nor-buprenorphine and by conjugation in the liver, producing inactive metabolites and weak active metabolites excreted through the biliary system. It increases spinal dynorphin to provide an analgesic effect (Trescot, 2016:55).

2.6.2.8 Tramadol

Tramadol works by inhibiting the absorption of monoamines and acting as a mild opioid agonist (Awadalla & Salah-Eldin, 2016:269; Islin *et al.,* 2017:63). The dual mechanism of action causes a reduction in the risk of opioid dependence, tolerability and abuse (Batta, 2016:12). As a synthetic 4-phenyl-piperidine counterpart of codeine, tramadol acts centrally to relieve pain without sedation or respiratory depression (Altun *et al.,* 2017:190; Molaakbari *et al.,* 2017:25). Tramadol is metabolised in the liver by CYP3A4 and CYP2D6 into O-desmethyltramadol, and 90% of it is excreted by the kidneys (Hollingworth *et al.,* 2015:629; Lotsch, 2005:S19; Mercadante, 2015:74).

2.6.2.9 Pethidine

Pethidine (also known as “meperidine”) is a synthetic opioid and is in the same therapeutic group as fentanyl and sufentanil (Phillips *et al.,* 2017:4). It acts as an agonist at the kappa opioid receptor (Wang *et al.,* 2016:3179). It is metabolised in the liver by CYP2B6, CYP3A4 and CYP2C19 into nor-meperidine (Hedrich *et al.,* 2016:420).

2.6.2.10 Methadone

Methadone is a synthetic opioid, which CYP2B6 metabolises into (S)-enantiomer and (R)-enantiomer of methadone (Hedrich *et al*., 2016:420). The analgesic effect is produced by the (R)-enantiomer of methadone binding to and activating the mu-opioid receptor (Hedrich *et al*., 2016:420). The (S)-enantiomer inhibits the cardiac potassium channel, causing unwanted cardiotoxicity (Hedrich *et al*., 2016:420).

2.6.3 Indications for opioid analgesics

Opioids can be used as a standard treatment for moderate to severe pain (Feingold *et al*., 2017:2; Fishbain *et al*., 2008:444; Ward, 2015:11). Opioids used to treat mild to moderate pain are referred to as "weak opioids" (Asturias-Arribas *et al*., 2014:315). Strong opioids are used to manage extreme pain, including surgical discomfort, such as during cancer patients' latter stages of agony from an injury or trauma (Gatoulis *et al*., 2012:139; Kashkin *et al*., 2018:91).

2.6.3.1 Morphine

Morphine is a strong opioid analgesic used to treat nociceptive pain and severe chronic pain, including terminal cancer pain, major post-traumatic pain or injury. Morphine has a synergetic effect on treating neuropathic pain when combined with antidepressants with analgesic properties (Cegielska-Perun *et al.,* 2015:90; Kashkin *et al.,* 2018:61; Kervezee *et al.,* 2017:S132; Ward, 2015:13). Morphine is available via various routes of administration and is also accessible in short and long-acting formulations (Enamandram *et al.,* 2015:577).

2.6.3.2 Hydromorphone

Hydromorphone is a strong, long-acting opioid analgesic (Marroquin *et al.,* 2017:16) used to treat moderate to severe pain (Yu *et al*., 2014:835). It is used as a second line of treatment for postoperative pain management (Ward, 2015:13). The common route of administration of hydromorphone is the intrathecal route in treating chronic pain. It is the recommended first-line intrathecal opioid agent for treating nociceptive, mixed and chronic neuropathic pain (Beatty *et al.,* 2013:380). The potency of hydromorphone is five times that of morphine (Enamandram *et al.,* 2015:577; Ward, 2015:13).

2.6.3.3 Codeine

Codeine is a weak opioid analgesic and is widely used in the treatment of mild to moderate pain (Asturias-Arribas *et al.*, 2014:315; Lam *et al.,* 2014:50). Codeine can be combined with non-opioid analgesics such as paracetamol to treat mild to moderate pain such as headaches (De Goffau *et al.*, 2017:615; Mercadante, 2015:73).

2.6.3.4 Hydrocodone

Hydrocodone is used in the treatment of mild to moderate acute pain. It is available only in combination with non-opioid analgesics such as acetaminophen, aspirin and ibuprofen (Ward, 2015:13). The analgesic potency of hydrocodone is comparable to that of oxycodone. The purpose of hydrocodone's abuse-resistant features is to prevent misuse aided by manipulation and subsequent injecting, chewing or snorting.

2.6.3.5 Oxycodone

Oxycodone is used to manage moderate to severe pain, including cancer pain. It is among the most abused opioid drugs (Graziani & Nistico, 2016:190; Romand *et al.,* 2017:129; You *et al.,* 2017:190). Oxycodone is more potent than morphine as a monotherapy or in combination with non-opioid analgesics (Ward, 2015:13).

2.6.3.6 Fentanyl

Fentanyl is used to increase the effects of anaesthesia (Hikin *et al.,* 2018:179) and as an analgesic in severe chronic pain management (Enamandram *et al.,* 2015:7577). It is highly lipophobic and suitable to be administered by oral transmucosal or transdermal routes (Matsumura *et al.,* 2016:109). The fentanyl buccal tablet is commonly used for episodic dyspnoea (Hui *et al.,* 2017:799). It is 75 times more potent than morphine for treating severe pain (Maguire & France, 2016:199; Matsumura *et al.,* 2016:109).

Due to its euphoric effect, fentanyl users can develop a dependence. Fentanyl is among the most abused opioid analgesics (Sinicina *et al*., 2017:286).

2.6.3.7 Tramadol

Tramadol is a centrally-acting analgesic used to treat mild to moderate pain (Bassiony *et al.*, 2015:206). It can be used in various conditions because it is available as a fixed-dose combination with acetaminophen and can be helpful to patients who cannot take NSAIDs (Enamandram *et al.,* 2015:577; Lofwall *et al.,* 2013:188). Tramadol is used primarily for patients with cardiopulmonary disease, smokers and obese patients, as opposed to conventional opioids. Its analgesic efficacy is associated with less respiratory depression than equal analgesic doses of codeine (Enamandram *et al.,* 2015:577).

2.6.3.8 Pethidine

Pethidine is a short-acting opioid used to treat acute traumatic pain and renal or biliary colic (Wang *et al.,* 2016:3179). It is used to manage pain during childbirth. However, it produces unwanted maternal effects, such as sedation, prolonged labour, vomiting and adverse neonatal effects (Fleet *et al.,* 2017:15). Pethidine is also used as a postoperative analgesic in adjuvants with NSAIDs such as ketoprofen (Desai & Santhosh, 2014:222).

2.6.3.9 Buprenorphine

Buprenorphine is used to manage adult CNCP and is administered as a transdermal patch or sublingual tablet (Damian *et al.,* 2017:129; Gonzalez-Saiz *et al.,* 2017:127).

Buprenorphine reduces opioid use by blocking its euphoric effect in opioid-dependent patients (Damian *et al.,* 2017:129; Gonzalez-Roldan *et al.,* 2016; Gonzalez-Saiz *et al.,* 2017:127; Haasen *et al.,* 2017:23; Haber *et al.,* 2017:132).

2.6.3.10 Methadone

Methadone is widely used in intensive care units for pain management (Elefritz *et al.,* 2016:84) and neuropathic and/or nociceptive pain management for patients with cancer (Haumann *et al.,* 2016:122).

Methadone is used as a first-line treatment for opioid use disorders or opioid dependence (Haber *et al.,* 2017:132; Tsai & Huang, 2017:46) and is used in the maintenance of treatment programmes (Farnia *et al.,* 2017:261; Ghaderi *et al.,* 2017:84).

2.6.3.11 Tapentadol

Tapentadol extended-release products have been used to treat lower back pain and osteoarthritis in patients who do not respond well to other analgesics (Buynak *et al.,* 2015:2420-2421).

The WHO Analgesic Treatment Ladder, which comprises a comprehensive list of equal analgesic potency conversions that provide oral morphine equivalence among various opioid medications for use in the Analgesic Quantification Algorithm (Chung *et al.,* 2014:227), serves as a summary of the above descriptions. See Table 2-3.

Table 2-3: Comparative summary of morphine equivalents of opioids' dosage forms and indications

Equivalent analgesic dose (mg)						
Products	**IV**	**SC**	**IM**	**PO**	**Oral morphine equivalent (OME)**	**Indications**
Morphine	10	10	10	30	30	Acts as a pure agonist, used in the treatment of nociceptive pain
Fentanyl*	0.1	0.1	0.1	2.4	30	Management of pain as intra-operative analgesic
Hydromorphone	1	1	1	5	20	Second-line treatment for postoperative pain
Methadone	10	10	10	20	30	Management of opioid dependence and withdrawal
Oxycodone	N/A	N/A	N/A	20	30	Chronic pain treatment
Hydrocodone	N/A	N/A	N/A	40	40	Treatment of mild-to-moderate acute pain

Equivalent analgesic dose (mg)						
Products	**IV**	**SC**	**IM**	**PO**	**Oral morphine equivalent (OME)**	**Indications**
Codeine	120	120	120	200	30	Weak opioid analgesics used in the treatment of mild-moderate pain
Tramadol	100	100	100	100	30	Used in the treatment of mild-to-moderate pain
Buprenorphine	0.3	0.3	0.3	0.2	30	CNCP treatment
Pentazocine	60	60	60	60	20	A partial agonist used to treat chronic pain
IV = intravenous; SC = subcutaneous; IM = intramuscular; OME = oral morphine equivalent; PO = oral. *Fentanyl, 0.1 mg transdermal also has an OME of 30 mg.						

2.6.4 Side-effects and special precautions of opioid analgesics

Opioid analgesic usage has increased dramatically worldwide, resulting in increased abuse and complications such as overdoses and death (Kelty & Hulse, 2017:54; Sandhu *et al.,* 2016:360). The effects can be acute and are associated with a single or continuous use for a short period. Mild effects can take the form of temporary constipation, loss of appetite, a decrease in body temperature and urinary retention. Continuous use for an extended period can cause chronic effects such as the development of tolerance and weight loss (Khademi *et al.,* 2016:872). Patients dependent on opioids are often also prescribed psychotropic medication, which might be associated with synergistic toxicities (Suvada *et al*., 2022:2).

The side effects of the drugs occur due to pharmacodynamic interactions (Ranchon *et al.*, 2015:190). The response of patients to opioid analgesic treatment is influenced by differences in the metabolic enzymes (Brennan, 2012:S16). Some side effects associated with the use of opioid analgesics are nausea, vomiting and addiction (Shang & Filizola, 2015:206). Codeine, although it is in the same family as morphine, produces a more negligible effect on respiratory depression and sedation (Asturias-Arribas *et al.,* 2014:315). More severe side effects associated with the increased usage of opioids are hormonal changes (Taylor & Erb, 2016:23). Additionally, the use of opioid analgesics might increase pain sensitivity, known as “hyperalgesia” (Arout *et al*., 2015:465). In individuals receiving replacement therapy for opioid dependence, methadone in therapeutic doses can potentially cause ventricular arrhythmias, including *Torsade de Pointes* tachycardia, which can result in sudden cardiac death (Lusetti *et al.,* 2016:80).

Patients should be screened appropriately and provided information on potential side effects when treated with opioid analgesics. Opioid analgesics are broad-spectrum agents because they affect several organ systems and influence bodily functions (Kelty & Hulse, 2017:54). It is crucial

for healthcare professionals to prescribe opioid analgesics for the treatment of CNCP to as few patients as possible and only in cases in which other solutions are not successful, due to the unwanted effects of opioids, such as dependence and addiction (Khademi *et al.,* 2016:872).

The side effects most frequently experienced when using opioid analgesics are listed in Table 2-4.

Table 2-4: Summary of side-effects most frequently caused by opioid analgesics

Products	Side-effects
Morphine	Constipation, nausea, vomiting, dyspepsia, dysphagia, headache, lethargy/fatigue/somnolence, hormonal effects, urinary complications (hesitancy, retention) (Hamza *et al*., 2012:1305; Khademi *et al*., 2016:871), histamine release (decreased blood pressure, fast heartbeat, increased sweating, redness or flushing of the face, wheezing, or troubled breathing), drowsiness, nausea and vomiting, constipation, unusual tiredness or weakness, confusion, insomnia, thinking disturbances, headache, involuntary muscle contractions, myoclonus, somnolence, bronchospasm, abdominal pain, anorexia, constipation, dry mouth, dyspepsia, vomiting, exacerbation of pancreatitis, hyperhidrosis, rash, aesthesia and pruritus (South African Health Products Regulatory Authority (SAHPRA, 2021a).
Fentanyl	Vomiting, sleepiness, nausea, sore mouth and bitter taste (Coombes *et al*., 2017:258), anorexia, hallucinations, sedation, nervousness, headache, CNS depression, dizziness, somnolence, vertigo, bradycardia, tachycardia, apnoea, difficulty breathing, hypoventilation, vomiting, constipation, dry mouth, dyspepsia, diaphoresis, pruritus, urinary retention, weakness and skin reaction at the site of application (usually subsides within 24 hours after removing the patch (Cicero *et al*., 2017:101-103).
Hydromorphone	Sleep disturbance, snoring, shortness of breath on awakening or with a headache, sleep disorders and daytime somnolence, nausea/vomiting, pruritus (Marroquin *et al*., 2017:18), sedation, dysphoria, hallucinations, myoclonus, orthostatic hypotension due to histamine release, constipation, immediate post-injection reaction or injection site pruritus (Gregory, 2013:2020; Oviedo-Joekes *et al*., 2017:59).
Methadone	Sedation, respiratory depression, constipation, dry mouth, sleepiness, dizziness, nausea and vomiting (Elefritz *et al*., 2016:85; Haumann *et al.,* 2016:125).
Oxycodone	Respiratory, pruritus and urinary retention (Richards *et al*., 2013:1231), constipation, nausea, vomiting, abnormal pain, diarrhoea, dry mouth, hiccups, dyspepsia, decreased appetite up to the loss of appetite, headache, dizziness, sedation (somnolence up to the depressed level of consciousness), syncope, paraesthesia, altered mood and personality change (e.g., anxiety, depression, euphoric mood), decreased activity, restlessness, psychomotor hyperactivity, agitation, nervousness, insomnia, abnormal thinking, confusion, urine retention, dysuria, micturition urgency, pruritus, hypotension, dyspnoea, skin reaction/rash and hyperhidrosis up to chills and asthenia (SAHPRA, 2021b).
Hydrocodone	Dizziness, drowsiness, headache, fatigue, sedation, sweating, nausea, vomiting, constipation, pruritus, respiratory depression, orthostatic hypotension, cough suppression, confusion, diarrhoea, miosis, abdominal pain, dry mouth, indigestion, anorexia, spasm of the biliary tract, urine retention and hallucinations (Malahyde Information Systems, 2017).
Codeine	Codeine dependence, constipation, nausea, vomiting, respiratory depression, excitation, dizziness, drowsiness, confusion, dry mouth, sweating, facial flushing, vertigo, bradycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, changes in mood and miosis. Micturition might be difficult and there

Products	Side-effects
	might be ureteric or biliary spasms; there is also an antidiuretic effect. Raised intracranial pressure might occur, as well as reactions such as urticaria and pruritis. Contact dermatitis has been reported (Malahyde Information Systems, 2017).
Tramadol	Respiratory depression, constipation, syncope, nausea, dizziness, headache, somnolence, tremor, mydriasis, respiratory depression, dyspnoea, palpitations, tachycardia, hyperhidrosis, fatigue, muscle weakness, skin reaction, vomiting, dry mouth, heartburn, constipation, fatigue, sedation, drowsiness, confusion, hallucinations and seizures (Malahyde Information Systems, 2017).
Buprenorphine	Respiratory depression, sedation, dizziness/vertigo, headache, miosis, hypotension, hypoventilation, nausea, vomiting and sweating (SAHPRA, 2022).
Pentazocine	Sedation, sweating, dizziness, light-headedness, nausea, vomiting, dry mouth, constipation, headache, flushing of the skin, disorientation, raised intracranial pressure, transient hypertension, mood changes, nightmares, anxiety, weird thoughts, hallucinations, paraesthesia, pruritus, biliary tract spasm and urinary retention (Malahyde Information Systems, 2017).
Tapentadol	Decreased appetite, anxiety, confusion, hallucinations, sleep disorder, abnormal dreams, dizziness, somnolence, headache, tremor, flushing, nausea, vomiting, constipation, diarrhoea, dyspepsia, dry mouth, pruritus, hyperhidrosis, rash, muscle spasms, asthenia, fatigue and a feeling of body temperature change (Janssen, 2017; Malahyde Information Systems, 2017).

2.6.5 Drug-drug interactions

When two or more drugs are administered simultaneously, the pharmacokinetics and/or pharmacodynamics of either one or all medications are altered, resulting in drug-drug interactions (Ranchon *et al.*, 2015:190). Pharmacokinetic interactions are observed during drug metabolism, although they can occur during the four steps of absorption, distribution, metabolism and elimination. Most opioid analgesics are metabolised in the liver, and about 86% of the drug-drug interactions occur through the cytochrome (CYP) 450 enzyme (Ranchon *et al.*, 2015:190).

Due to high systemic concentrations of the active parent medicines and the therapeutic failure of prodrugs in patients with weak metabolic capacity, drug interactions between codeine and tramadol carry a higher risk of side effects (Brennan, 2012:S16).

The concomitant use of other drugs can cause opioid treatment to have other than the expected outcomes. For example, macrolides and related antibiotics such as clarithromycin and erythromycin increase the plasma concentration of opioid analgesics when concomitantly administered with opioids such as buprenorphine, codeine or fentanyl, resulting in toxicity (Brennan, 2012:S12). Table 2-5 (compiled from Tatro, 2014:1454-1460) is a summary of the “significance”, meaning “the severity of drug interaction”, with significance one referring to major (life-threatening or permanent damage) drug-drug interactions that might occur with opioids.

Table 2-5: Potential opioid-related drug-drug interactions

Opioid analgesics	Interacting drug(s)	Significance*	Effects	Mechanism
Buprenorphine Fentanyl Methadone Oxycodone Sufentanil	Fluconazole Itraconazole Ketoconazole Miconazole Voriconazole	Major – 1	Azole antifungal agents increase the pharmacological effects and adverse reactions of opioid analgesics	Azole antifungal agents inhibit the CYP3A4 metabolism of opioid analgesics.
Buprenorphine methadone	Alprazolam Clonazepam Clorazepate Diazepam Lorazepam Midazolam Oxazepam Temazepam Triazolam	Major – 1	Increase the risk of sedation and life-threatening respiratory depression, especially in overdosage	Synergistic effects causing sedation
Fentanyl Alfentanyl Sufentanyl	Diltiazem	Major – 1	Diltiazem increases the plasma concentration of fentanyl, resulting in toxicity	Diltiazem inhibits the metabolism of opioid analgesics through CYP3A4
Alfentanil Buprenorphine Codeine Fentanyl Hydromorphone Methadone Morphine Oxycodone	Cimetidine	Major – 1	Cimetidine increases opioid analgesics, resulting in toxicity	Cimetidine decreases the metabolism of opioid analgesics
Buprenorphine Codeine Fentanyl Methadone Oxycodone Sufentanil	Clarithromycin Erythromycin Telithromycin	Major – 1	Macrolides and related antibiotics increase the plasma concentration of opioid analgesics, resulting in toxicity	Decrease metabolism of opioid analgesics
Alfentanil Buprenorphine Fentanyl Oxycodone Sufentanil	Atanazavir Indinavir Lopinavir Ritonavir	Major – 1	Protease inhibitors increase plasma concentrations May cause respiratory depression	Opioid analgesic metabolism is inhibited through CYP3A4
* Significance refers to the severity level of drug interaction, with ‘1’ referring to major (life-threatening or permanent damage) (Tatro, 2014:XI).				

2.7 Chronic pain and psychiatric conditions

Regardless of the underlying reasons, chronic pain disorders have a number of comorbidities in common. These comorbidities include neurocognitive changes, mood changes (such as depression), anxiety, sleep issues, fatigue or a lack of energy, and other nebulous symptoms, such as generalised diffuse pain (Ahn *et al.,* 2017:1230; Alavi *et al.,* 2016:4; Goesling *et al.,* 2013:421).

An increased number of studies have shown a link between chronic pain and psychiatric disorders and also demonstrated that patients who present with chronic pain have higher rates of depression and anxiety than patients who do not have chronic pain (Ahn *et al.,* 2017:1230; Alavi *et al.,* 2016:4; Alev *et al*., 2017:200; Apfelbacher *et al.,* 2017:49-50; Goesling *et al.,* 2015:1434; Rajmohan & Kumar, 2013:146; Scherrer *et al.,* 2017:125; Scherrer *et al*., 2016:110-111; Scherrer *et al.,* 2014:491; Smith *et al.,* 2015:73-74).

Due to problems with treatment outcomes, comorbidity considerably lowers the quality of life, functionality and disability and most commonly impacts women, older people and members of lower socioeconomic categories (Barrett & Chang, 2016:346). Psychiatric disorders, which are the most comorbid with chronic pain, are indicated briefly in the following paragraphs.

2.7.1 Depression

The most common comorbid diseases in clinical settings worldwide are depression and pain (Birgenheir *et al.,* 2013:480). In a Canadian study, patients without pain had a depression prevalence of 5.9%, whereas those with chronic lower back pain had a prevalence of 19.8% (Munce & Stewart, 2007:394-395).

Patients with depression often have a pain prevalence of about 65% and are more likely to experience medically unexplained somatic complaints such as headaches, backaches and stomach aches (Birgenheir *et al.,* 2013:480). According to the biochemical theory of depression, a neurochemical imbalance of monoamines (such as serotonin) causes depression (Fischer *et al.*, 2016:332; Thompson *et al.*, 2016:1258). These neurotransmitters play a significant role in modulating pain pathways and result in altered pain perception. Thus, patients with depression might experience musculoskeletal pain, leading to chronic lower back pain (Fischer *et al*., 2016:332; Thompson *et al*., 2016:1258). According to Fishbain *et al.* (2008:445), the effect of antidepressant medicine on depression response or remission might, thus, be impacted by the presence of pain. A study showed that 69% of patients with depression tended to be misdiagnosed as having a somatic symptom, which can be detrimental because it often worsens depression, leading to poorer outcomes (Thompson *et al.,* 2016:1258).

According to Fischer *et al.* (2016:332), patients with psychiatric conditions are more likely than patients without psychiatric disorders to be prescribed (short- and long-term) opioid medicines for chronic pain. Patients clinically diagnosed as depressive also have symptoms other than depressive mood. These include somatic conditions, such as obesity, sleep disturbances, arterial hypertension and chronic pain (Hermesdorf *et al.,* 2016:609). These sensations are linked to altered experimental pain perception and might be brought on by differences in pain thresholds between depressed patients and healthy individuals (Hermesdorf *et al.,* 2016:607; Saber-Tehrani *et al.,* 2011:1-2; Scheidt *et al.,* 2013:160). Patients with pain and depression are more likely to be prescribed opioids, use them for longer periods and in higher dosages, and abuse them, which can result in undesirable side effects, compared to patients without depression (Batkis *et al.,* 2010:16; Dobscha, 2013:1447; Scherrer *et al.*, 2014:491; Scherrer *et al.,* 2016:110).

Depression is one of the most common illnesses, affecting more than 10% of the general population (Chang, M., *et al.*, 2015:895-896). It is also the most studied comorbid disease with chronic pain compared to other psychiatric disorders (Mehraban *et al.*, 2014:203). Patients with chronic pain have shown a prevalence of depression ranging from 31% to 100% (Munce & Stewart, 2007:394-395; Siebenhuener *et al.,* 2017:6).

Depression risk rises with pain symptom intensity, frequency, duration and number (Tatro, 2014). According to the IASP's (2018) Classification of Chronic Pain, there are roughly twice as many pain disorders and a higher prevalence in women than men. The most common chronic pains are headaches, orofacial pain and musculoskeletal pain (Munce & Stewart, 2007:394-395). Additionally, women are more likely than men to experience both chronic pain and depression, suggesting that men and women might experience different types of pain, suggesting that pain characteristics might differ between men and women (Munce & Stewart, 2007:394-395). Women's reported pain severity has been linked to depression, whereas men's reported pain severity has been linked to functional impairment due to depression (Munce & Stewart, 2007:394-395). The most common disorder in the general population is chronic pain, with a prevalence of 10–42%, resulting in disability and despair.

2.7.2 Stress

Several studies have indicated chronic pain, particularly headaches, as the leading cause of stress, which negatively induces psychological or physical distress (Ahn *et al.,* 2017:1230; Arias *et al.,* 2016:140; Feingold *et al.*, 2017:1; Kato, 2015:506). The inability to safely adjust to life's events because of stress reactions increases secondary disruptions, especially in pain management mechanisms (Woda *et al.,* 2016:128). Public safety personnel, in particular, are exposed to emotional and physically stressful events such as fires, resuscitations and arrests,

which can be traumatic or cause injuries, which, in turn, can increase the risk of several mental disorders and physical injuries (Carleton *et al.*, 2018:48).

2.7.3 Major depressive disorder

Major depressive disorder affects about 50% of patients in chronic pain clinics and rehabilitation centres (Mehraban *et al.*, 2014:203).

Reduced experimental pain perception is typically observed in patients with serious depression. However, it is crucial to highlight that a number of factors influence how pain perception is measured and interpreted by depressed patients (Hermesdorf *et al.,* 2016:607). Hyposensitivity to pain has been observed in patients with significant depression, but this is thought to be a temporary symptom of the disease (Hermesdorf *et al*., 2016:607). According to Chang, M., *et al.* (2015:895-896), comorbidity between fibromyalgia and current major depressive episodes has been found in about 6–35% of patients.

Patients with intermittent explosive disorder frequently also have major depression, which is four times more common in these patients than in the general population (Medeiros *et al.,* 2018:209). In the general population, rates of depression and chronic pain are lower than in the clinical samples (Duffield *et al.,* 2017:130). In the USA, there is a high prevalence of major depressive disorders among mothers of young children, ranging from 3–39% and 10–45% during antenatal and postnatal periods respectively (Owora & Carabin, 2018:80).

2.7.3.1 Bipolar disorder

The results from the *National Comorbidity Study-Replication* indicated that patients with bipolar disorder experienced persistent spinal pain more frequently than people without a serious mental disease such as schizophrenia or bipolar disorder (Birgenheir *et al.*, 2013:480). Compared to the general population, people with bipolar illness were frequently found to experience lower back discomfort and complain of chronic pain in 40% of cases (Birgenheir *et al*., 2013:481). According to Engels *et al.* (2014:457), most experimental studies on pain have concluded that patients with schizophrenia appear to be less sensitive to pain in comparison with healthy individuals, or there might be less reporting of pain symptoms by people with schizophrenia rather than less pain.

2.7.3.2 Anxiety disorders

Chronic pain and anxiety disorders are often comorbid (Feingold *et al.,* 2017:1; Mehraban *et al.*, 2014:204), with about one-third of patients being treated for chronic pain also presenting with an anxiety disorder. Neuroanatomical pathways shared across the two illnesses are also altered, as are the serotonin, endogenous opioid and autonomic nervous systems (Dobscha, 2013:1447).

Additionally, receiving opioid prescriptions is highly linked to anxiety problems, particularly posttraumatic stress disorder. According to Dobscha (2013:1447), 30–40% of individuals who receive long-term opioid prescriptions also receive benzodiazepines. The association between several pain conditions and anxiety disorders have been found to be stronger than for depression (Blay *et al.,* 2018:204-205; Rajmohan & Kumar, 2013:146). Fibromyalgia is frequently associated with psychiatric and psychological symptoms, such as sleep difficulties and cognitive impairments (Alev *et al*., 2017:200; Goesling *et al.,* 2015:1434; Scheidt *et al.,* 2013:160).

Diathesis-stress and shared vulnerability are two psychological models that were created to explain the close connection between anxiety disorders and chronic pain. Pain exacerbates a person's pre-existing physical, psychological and physiological disorders, as well as life experiences, leading to pathology and disability (Dobscha, 2013:1447).

According to a maintenance model, the cognitive, affective and behavioural aspects of pain serve to maintain the symptoms of anxiety disorders, whereas the physiological, affective and behavioural aspects of anxiety disorders aid in maintaining or aggravating the symptoms of chronic pain (Dobscha, 2013:1447). Opioid long-term therapy is widely used to treat trauma's physical and mental impacts. Patients with comorbid anxiety and pain are more likely to appear in a professional setting with significant fear and distress, which raises the prospect of co-prescribing benzodiazepines to those patients (Aguglia *et al.,* 2011:263; Dobscha, 2013:1447). In addition, chronic pain is more prevalent than diabetes, coronary heart failure, cancer and stroke (Diaz-delCastillo *et al*., 2017:162).

Chronic non-cancer pain conditions associated with depression are similar due to the presence of the same biological pathways and neurotransmitters in patients, with the same trends in developed and developing countries (Edwards *et al*., 2016:T70; Feingold *et al*., 2017:1). Polypharmacy is linked to a patient's diagnosis of multiple chronic diseases, with pain medication being among the medicines found in polypharmacy (Lin *et al.*, 2018:236; Prithviraj *et al.*, 2012:229).

2.8 Regulatory policies and guidelines governing opioid prescribing worldwide

According to Chueng *et al*. (2014:401), most guidelines for opioid use in the management of chronic pain, in particular CNCP, including the USA guidelines, the European Medicines Agency, the Canadian National Opioid Use Guideline Group (NOUGG, 2017), the Australian and New Zealand College of Anaesthetists and the Medicines and the Healthcare Products Regulatory Agency in the United Kingdom (UK), have similar methods for managing patients, beginning with a thorough assessment of the patient and concentrating on particular on indicators of probable drug abuse and misuse. The guidelines indicate that opioids are not recommended as first-line

treatment for CNCP. However, should doctors decide to use them, close monitoring of patients is required for non-responsiveness, adverse effects or abnormal behaviour. The guidelines are outlined briefly, including the South African guidelines for opioid therapy for CNCP, in the following sections.

Notably, buprenorphine and methadone are regulated under the International Regulatory Framework, according to which nations have to comply with international regulations, such as the Convention on Narcotic Drugs, 1961 (as revised in the 1972 protocol) and the Convention on Psychotropic Substances, 1971 (Dowell *et al.,* 2016:1-49; WHO, 2008a).

2.8.1 United States of America

According to the American Society of Interventional Pain Physicians (ASIPP), ineffective pain management has been linked to ignorance of available pain management options, a poor understanding of addiction, or fears about being investigated by or subjected to punishment by the federal, state or local regulatory authorities (Manchikanti *et al*., 2012:S96). The ASIPP advises starting with modest doses when beginning therapy on opioids for maintenance therapy to minimise problems and side effects, particularly when opioid treatment is paired with other modalities such as interventional procedures (Manchikanti *et al*., 2012:S96).

Table 2-6 indicates the recommended low doses of opioids for initial and maintenance treatment based on the ASIPP guidelines (Manchikanti *et al*., 2012:S89).

Table 2-6: Low-dose opioid therapy for select opioids showing starting doses and maintenance doses

Opioid	Recommended starting dose for opioid-naive patients	Recommended starting dose for opioid exposed patient's high doses leading to high risks	Recommended maintenance dose
Hydrocodone	5 to 10 mg, 2 to 3 times daily	5 to 10 mg, 3 to 4 times daily	30 to 40 mg for 24 hours
Morphine Immediate Release	Not recommended	10 mg, 2 to 3 times	30 to 60 mg per day
Morphine Sustained Release	Not recommended	15 to 30 mg twice daily	60 to 90 mg daily
Oxycodone	5 to 10 mg, 2 to 3 times daily	5 to 10 mg, 3 to 4 times daily	30 to 40 mg per day
Oxycodone Sustained Release	Not recommended	10 mg for 12 hours	30 to 60 mg for 24 hours
Methadone	Not recommended	10 mg for 12 hours	30 to 60 mg for 24 hours
Transdermal Fentanyl	Not recommended	2 to 5 mg, 2 to 3 times daily	10 to 30 mg per day

Opioid	Recommended starting dose for opioid-naive patients	Recommended starting dose for opioid exposed patient's high doses leading to high risks	Recommended maintenance dose
Hydromorphone Immediate Release	2 mg 2 to 3 times daily	2 to 4 mg, 2 to 3 times daily	8 to 16 mg per day
Hydromorphone Sustained Release	Not recommended	5 mg to 10 mg, 2 times daily	20 to 40 mg daily
Codeine	15 mg 2 to 3 times daily	30 mg 2 to 3 times daily	120 to 160 mg daily
Oxymorphone Immediate Release	5 mg 2 to 3 times daily	5 to 10 mg 2 to 3 times daily	30 to 40 mg per day
Oxymorphone Sustained Release	Not recommended	10 mg 12-hourly	40 to 60 mg per day
Tramadol	50 mg 2 to 3 times daily	50 mg 3 to 4 times daily	150 to 300 mg per day
Tramadol Sustained Release	Not recommended	200 mg daily	200 to 350 mg per day

2.8.2 Canada

In Canada, the guidelines (NOUGG, 2017) recommend comprehensive documentation of a patient's history, such as their psychosocial history, psychiatric status, pain conditions, general medical condition and history of substance abuse. The detailed records for each patient to indicate patient assessment include informed consent, a treatment plan, a discussion of the risks and benefits of the opioids prescribed and outcomes (NOUGG, 2017). The guidelines strongly recommend a non-opioid approach to pharmacotherapy and non-pharmacological therapy (NOUGG, 2017:15). When patients with CNCP do not respond to this approach, the following guidelines should be followed:

- "For patients beginning long-term opioid treatment, the recommendation is to restrict prescribed opioid doses to less than 90 mg of morphine equivalents daily.
- For patients currently using opioids with persistent pain and/or problematic adverse effects, rotation to other opioids of the same dosage form is recommended.
- For patients currently using 90 mg morphine equivalents of opioids per day or more, tapering opioids to the lowest effective dose and considering discontinuation of opioids is also recommended.
- A formal multidisciplinary programme involving different healthcare professionals is recommended for patients using opioids and experiencing serious challenges in tapering opioids" (NOUGG, 2017:15-68).

2.8.3 The United Kingdom

Patient history assessment is also recommended in the UK guidelines, including a biopsychosocial assessment, identifying the type of pain, namely neuropathic/nociceptive/mixed and the severity of the pain and functional impact on patients with chronic pain to assist in the selection of treatment options. Self-support programmes are recommended at an early stage of pain conditions, whereby healthcare professionals identify local service points to assist the patient with their journey during pain management. Patients using analgesics are evaluated once a year or if their pharmaceutical regimen, pain syndrome or underlying comorbidities change. Patients with osteoarthritis or persistent lower back pain might benefit from taking potent opioids for pain management. The intervention of a specialist is recommended if there are concerns about rapid-dose increases or if a > 180 mg/day morphine equivalent dose is required (SIGN, 2013).

2.8.4 South Africa

The South African Society of Anaesthesiologists (SASA) has published guidelines on the management of chronic pain in general (Raff *et al*., 2014). According to Raff *et al.* (2014:79), the SASA guideline for the use of chronic opioid therapy for chronic non-cancer pain is aligned with four international guidelines, i.e., the British Pain Society guidelines, the American Academy of Pain Medicine Opioids Guidelines Panel, the Canadian National Opioid Use Guideline Group and the American Society of Interventional Pain Physicians.

The guidelines highlight the importance of a multidisciplinary approach to chronic pain management. The guidelines also emphasise the importance of conducting a comprehensive pain assessment for each patient, considering factors such as the location, severity, duration and impact of the pain on the patient's quality of life. The assessment should also consider the patient's medical history, any relevant physical or psychological comorbidities, as well as their personal and social circumstances.

The guidelines recommend the use of a range of non-pharmacological interventions for chronic pain management, such as physical therapy, cognitive-behavioural therapy, and interventional pain procedures, such as nerve blocks or epidural injections. The guidelines also suggest the use of non-opioid medications, such as NSAIDs, anticonvulsants and antidepressants, for certain types of chronic pain.

If opioids are considered necessary for the management of chronic pain, the guidelines recommend that they be used judiciously and only after other non-opioid options have been tried and found ineffective or insufficient. Opioids should be prescribed at the lowest effective dose for the shortest duration possible, and patients should be closely monitored for signs of misuse, abuse or addiction. Non-injectables that are marketed in South Africa that may be suitable for the

treatment of chronic pain include the strong opioids buprenorphine, fentanyl, hydromorphone, morphine, and oxycodone, and the weak opioids codeine, dihydrocodeine and tramadol (Raff *et al.,* 2014:81). The SASA guidelines (Raff *et al.,* 2014:82) recommends step-wise therapy for the management of CNCP as shown in Table 2-7.

Table 2-7: Step-wise therapy for the management of chronic non-cancer pain in South Africa

Opioid	Mild-to-moderate pain	Severe pain
First-line	Codeine or tramadol	Morphine, high-dose oxycodone, hydromorphone or buprenorphine
Second-line	Morphine, dihydrocodeine, low-dose oxycodone, hydromorphone or buprenorphine	Fentanyl

The guidelines also emphasise the importance of patient education, informed consent and shared decision-making in chronic pain management and recommend regular follow-up appointments to assess the patient's pain level, functional status and any adverse effects related to therapy (Raff *et al*., 2014:82).

Where CNCP affects the functionality and/or the quality of life of the patients, opioids are carefully selected for long-term use (Raff *et al.*, 2014:81). Opioid analgesics are not recommended as the first line of treatment but are included when the first line has not been successful (Raff *et al.*, 2014:81).

In South Africa, medicines and devices are regulated by the South African Health Product Regulatory Authority (SAHPRA), as stipulated in the *Medicines and Related Substances Control Act* 101 of 1965. This body aims to ensure that all registered and non-registered medicines comply with all the requirements for safety, quality and efficacy.

Narcotic analgesics (e.g., fentanyl, morphine, codeine, dihydrocodeine, hydromorphone, oxycodone, pethidine, pentazocine, buprenorphine, and tilidine) are classified as Schedule 6 medicines. Combination analgesics containing codeine or norcodeine containing 10 milligrams or less of codeine (calculated as base) per dosage unit and liquid oral preparations and mixtures containing 10 milligrams or less of codeine (calculated as base) per 5-millilitre dosage unit, however, are regulated in terms of Schedule 2 and Schedule 3 to the Medicines Act, whereas combinations with meprobamate are classified as Schedule 5 medicine. Tramadol is also classified as a Schedule 5 medicine in terms of the Act in South Africa, meaning they are highly controlled and are not easily accessible to the public. These types of medicines are controlled by

the process of purchasing, manufacturing, handling and dispensing opioids, as stipulated in the *Medicines and Related Substances Control Act* 101 of 1965. The SAHPRA, together with the Department of Health, issued an amendment to this Act, providing guidelines with regard to the control and prescribing of medicine Act 72 of 2008. The guidelines specifically pertaining to the prescribing of Schedule 6 medicines such as narcotic analgesics include the following:

- "May not be repeated without a new prescription being issued;

- In an emergency in which the health or life of a patient is at stake, a pharmacist engaged in wholesale practice may, on receipt of a telephonic or telefaxed or other electronic request, supply a Schedule 6 substance to a pharmacist, medical practitioner, dentist, veterinarian, practitioner, nurse or other person registered under the Health Professions Act 53 of 1974, without a written order: Provided that:

  (i) it shall be the responsibility of such pharmacist, medical practitioner, dentist, veterinarian, practitioner, nurse or other persons to ensure that such pharmacist receives a written order within seven days.

  (ii) the Schedule 6 substance shall be supplied in the smallest unit sales pack available.

  (iii) a permanent record is made and kept of such supply;

- In an emergency, a pharmacist may sell any Schedule 6 substance in a quantity not greater than that required for continuous use for 48 hours under the verbal instructions of a medical practitioner, dentist, veterinarian, practitioner, nurse or other person registered under the Health Professions Act 53 of 1974, who is known to such pharmacist, but the prescriber who has given such verbal instructions shall, within 72 hours after giving such instructions, furnish to such pharmacist a written prescription confirming the instructions;

- Any person may possess a Schedule 6 [substance] if they are in possession of a prescription issued by an authorised prescriber;

- Schedule 6 substances may only be sold if the course of treatment does not exceed 30 consecutive days;

- The sale of a specified Schedule 6 substance by a manufacturer of or wholesale dealer in pharmaceutical products shall be recorded in a register, which shall be kept in the prescribed manner and shall be balanced to show clearly the quantity of every specified Schedule 6 substance remaining in stock as on the last day of March, June, September and December of each year, and such balancing shall be completed within the 14 days following each of the said dates;

- No person shall manufacture, use or supply any Schedule 6 substance for other than medicinal purposes unless the Director-General has issued them a permit for such manufacture, use or supply upon the prescribed conditions."

The legislation for Schedule 5 preparations is stipulated as below:

"a. All schedule 5 preparations or mixtures containing substances that are chemically related and incorporates a structural fragment into its structure that is similar to the structure of a listed substance and /or exhibits pharmacodynamic properties similar to the listed substance referred to in this Schedule include the following:

(i) The salts and esters of such substances, where the existence of such salts and esters is possible; and

(ii) all preparations and mixtures of such substances where such preparations and mixtures are not expressly excluded.

(iii) all homologues of listed substances (being any chemically related substances that incorporate a structural fragment into their structures that is similar to the structure of a listed substance and/or exhibit pharmacodynamic properties similar to the listed substance in the schedules), unless listed separately in the Schedules.

b. In terms of Section 22A(5)(f) of the Act, a practitioner, nurse or a person registered under the Health Professions Act, 1974, other than a medical practitioner or dentist, may prescribe and apply, only within his/her scope of practice and subject to the indication for use of such substances and medicines and to the conditions determined by the Authority, to patients under his/her care, the Schedule 5 and Specified Schedule 5 substances and medicines provided for in the Annexures to this Schedule published in the Gazette in terms of the Act.

c. Specified Schedule 5 substances listed in this schedule are subject to additional control in terms of section 22A of the Act as required under the provisions of the 1971 Convention on Psychotropic Substances."

The legislation for Schedule 2 containing codeine stipulates as below:

- "i) Active ingredient such as Codeine oral solid preparations, in combination with one or more therapeutically active substances, containing not more than 10 milligrams of codeine (calculated as base) per dosage unit, with a maximum daily dose not exceeding 80 milligrams, and in packs containing sufficient dosage units for a maximum treatment period of 5 days, and limited to one pack per customer, when contained in products registered in terms of the Act, and not intended for export;

- ii) liquid oral preparations and mixtures, in combination with one or more therapeutically active substances, containing not more than 10 milligrams of codeine (calculated as base) per 5 millilitre dosage unit, with a maximum daily dose not exceeding 80 milligrams, and with a pack size not exceeding 100 millilitres, when contained in products registered in terms of the Act, and not intended for export;

- iii) Oral solid preparations, in combination with one or more therapeutically active substances, containing more than 10 milligrams of codeine (calculated as base) per dosage unit are classified as schedule 3 (S3)iv) Liquid oral preparations and mixtures, in combination with one or more therapeutically active substances, containing more than 10 milligrams of codeine (calculated as base) per 5 millilitre dosage unit are classified as schedule 3 (S3).”

2.9 Chapter summary

The literature in this chapter indicates that chronic pain is a common problem worldwide. There is a higher prevalence of chronic pain in the low- and middle-income groups in developing countries than in developed countries. Chronic pain is common in elderly patients 65 years old and above. The literature indicates that manging chronic pain is not limited to medication; other methods can be used to manage chronic pain. The following chapter consists of a description of the empirical part of the study.

CHAPTER 3 RESULTS AND DISCUSSION

3.1 Introduction

This chapter consists of the results and discussion of the empirical investigation. Figure 3-1 is a schematic representation of the data presentation.

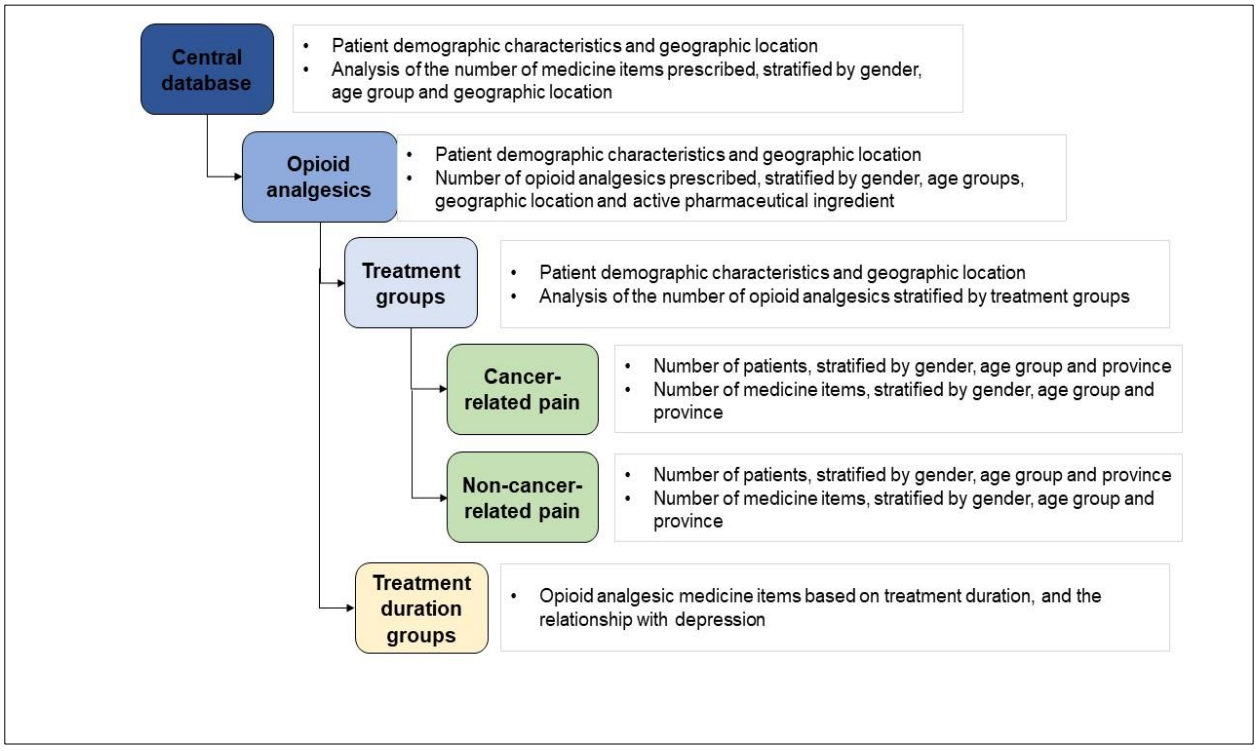

Figure 3-1: Flow diagramme illustrating the data analysis and presentation of results

The results are presented in three main parts corresponding to the objectives. Part one (paragraph 3.3) briefly describes the PBM's central database. Part two (paragraph 3.4) is a general analysis of the prescribed opioid analgesics. This section includes a discussion of the prescribing patterns of claimed opioid analgesics, stratified into two chronic pain treatment groups (cancer-related pain vs CNCP), whereas the last part (paragraph 3.5) details the results of an analysis to determine the association between depression and opioid analgesic treatment duration.

3.2 Annotations concerning the data analysis

The notes and explanations that follow apply to the data analysis and results:

- The term "central database" refers to all medicine claims data from the study periods (i.e., 2011 to 2017) supplied by the PBM company.
- The term "beneficiaries" in this study refers to main members and their dependants

registered on medical aid schemes in South Africa in terms of the Medical Schemes Act 131 of 1998 for the period 1 January 2011 to 31 December 2017 (without any reference to the utilisation of healthcare services).

- A “patient” is a person who has been prescribed medicine items, dispensed and recorded as a “claim” in the medicine claims database.
- “Geographic location” refers to the province in which the patient resides. This was estimated using the postal code of the prescriber as a proxy.
- The assessment of changes in prescribing patterns of prescribed opioid treatment by repeated cross-sectional estimates for each year (1 January 2011 to 31 December 2017) was stratified into two treatment groups: cancer-related and CNCP treatment.
  - Non-cancer pain treatment was defined as claims for opioids reimbursed from chronic or PMB benefits on the database.
  - Cancer-related pain treatment refers to medicine claims for opioids reimbursed from oncology benefits.
- The term “treatment episode” denote unique sets of mutually exclusive “days of treatment” determined for each patient per tradename product received over the study period.
- To determine the association between depression (ICD-10 codes F30-F39) and opioid analgesic treatment duration, treatment episodes were divided into two groups, namely short-term and long-term treatment duration:
  - Short-term treatment duration was defined as the total days of treatment < 90 days.
  - Long-term treatment duration was defined as the total days of treatment of ≥ 90 days.
- Because percentages in the data have been rounded to the nearest decimal point, the cumulative total might not add up to 100%.

3.3 General overview of the central database

This section includes an overview of the central database to put the data into perspective. The discussion in this section is based on the data presented in Tables 3-1 and 3-2. Table 3-1 shows the patients’ demographic and geographic characteristics. Table 3-2 indicates the total number of medicine items claimed, as recorded in the central database, stratified by gender, age group and geographic location.

Table 3-1: Demographic characteristics of patients in the PBM's central database

	2011 *n* (%)	2012 *n* (%)	2013 *n* (%)	2014 *n* (%)	2015 *n* (%)	2016 *n* (%)	2017 *n* (%)
Patients, database, *N*	**864 962**	**815 792**	**809 838**	**838 618**	**843 792**	**858 890**	**1 103 167**
Gender							
Female	462 470 (53.5)	431 630 (52.9)	430 077 (53.1)	446 382 (53.2)	445 626 (52.8)	454 966 (53.0)	589 489 (53.4)
Male	402 488 (46.5)	384 159 (47.1)	379 756 (46.9)	392 235 (46.8)	398 166 (47.2)	403 624 (47.0)	513 678 (46.6)
Unknown	4 (0.0005)	3 (0.0004)	5 (0.0006)	1 (0.0001)	0	0	0
Age groups (years)							
Age ≤57	664 517 (76.8)	620 654 (76.1)	629 457 (77.7)	655 439 (78.2)	668 679 (79.3)	677 822 (79.0)	805 819 (73.1)
57> Age ≤66	88 628 (10.3)	85 036 (10.4)	85 044 (10.5)	85 586 (10.2)	83 093 (9.9)	84 267 (9.8)	120 857 (11.0)
66> Age ≤75	58 001 (6.7)	56 956 (7.0)	55 620 (6.9)	56 024 (6.7)	52 447 (6.2)	54 422 (6.3)	90 337 (8.2)
Age >75	53 816 (6.2)	53 146 (6.5)	39 717 (4.9)	41 569 (5.0)	39 573 (4.7)	42 079 (4.9)	86 154 (7.8)
Province							
Eastern Cape	59 954 (6.9)	56 164 (6.9)	53 549 (6.6)	56 461 (6.7)	57 525 (6.8)	56 961 (6.6)	70 169 (6.4)
Free State	51 107 (5.9)	50 913 (6.2)	55 927 (6.9)	58 955 (7.0)	60 747 (7.2)	63 071 (7.4)	77 356 (7.0)
Gauteng	407 360 (47.1)	380 727 (46.7)	391 840 (48.4)	407 162 (48.6)	384 914 (45.6)	400 359 (46.6)	506 139 (45.9)
Kwazulu-Natal	109 150 (12.6)	98 395 (12.1)	99 750 (12.3)	100 484 (12.0)	95 744 (11.4)	95 115 (11.1)	120 411 (10.9)
Limpopo	31 578 (3.7)	28 835 (3.5)	25 227 (3.1)	26 579 (3.2)	29 153 (3.5)	29 404 (3.4)	34 504 (3.1)
Mpumalanga	48 560 (5.6)	47 040 (5.8)	44 319 (5.5)	43 674 (5.2)	38 490 (4.6)	38 457 (4.5)	49 949 (4.5)
North West	45 066 (5.2)	44 398 (5.4)	33 158 (4.1)	33 010 (3.9)	35 501 (4.2)	33 781 (3.9)	37 723 (3.4)
Northern Cape	15 484 (1.8)	15 836 (1.9)	14 888 (1.8)	15 527 (1.9)	18 256 (2.2)	18 412 (2.1)	24 990 (2.3)
Western Cape	93 243 (10.8)	90 969 (11.2)	88 693 (11.0)	93 703 (11.2)	119 239 (14.1)	123 030 (14.3)	176 245 (16.0)
Not indicated	3 460 (0.4)	2 515 (0.3)	2 487 (0.3)	3 063 (0.4)	4 223 (0.5)	0	5 681 (0.5)

3.3.1 Patient demographic characteristics and geographic location

Medicine claims data were obtained for analysis from the central database of the PBM company from 2011 to 2017. In 2011, these patients represented 10.1% (*N* = 8 526 409) of all beneficiaries covered by medical aid schemes in South Africa (Council for Medical Schemes (CMS), 2012:8) in that year (Table 3-1). A marginal increase to 12.4% (*N* = 8 872 036) was observed in 2017 (CMS, 2018:4). This is consistent with South Africa's static medical aid scheme beneficiary numbers during the past 10 years (CMS, 2020).

Slightly fewer male than female patients were recorded in the central database over the study period. These trends are similar to the demographic profile of the beneficiaries covered by medical aid schemes registered in South Africa in terms of the Medical Schemes Act (131 of 1998) from 2011 to 2017. Most patients in the central database were in age group 1 (i.e., patients 57 years and younger). This age distribution is in accord with the 2020/21 industry report (CMS, 2020), which stated that the average age of beneficiaries on medical schemes was 33.4 years.

Analysis per province showed that the majority of the patients captured in the PBM's central database were from Gauteng, Western Cape and KwaZulu-Natal, following the general trends observed in the entire South African medical schemes industry, with Gauteng at 39%, Western Cape at 16% and KwaZulu-Natal at 15% of medical aid members (CMS, 2020). Statistics South Africa data confirms that Gauteng has the largest number of people at 16.1 million (26.6%), which aligns with the PBM's central database, which shows that most patients are from Gauteng. KwaZulu-Natal has the second largest population at 11.5 million (19.0%) and Western Cape is the third largest province, with 7.2 million (11.9%) people (StatsSA, 2022). Analysis of the central database showed that an increase was observed in the number of patients residing in the Free State (5.9%, *N* = 864 962) in 2011 to 7.0% (*N* = 1 103 167) in 2017. An increasing trend was also observed for the Northern Cape (from 1.8% in 2011 to 2.9% in 2017) and the Western Cape (10.8% vs 16.0%), compared to decreases in the other provinces from 2011 to 2017.

3.3.2 Number of medicine items prescribed

Table 3-2 shows the number of prescribed medicine items captured on the central database from 2011 to 2017, stratified by age, gender and geographic area.

Table 3-2: Total number of medicine items prescribed on the central database per age, gender and geographic location

	2011 *n* (%) (*N* = 18 099 133)	2012 *n* (%) (*N* = 16 744 033)	2013 *n* (%) (*N* = 16 786 417)	2014 *n* (%) (*N* = 18 583 019)	2015 *n* (%) (*N* = 18 891 385)	2016 *n* (%) (*N* = 19 250 285)	2017 *n* (%) (*N* = 20 236 841)
Gender							
Female	10 526 005 (58.2)	9 426 655 (56.3)	954 8414 (56.9)	10 568 777 (56.9)	10 592 769 (56.1)	10 825 287 (56.2)	11 424 937 (56.5)
Male	7 573 108 (41.8)	7 317 378 (43.7)	7 238 003 (43.1)	8 014 242 (43.1)	8 298 616 (43.9)	8 424 998 (43.8)	8 811 904 (43.5)
Age group (yr)							
Age ≤57	10 199 380 (56.4)	9 567 843 (57.1)	9 880 895 (58.9)	11 041 917 (59.4)	11 620 655 (61.5)	11 591 278 (60.2)	11 124 185 (55.0)
57> Age ≤66	2 930 471 (16.2)	2 862 922 (17.1)	2 865 380 (17.1)	3 099 346 (16.7)	3 052 784 (16.2)	3 145 061 (16.3)	3 262 026 (16.1)
66> Age ≤75	2 394 275 (13.2)	2 294 046 (13.7)	2 247 472 (13.4)	2 434 347 (13.1)	2 290 147 (12.1)	2 431 184 (12.6)	2 863 129 (14.2)
Age >75	2 574 987 (14.2)	2 019 222 (12.1)	1 792 670 (10.7)	2 007 409 (10.8)	1 927 799 (10.2)	2 082 762 (10.8)	2 987 501 (14.8)
Provinces							
Eastern Cape	1 238 545 (6.8)	1 142 481 (6.8)	1 095 134 (6.4)	1 182 278 (6.4)	1 214 386 (6.4)	1 185 587 (6.2)	1 263 037 (6.2)
Free State	924 377 (5.1)	867 469 (5.2)	920 026 (5.9)	1 099 591 (5.9)	1 157 168 (6.1)	1 206 188 (6.3)	1 254 367 (6.2)
Gauteng	7 414 988 (41.0)	6 791 817 (40.6)	6 923 163 (40.6)	7 550 245 (40.6)	6 942 028 (36.8)	7 159 951 (37.2)	7 493 805 (37.0)
KwaZulu-Natal	2 580 776 (14.3)	2 320 308 (13.9)	2 372 971 (13.9)	2 587 477 (13.9)	2 489 706 (13.2)	2 543 945 (13.2)	2 558 069 (12.6)
Limpopo	644 940 (3.6)	593 898 (3.6)	543 737 (3.2)	601 684 (3.2)	647 262 (3.4)	690 795 (3.6)	662 415 (3.3)
Mpumalanga	1 052 629 (5.8)	1 041 588 (6.2)	1 022 140 (6.1)	1 126 837 (6.1)	1 056 723 (5.6)	1 105 360 (5.7)	1 093 549 (5.4)
North West	964 621 (5.3)	920 098 (5.5)	805 839 (4.7)	863 347 (4.7)	906 141 (4.8)	847 214 (4.4)	766 170 (3.8)
Northern Cape	323 469 (1.8)	328 809 (2.0)	329 135 (2.0)	375 260 (2.0)	447 877 (2.4)	536 474 (2.8)	583 811 (2.9)
Western Cape	2 869 722 (15.9)	2 665 057 (15.9)	2 698 712 (16.6)	3 084 680 (16.6)	3 888 519 (20.6)	3 974 768 (20.7)	4 396 849 (21.7)
Not indicated	85 046 (0.5)	72 508 (0.4)	75 560 (0.6)	111 620 (0.6)	141 575 (0.8)	3 (0.0)	164 769 (0.8)

3.3.2.1 Analysis of the total number of medicine items in the central database per gender

A total of 18 million medicine items were claimed in 2011, decreasing to a low of just under 16.8 million items in 2012 and 2013 and thereafter increasing by 20.6% to over 20 million in 2017. The majority of medicine items in the central database over the study period were for female patients, decreasing marginally from 58.2% (*N* = 18 099 133) in 2011 to 56.5% (*N* = 20 236 841) in 2017 (Table 3-2).

Female patients typically have higher prescription claim rates per patient than male patients (Orlando *et al*., 2020:6). The sexes differ in their perspectives on symptoms, medical treatment, medications and self-care, which might account for the higher claim rate among women in an industrialised nation. Women often have more debilitating conditions than men but with comparatively less severe conditions (Crimmins *et al*., 2019:135). These frequent symptoms cause women to limit their activities, whereas men experience diseases and injuries less frequently, but they tend to be more severe, resulting in longer-lasting disabilities and hospitalisation (Crimmins *et al*., 2019:138).

3.3.2.2 Analysis of the total number of medicine items in the central database per age group

The under-57-year age group had a higher number of claimed medicine items, ranging from 56.4% (*N* = 18 099 133) in 2011 to 61.5% (*N* = 18 891 385) in 2015, followed by a slight decrease to 60.2% (*N* = 19 250 285) in 2016 and 55.0% (*N* = 20 236 841) in 2017. The least number of medicine items were claimed for the above 75-years age group, increasing marginally from 14.2% in 2011 to 14.8% in 2017. This could be ascribed to the distribution of patients per age group in the central database (refer to Table 3-1).

3.3.2.3 Analysis of the total number of medicine items in the central database per geographic location

Analysis based on province showed that the medicine items claimed in Gauteng accounted for the highest number of claims, decreasing from 41.0% (*N* = 18 099 133) in 2011 to 37.0% (*N* = 20 236 841) in 2017 (Table 3-2). The number of medicine items claimed was the second highest in the Western Cape, at 15.9% (*n* = 2 869 722) in 2011 and increasing to 21.7% (*n* = 4 396 849) in 2017, followed by KwaZulu-Natal at 14.3% (*n* = 2 580 776) in 2011 decreasing to 12.6% (*n* = 2 558 069) in 2017. This trend is in accordance with the distribution of patients observed in the central database (see Table 3-1).

The following section contains a general overview of opioid analgesic prescribing patterns.

3.4 General overview of opioid analgesic prescribing patterns

This section contains a general overview of the dataset used to determine the changes in prescribing patterns of opioid analgesics for chronic pain claimed from 1 January 2011–31 December 2017. The study population for this analysis consisted of all the patients with at least one opioid analgesic on the database in the prescribed period and reimbursed from chronic, PMB or oncology benefits, excluding all injections and suppositories (refer to Chapter 1, Table 1-1).

The discussion in this section is based on the number of patients (see Table 3-3) and medicine items (see Table 3-4) in the dataset.

Table 3-3: General characteristics of patients receiving at least one opioid analgesic medicine item during the study period

	2011 *n* (%)	2012 *n* (%)	2013 *n* (%)	2014 *n* (%)	2015 *n* (%)	2016 *n* (%)	2017 *n* (%)
Patients, *N*	**2 499**	**3 079**	**2 954**	**3 951**	**3 871**	**3 998**	**5 636**
Gender							
Female	1 343 (53.7)	1 642 (53.3)	1 539 (52.1)	2158 (54.6)	2008 (51.9)	2224 (55.6)	2997 (53.2)
Male	1 156 (46.3)	1 437 (46.7)	1415 (47.9)	1793 (45.4)	1863 (48.1)	1774 (44.4)	2639 (46.8)
Age groups (years)							
Age ≤57	678 (27.1)	948 (30.8)	843 (28.5)	1060 (26.8)	1066 (27.5)	1071 (26.8)	1476 (26.2)
57> Age ≤66	651 (26.1)	748 (24.3)	757 (25.6)	989 (25.0)	899 (23.2)	920 (23.0)	1181 (21.0)
66> Age ≤75	578 (23.1)	736 (23.9)	790 (26.7)	1067 (27.0)	1077 (27.8)	1118 (28.0)	1425 (25.3)
Age >75	592 (23.7)	647 (21.0)	564 (19.1)	835 (21.1)	829 (21.42)	889 (22.2)	1554 (27.6)
Province							
Eastern Cape	100 (4.0)	131 (4.3)	93 (3.2)	139 (3.5)	118 (3.1)	124 (3.1)	210 (3.7)
Free State	130 (5.2)	144 (4.7)	231 (7.8)	242 (6.1)	285 (7.4)	244 (6.1)	370 (6.6)
Gauteng	1090 (43.6)	1399 (45.4)	1180 (40.0)	1546 (39.1)	1430 (36.9)	1631 (40.8)	2210 (39.2)
Kwazulu-Natal	493 (19.7)	563 (18.3)	650 (22.0)	984 (24.9)	954 (24.6)	920 (23.0)	1175 (20.1)
Limpopo	37 (1.5)	58 (1.9)	62 (2.1)	72 (1.8)	51 (1.3)	58 (1.5)	80 (1.4)
Mpumalanga	63 (2.5)	133 (3.7)	108 (3.7)	146 (3.7)	161 (4.2)	136 (3.4)	194 (3.4)
North West	83 (3.3)	98 (3.2)	77 (2.6)	91 (2.3)	91 (2.4)	87 (2.2)	126 (2.2)
Northern Cape	23 (0.9)	33 (1.1)	42 (1.4)	62 (1.6)	65 (1.7)	75 (1.9)	97 (1.7)
Western Cape	468 (18.7)	516 (16.8)	504 (17.1)	657 (16.6)	695 (18.0)	723 (18.1)	1154 (20.5)
Not indicated	12 (0.5)	24 (0.8)	7 (0.3)	12 (0.3)	21 (0.5)	0	20 (0.4)

3.4.1 Patient demographic characteristics and geographic location

As a percentage of the total number of patients in the central database (see Table 3-1), the patients who received at least one opioid analgesic (claimed from chronic, oncology or PMBs) during the respective years increased marginally from 0.3% (*N* = 864 962) in 2011 to 0.5% (*N* = 1 103 167) in 2017 (Table 3-3).

Similar to results based on the central database, analysis based on gender also showed that there were more female than male patients with at least one claim for an opioid over the respective study years. The number of female patients decreased marginally from 53.7% (*N* = 2 499) in 2011 to 53.2% (*N* = 5 636) in 2017, corresponding to the increase in male patients from 46.3% in 2011 to 46.8% in 2017. The male-to-female ratio per year remained relatively stagnant over the seven years.

The results in Table 3-3 further indicate that the number of patients with at least one prescription for opioid analgesics in age groups 1 and 2 (i.e., patients 57 years old and younger and those between the ages of 58 and 66 years) decreased from 27.1% (*n* = 678) and 26.1% (*n* = 651) in 2011 to 26.2% (*n* = 1 476) and 21% (*n* = 1 181) in 2017 respectively. In contrast, the number of patients in age groups 3 and 4 (i.e., older than 66 years) with at least one prescription for opioid analgesics increased over the study period.

The analysis showed similar trends to those observed in the central database, with most patients in this study population residing in Gauteng, followed by the Western Cape and KwaZulu-Natal in the second and third position, respectively (refer to section 3.3.1). As a percentage of the number of patients per province (i.e., using the number of patients on the central database per province as the denominator, Table 3-1), however, there were proportionally more patients from KwaZulu-Natal in this population than in the other provinces, at 0.5% (*N* = 109 150) in 2011, increasing to 1.0% (*N* = 120 411) in 2017. In comparison, the number of patients in this population in Gauteng represented 0.3% (*N* = 407 360) in 2011, increasing marginally to 0.4% (*N* = 506 139) in 2017.

3.4.2 Number of opioid analgesics prescribed

Prescriptions for patients who received one or more opioid analgesic medicine items during the study period were analysed by gender, age group and province, as depicted in Table 3-4. A mean of 1.16 ± 0.46 (95% CI, 1.15–1.17) of opioid analgesic medicine items was prescribed per prescription over the study period. There was no practically significant difference in the mean number of opioid analgesics per patient between the years under study (Cohen's $d < 0.1$), ranging from 1.13 ± 0.39 (1.12 – 1.14) in 2011 to 1.17 ± 0.47 (1.16 – 1.18) in 2017. In the following paragraphs, the analysis of the total and the mean (*SD*) number of opioid analgesics per prescription, as stratified by gender, age group and province, is presented.

Table 3-4: Mean (*SD*) number of opioid analgesics (medicine items) prescribed per prescription (2011–2017), per gender, age group and province

	2011 *n* (%)	2012 *n* (%)	2013 *n* (%)	2014 *n* (%)	2015 *n* (%)	2016 *n* (%)	2017 *n* (%)
Total dataset							
Prescriptions, *N*	5 133	5 574	5 450	7 253	6 993	7 151	10 195
Medicine items, *N*	5 797	6 423	6 330	8 486	8 228	8 404	12 018
Items/prescription, mean (SD) (95% CI)	1.13 ± 0.39 (1.12 – 1.14)	1.15 ± 0.43 (1.14 – 1.16)	1.16 ± 0.46 (1.15 – 1.17)	1.17 ± 0.47 (1.16 – 1.18)	1.17 ± 0.48 (1.16 – 1.19)	1.17 ± 0.46 (1.16 – 1.18)	1.17 ± 0.47 (1.16 – 1.18)
Gender							
Females							
Prescriptions, n (%)	2 899 (56.5)	3 002 (53.9)	2 945 (54.0)	4 101 (56.5)	3 732 (53.4)	4 096 (57.3)	5 624 (55.2)
Medicine items, n (%)	3 281 (56.6)	3 419 (53.2)	3 358 (53.1)	4 772 (56.2)	4 337 (52.7)	4 809 (57.2)	6 543 (54.4)
Items/prescription, mean (SD) (95% CI)	1.13 ± 0.41 (1.12 – 1.15)	1.13 ± 0.40 (1.11 – 1.14)	1.14± 0.42 (1.12 – 1.15)	1.16 ± 0.45 (1.14 – 1.17)	1.16 ± 0.45 (1.15 – 1.18)	1.17 ± 0.45 (1.16 – 1.18)	1.16 ± 0.46 (1.15 – 1.17)
Males							
Prescriptions, n (%)	2 234 (43.5)	2 572 (46.1)	2 505 (46.0)	3 152 (43.5)	3 261 (46.6)	3 055 (42.7)	4 571 (44.8)
Medicine items, n (%)	2 516 (43.4)	3 004 (46.8)	2 972 (47.0)	3 714 (43.8)	3 891 (47.3)	3 595 (42.8)	5 475 (45.6)
Items/prescription, mean (SD) (95% CI)	1.13 ± 0.37 (1.11 – 1.14)	1.17 ± 0.47 (1.15 – 1.19)	1.18 ± 0.51 (1.16 – 1.20)	1.18 ± 0.49 (1.16 – 1.19)	1.19 ± 0.51 (1.17 – 1.21)	1.17 ± 0.47 (1.16 – 1.19)	1.19 ± 0.48 (1.17 – 1.20)
Age groups (years)							
Age ≤57							
Prescriptions, n (%)	1 300 (25.3)	1 548 (27.8)	1 440 (26.4)	1 823 (25.1)	1 721 (24.6)	1 738 (24.3)	2360 (23.2)
Medicine items, n (%)	1 478 (25.5)	1 749 (27.2)	1 644 (26.0)	2 177 (25.7)	2 058 (25.0)	2 099 (25.0)	2 870 (23.9)
Items/prescription, mean (SD) (95% CI)	1.14 ± 0.41 (1.12 – 1.16)	1.13 ± 0.37 (1.11 – 1.14)	1.14 ± 0.41 (1.12 – 1.16)	1.19 ± 0.51 (1.17 – 1.22)	1.19 ± 0.49 (1.17 – 1.22)	1.20 ± 0.48 (1.18 – 1.22)	1.21 ± 0.51 (1.19 – 1.24)
57> Age ≤66							
Prescriptions, n (%)	1 243 (24.2)	1 323 (23.7)	1 338 (24.6)	1 693 (23.3)	1 671 (23.9)	1 621 (22.7)	2 080 (20.4)
Medicine items, n (%)	1 436 (24.8)	1 609 (25.1)	1 629 (25.7)	2 014 (23.7)	2 033 (24.7)	1 976 (23.5)	2 500 (20.8)
Items/prescription, mean (SD) (95% CI)	1.15 ± 0.43 (1.13 – 1.17)	1.19 ± 0.52 (1.17 – 1.22)	1.12 ± 0.52 (1.18 – 1.24)	1.18 ± 0.50 (1.16 – 1.21)	1.21 ± 0.53 (1.18 – 1.23)	1.21 ± 0.49 (1.19 – 1.24)	1.19 ± 0.51 (1.17 – 1.21)
66> Age ≤75							
Prescriptions, n (%)	1 159 (22.6)	1 425 (26.6)	1 488 (27.3)	2 008 (27.7)	1 944 (27.8)	1 994 (27.9)	2 684 (26.3)
Medicine items, n (%)	1 318 (22.7)	1 649 (25.7)	1 732 (27.4)	2 358 (27.8)	2 271 (27.6)	2 333 (27.8)	3 189 (26.5)
Items/prescription, mean (SD) (95% CI)	1.14 ± 0.41 (1.11 – 1.16)	1.16 ± 0.45 (1.13 – 1.18)	1.16 ± 0.49 (1.14 – 1.19)	1.17 ± 0.46 (1.15 – 1.19)	1.17 ± 0.47 (1.15 – 1.19)	1.17 ± 0.48 (1.15 – 1.19)	1.18 ± 0.49 (1.16 – 1.20)
Age >75							

	2011 *n* (%)	2012 *n* (%)	2013 *n* (%)	2014 *n* (%)	2015 *n* (%)	2016 *n* (%)	2017 *n* (%)
Prescriptions, n (%)	1 431 (27.9)	1 278 (22.9)	1 184 (21.7)	1 729 (23.8)	1 657 (23.7)	1 798 (25.1)	3 071 (30.1)
Medicine items, n (%)	1 565 (27.0)	1 416 (22.1)	1 325 (20.9)	1 937 (22.8)	1 866 (22.7)	1 996 (23.8)	3 459 (28.8)
Items/prescription, mean (SD) (95% CI)	1.09 ± 0.33 (1.08 – 1.11)	1.11 ± 0.37 (1.09 – 1.13)	1.12 ± 0.41 (1.10 – 1.14)	1.12 ± 0.38 (1.10 – 1.13)	1.13 ± 0.41 (1.11 – 1.15)	1.11 ± 0.35 (1.09 – 1.12)	1.12 ± 0.38 (1.11 – 1.14)
Province							
Eastern Cape							
Prescriptions, n (%)	202 (3.9)	257 (4.6)	168 (3.1)	231 (3.2)	217 (3.1)	230 (3.2)	400 (3.9)
Medicine items, n (%)	213 (3.7)	279 (4.3)	177 (2.8)	266 (3.1)	237 (2.9)	255 (3.0)	425 (3.5)
Items/prescription, mean (SD) (95% CI)	1.06 ± 0.32 (1.01 – 1.10)	1.09 ± 0.32 (1.05 – 1.13)	1.05 ± 0.30 (1.01 – 1.10)	1.15 ± 0.38 (1.10 –1.20)	1.09 ± 0.33 (1.05 –1.14)	1.11 ± 0.31 (1.07 – 1.49)	1.06 ± 0.29 (1.03 – 1.09)
Free State							
Prescriptions, n (%)	324 (6.3)	287 (5.1)	462 (8.5)	454 (6.3)	492 (7.0)	474 (6.6)	770 (7.6)
Medicine items, n (%)	358 (6.2)	313 (4.9)	535 (8.5)	542 (6.4)	573 (7.0)	558 (6.6)	993 (8.3)
Items/prescription, mean (SD) (95% CI)	1.10 ± 0.33 (1.07 – 1.41)	1.09 ± 0.29 (1.06 – 1.12)	1.16 ± 0.41 (1.12 – 1.20)	1.18 ± 0.49 (1.13 –1.22)	1.17 ± 0.42 (1.13 –1.20)	1.16 ± 0.45 (1.07 – 1.15)	1.06 ± 0.62 (1.24 – 1.33)
Gauteng							
Prescriptions, n (%)	2 099 (40.9)	2 444 (43.8)	2 155 (39.5)	2 899 (40.0)	2 659 (38.0)	2 917 (40.8)	3 996 (39.2)
Medicine items, n (%)	2 426 (41.8)	2 851 (44.4)	2 518 (39.8)	3 481 (41.0)	3 183 (38.7)	3 531 (42.0)	4 753 (39.5)
Items/prescription, mean (SD) (95% CI)	1.15 ± 0.43 (1.13 – 1.17)	1.15 ± 0.45 (1.14 – 1.17)	1.16 ± 0.48 (1.14 – 1.19)	1.20 ± 0.51 (1.18 –1.22)	1.19 ± 0.48 (1.18 – 1.21)	1.21 ± 0.50 (1.19 – 1.23)	1.18 ± 0.49 (1.17 – 1.20)
Kwazulu-Natal							
Prescriptions, n (%)	1 044 (20.3)	1 029 (18.5)	1 136 (20.8)	1 819 (25.1)	1 680 (24.0)	1 602 (22.4)	2 005 (19.7)
Medicine items, n (%)	1 141 (19.7)	1 183 (18.4)	1 257 (19.9)	2 033 (24.0)	1 954 (23.7)	1 772 (21.1)	2 239 (18.6)
Items/prescription, mean (SD) (95% CI)	1.15 ± 0.43 (1.13 – 1.17)	1.15 ± 0.46 (1.12 – 1.18)	1.10 ± 0.37 (1.08 – 1.19)	1.12 ± 0.38 (1.10 –1.14)	1.16 ± 0.51 (1.14– 1.19)	1.10 ± 0.34 (1.08 – 1.12)	1.12 ± 0.36 (1.10 – 1.13)
Limpopo							
Prescriptions, n (%)	111 (2.2)	120 (2.2)	95 (1.7)	128 (1.8)	82 (1.2)	114 (1.6)	147 (1.4)
Medicine items, n (%)	126 (2.2)	128 (2.0)	110 (1.7)	161 (1.9)	94 (1.1)	125 (1.5)	171 (1.4)
Items/prescription, mean (SD) (95% CI)	1.14 ± 0.39 (1.06 – 1.21)	1.07 ± 0.25 (1.02 – 1.11)	1.16 ± 0.40 (1.08 – 1.24)	1.26 ± 0.59 (1.15 – 1.36)	1.15 ± 0.48 (1.05 – 1.25)	1.10 ± 0.33 (1.04 – 1.16)	1.16 ± 0.39 (1.10 – 1.23)
Mpumalanga							
Prescriptions, n (%)	119 (2.3)	187 (3.6)	208 (3.8)	292 (4.0)	280 (4.0)	256 (3.6)	373 (3.7)
Medicine items, n (%)	138 (2.4)	209 (3.3)	241 (3.8)	327 (3.9)	338 (4.1)	322 (3.8)	454 (3.8)
Items/prescription, mean (SD) (95% CI)	1.16 ± 0.41 (1.09 – 1.23)	1.12 ± 0.32 (1.07 – 1.16)	1.16±0.39 (1.11 – 1.21)	1.12± 0.36 (1.08 – 1.16)	1.19 ± 0.42 (1.14 – 1.24)	1.26± 0.58 (1.19– 1.33)	1.21 ± 0.48 (1.16 – 1.26)
North West							
Prescriptions, n (%)	155 (3.0)	148 (2.7)	157 (2.9)	137 (1.9)	158 (2.6)	144 (2.0)	186 (1.8)

	2011 *n* (%)	2012 *n* (%)	2013 *n* (%)	2014 *n* (%)	2015 *n* (%)	2016 *n* (%)	2017 *n* (%)
Medicine items, n (%) Items/prescription, mean (SD) (95% CI)	175 (3.0) 1.13 ± 0.37 (1.07 – 1.19)	164 (2.6) 1.11 ± 0.31 (1.11 – 0.31)	191 (3.0) 1.22 ± 0.62 (1.12 – 1.32)	162 (1.9) 1.15 ± 0.46 (1.07 – 1.22)	180 (2.2) 1.14 ± 0.35 (1.09 – 1.19)	169 (2.0) 1.17 ± 0.45 (1.10– 1.25)	212 (1.8) 1.14 ± 0.39 (1.08 – 1.20)
Northern Cape Prescriptions, n (%) Medicine items, n (%) Items/prescription, mean (SD) (95% CI)	 41 (0.8) 43 (0.7) 1.05 ± 0.22 (0.98 – 1.12)	 47 (0.8) 49 (0.8) 1.04 ± 0.20 (0.98 – 1.10)	 70 (1.3) 78 (1.2) 1.11 ± 0.44 (1.01 – 1.22)	 132 (1.8) 146 (1.7) 1.11 ± 0.36 (1.05 – 1.17)	 106 (1.5) 116 (1.4) 1.09 ± 0.29 (1.04 – 1.15)	 120 (1.7) 135 (1.6) 1.13 ± 0.40 (1.05 – 1.20)	 142 (1.4) 149 (1.2) 1.05 ± 0.25 (1.01 – 1.09)
Western Cape Prescriptions, n (%) Medicine items, n (%) Items/prescription, mean (SD) (95% CI)	 1 019 (19.9) 1 158 (20.0) 1.14 ± 0.40 (1.11 – 1.16)	 1 018 (18.3) 1 209 (18.8) 1.19 ± 0.48 (1.16 – 1.22)	 992 (18.2) 1 216 (19.2) 1.23 ± 0.54 (1.19 – 1.26)	 1 138 (15.7) 1 344 (15.8) 1.17 ± 0.48 (1.15 – 1.20)	 1 293 (18.5) 1 526 (18.5) 1.18 ± 0.51 (1.15 – 1.21)	 1 294 (18.1) 1 537 (18.3) 1.18 ± 0.48 (1.16 – 1.21)	 2 136 (21.0) 2 582 (21.5) 1.20 ± 0.25 (1.17 – 1.22)
Not indicated Prescriptions, n (%) Medicine items, n (%) Items/prescription, Mean (SD) (95% CI) / Median* (IQR)	 19 19 (0.3) 1*	 37 38 (0.6) 1* (1-4)	 7 7 (0.1) 1*	 23 24 (0.3) 1.04 ± 0.21 (0.95 – 1.13)	 26 27 (0.3) 1.04 ± 0.20 (0.96 – 1.12)	 0	 40 40 (0.3) 1*

3.4.2.1 Analysis of the total number of opioid analgesic medicine items per gender

As a percentage of the total number of medicine items claimed in the central database (see Table 3-2), the number of opioid analgesics claimed during the years under study increased from 0.03% (*N* = 18 099 133) in 2011 to 0.06% (*N* = 20 236 841) in 2017 (Table 3-4). A recent study by Jayawardana *et al*. (2021:3) indicated a 30% decrease in global opioid consumption from 2009 to 2019. The main factors contributing to the global opioid consumption volume being lower in 2019 than in 2009 were decreased consumption in the USA, Germany and Canada. Although there was significant diversity in consumption rates and opioid types, rising opioid consumption rates were seen in the majority of other high-income countries. Opioid consumption rates in upper-middle-income and low-to-middle-income nations, on the other hand, were significantly lower and increased very slightly between 2009 and 2019. The literature shows that the consumption of opioids in South Africa has decreased compared to other African countries, with a DDD of less than 200 mg/day/100 000 people (Ju *et al*., 2022:e338; Powell *et al*., 2014:117). The study findings are, therefore, in accord with global trends because the World Bank has categorised South Africa as an upper-middle-income country (World Bank, 2022).

Similarly to results based on the central database, analysis based on gender showed that there were more opioid analgesic claims in total for female than male patients over the study years. Medicine item claims for female patients decreased marginally from 56.6% (*N* = 5 797) in 2011 to 54.4% (*N* = 12 018) in 2017. Although there was a slight increase in the mean number of opioid analgesics claimed per prescription from 2011 to 2017 for both female (1.13 ± 0.41 [95% CI: 1.12, 1.15] vs 1.16 ± 0.46 [95% CI: 1.15, 1.17] and male patients (1.13 ± 0.37 [95% CI: 1.11, 1.14] vs 1.19 ± 0.48 [95% CI: 1.17, 1.20]), the difference in means were not practically significant (*d* = 0.07 and 0.13 for females and males respectively). There was also no practically significant difference in the mean number of opioid analgesics per prescription between male and female patients (*d* < 0.1 for 2012–2015 and 2017).

Doctors give opioids to female patients more frequently than to male patients (Foy *et al*., 2016:4; Muench *et al*., 2020:6; Pisanu *et al.,* 2019:2; Serdarevic *et al*., 2017:6; Suvada *et al*., 2022:3-4). Women furthermore use prescription opioids at higher rates than men (Foy *et al*., 2016:4; Serdarevic *et al*., 2017:6). This might be explained by pain sensitivity and pain tolerance, with women reporting more chronic pain-causing diseases (LeResche *et al*., 2015:632; Pisanu *et al*., 2019:2). Chronic pain problems such as fibromyalgia, migraines and osteoarthritis are more prevalent in women than in men and might be linked to increased opioid prescription rates (Darnall *et al*., 2012:1182; Pisanu *et al*., 2019:2). These studies showed that there is gender-specific disparities in prescription opioid use and usage patterns.

3.4.2.2 Analysis of the total number of opioid analgesic medicine items per age group

The results from Table 3-4 show that the total number of opioid analgesic items claimed per age group followed the same trend as for the central database's distribution, with opioid analgesic claims for patients in age groups 1 and 2 (i.e., patients aged 57 years and younger and those between 58 and 66 years) marginally decreasing from 25.5% and 24.8% in 2011 (*N* = 5 797) to 23.9% and 20.8% in 2017 (*N* = 12 018) respectively. In contrast, opioid analgesic medicine items claimed for patients older than 66, ≤ 75 years, and those older than 75 years increased by 3.8% and 1.8% respectively. Older patients above the age of 65 years are more likely than younger patients to receive opioids (Foy *et al.,* 2016:6; Weesie *et al.*, 2020). This could be explained by the fact that chronic pain affects up to 62% of persons over the age of 75 years and is more common as people age (Fayaz *et al*., 2016).

Despite the decrease in the total number of opioid analgesic items claimed per age group for age groups 1 and 2, there was a slight increase in the mean number of opioid analgesics claimed per prescription. For example, the mean (SD) opioid analgesics claimed per prescription increased marginally from 2011 to 2017 for age group 1 (1.14 ± 0.41 [95% CI: 1.12, 1.16] vs 1.21 ± 0.51 [95% CI: 1.19, 1.24] and age group 2 (1.15 ± 0.43 [95% CI: 1.13, 1.17] vs 1.19 ± 0.51 [95% CI: 1.17, 1.21]). There was, however, no practically significant difference in the mean number of medicine items claimed per prescription from 2011 to 2017 ($d < 0.1$) or between the age groups per year ($d < 0.2$).

3.4.2.3 Analysis of the total number of opioid analgesic medicine items per geographic area

The analysis showed that most opioid analgesic medicine items were claimed in Gauteng, followed by the Western Cape and KwaZulu-Natal. Table 3-4 shows that the mean number of opioid analgesics per prescription increased marginally in Gauteng, Limpopo, Mpumalanga, North West and Western Cape provinces, in contrast to a decrease in items per prescription for the Free State and KwaZulu-Natal. However, the differences in means were not practically significant ($d < 0.2$).

3.4.2.4 Analysis of the total number of active pharmaceutical ingredients per prescription

Table 3-5 shows the number of active pharmaceutical ingredients (APIs) prescribed per prescription over the study period. The APIs were counted the first time they were prescribed. Active pharmaceutical ingredients with different strengths were counted separately.

In conjunction with the low mean number of opioid analgesics claimed per prescription during the study period (see section 3.4.2), the majority of prescriptions for patients in the study population contained only one API, decreasing from 89.1% (*N* = 5 133) in 2011 to 85.8% (*N* = 10 195) in 2017. Up to six different APIs were prescribed per prescription over the study period (see Table 3-5).

Table 3-6 depicts the top 10 APIs for each year of study based on prescribing frequency (rank shown in brackets). The combination of tramadol and paracetamol was the most prescribed API over the study period, decreasing from 26.2% (*N* = 5 133) in 2011 to 24.2% (*N* = 10 195) in 2017. Fentanyl (14.6%, *N* = 5 133) was the second most claimed API in 2011; prescribing, however, declined over the study period to 4.5% (*N* = 10 195) in 2017. From 2012 to 2017, the second position on the top 10 list was replaced by a combination product comprising paracetamol/codeine/meprobamate at a prevalence of 14.4% (*N* = 5 574) in 2012 and increasing to 19.3% (*N* = 10 195) in 2017. Prescribing of morphine constantly decreased from 9.4% (*N* = 5 133) in 2011 to 4.4% (*N* = 10 195) in 2017, whereas prescriptions of oxycodone, which did not appear on the top 10 list for 2011, increased from 1.5% (*N* = 5 574) in 2012 to 4.6% (*N* = 10 195) in 2017, after peaking at 6.2% (*N* = 7 253) in 2014 and 8.9% (*N* = 6 993) in 2015. Prescribing of buprenorphine increased by 1.3% from 2011 to 2017. Hydromorphone and the paracetamol/codeine/doxylamine succinate combination mainly occupied the ninth and 10th positions of the top 10 lists from 2012 to 2017.

The prescribing patterns of buprenorphine, codeine, dihydrocodeine, fentanyl, tramadol and morphine from 2011 to 2017 were further investigated using the DDD per 1 000 inhabitants per day (see section 3.4.2.4.1).

Table 3-5: Number of active pharmaceutical ingredients per prescription (2011–2017)

Number of active substances	2011 *n* (%) *N* = 5 133	2012 *n* (%) *N* = 5 574	2013 *n* (%) *N* = 5 450	2014 *n* (%) *N* = 7 253	2015 *n* (%) *N* = 6 993	2016 *n* (%) *N* = 7 151	2017 n (%) *N* = 10 195
One	4 572 (89.1)	4 897 (87.9)	4 739 (87.0)	6 260 (86.3)	5 988 (85.6)	6 121 (85.6)	8 747 (85.8)
Two	478 (9.3)	570 (10.2)	654 (12.0)	843 (11.6)	854 (12.2)	875 (12.2)	1 197 (11.7)
Three	69 (1.3)	85 (1.5)	53 (1.0)	103 (1.4)	116 (1.7)	118 (1.7)	201 (2)
Four	13 (0.3)	16 (0.3)	2 (0.04)	39 (0.5)	26 (0.4)	33 (0.5)	41 (0.4)
Five	1 (0.02)	5 (0.1)	-	5 (0.1)	5 (0.1)	3 (0.04)	7 (0.1)
Six	-	1 (0.02)	2 (0.04)	3 (0.04)	4 (0.06)	1 (0.01)	2 (0.02)

Table 3-6: Frequency and ranking order of active pharmaceutical ingredients prescribed over the study period (2011–2017)

Active pharmaceutical ingredient	2011 (*N* = 5 133)	2012 (*N* = 5 574)	2013 (*N* = 5 450)	2014 (*N* = 7 253)	2015 (*N* = 6 993)	2016 (*N* = 7 151)	2017 (*N* = 10 195)
Tramadol/paracetamol	1 342 (1)	1 442 (1)	1 404 (1)	1 741 (1)	1 695 (1)	1 435 (1)	2 463 (1)
Fentanyl	749 (2)	570 (3)	579 (3)	675 (3)	530 (6)	488 (5)	462 (6)
Tramadol	656 (3)	568 (4)	476 (4)	633 (5)	546 (5)	567 (4)	926 (3)
Paracetamol/codeine/meprobamate	647 (4)	801 (2)	681 (2)	1 026 (2)	1 054 (2)	1 346 (2)	1 963 (2)
Morphine	481 (5)	435 (6)	440 (6)	443 (7)	407 (7)	335 (7)	449 (7)
Ibuprofen/paracetamol/codeine	319 (6)	470 (5)	443 (5)	666 (4)	580 (4)	666 (3)	799 (4)
Codeine	91 (7)		92 (9)	110 (9)	66 (10)	79 (10)	
Oxycodone		89 (8)	217 (7)	448 (6)	619 (3)	418 (6)	468 (5)
Buprenorphine	60 (9)	78 (10)	124 (8)	250 (8)	165 (8)	236 (8)	250 (8)
Dihydrocodeine	63 (8)						
Paracetamol / codeine	55 (10)	113 (7)					250 (9)
Hydromorphone		79 (9)	59 (10)	64 (10)			
Paracetamol/codeine doxylamine succinate					74 (9)	100 (9)	95 (10)

3.4.2.5 Analysis of active pharmaceutical ingredients per prescription using the DDD methodology

The most popular measuring unit used in drug consumption research is the DDD, which is used to assess drug consumption or prescribing (WHO, 2007). Table 3-7 indicates the prescribing of buprenorphine, codeine, dihydrocodeine, fentanyl, tramadol and morphine from 2011 to 2017 as the DDD per 1 000 inhabitants/day.

Figures 3-2 to 3-6 illustrate the results of the joinpoint regression analysis used to detect changes over time based on the values in Table 3-7.

Table 3-7: Prescribing of active pharmaceutical ingredients in DDD per 1 000 inhabitants/day

	DDD per 1 000 inhabitants/day (mg)						
	2011	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
Buprenorphine	0.006	0.012	0.039	0.072	0.476	0.083	0.078
Codeine	0.002	0.001	0.001	0.002	0.001	0.001	0.001
Dihydrocodeine	0.009	0.010	0.004	0.009	0.009	0.006	0.004
Fentanyl	0.487	0.441	0.456	0.444	0.362	0.348	0.295
Morphine	0.129	0.174	0.173	0.177	0.184	0.153	0.188
Tramadol	0.103	0.102	0.074	0.084	0.077	0.075	0.087

Figure 3-2 illustrates the change in the DDD/1 000 inhabitants per day for buprenorphine from 2011 to 2017, as determined by joinpoint analysis. Prescribing of buprenorphine in DDD/1 000 inhabitants per day increased from 2011 to 2015, with an annual percentage change (APC) of 172.6 (95% CI: 101.3, 269.1) ($p = 0.005$). From 2015 to 2017, prescribing decreased with an APC of -53.2 (95% CI: -82.1, 22.1) ($p = 0.076$). The average annual per cent change (AAPC) of buprenorphine was 51.5 (95% CI: 27.5, 80.0) ($p < 0.001$).

Figure 3-3 shows that codeine's overall prescribing in the DDD/1 000 inhabitants per day decreased from 2011 to 2017, with an AAPC of -6.9 (95% CI: -20.8, 9.5) ($p = 0.308$). Similar trends were observed for fentanyl (see Figure 3-4), dihydrocodeine (see Figure 3-5) and tramadol (see Figure 3-6), decreasing from 2011 to 2017 with AAPCs -7.6; 95% CI: -10.7, -4.4) ($p = 0.002$), -9.4; 95% CI: -24.6, 8.9) ($p = 0.226$), and -3.8 (95% CI: -9.4, 2.0) ($p = 0.150$), respectively (Figures 3-4 – 3.6).

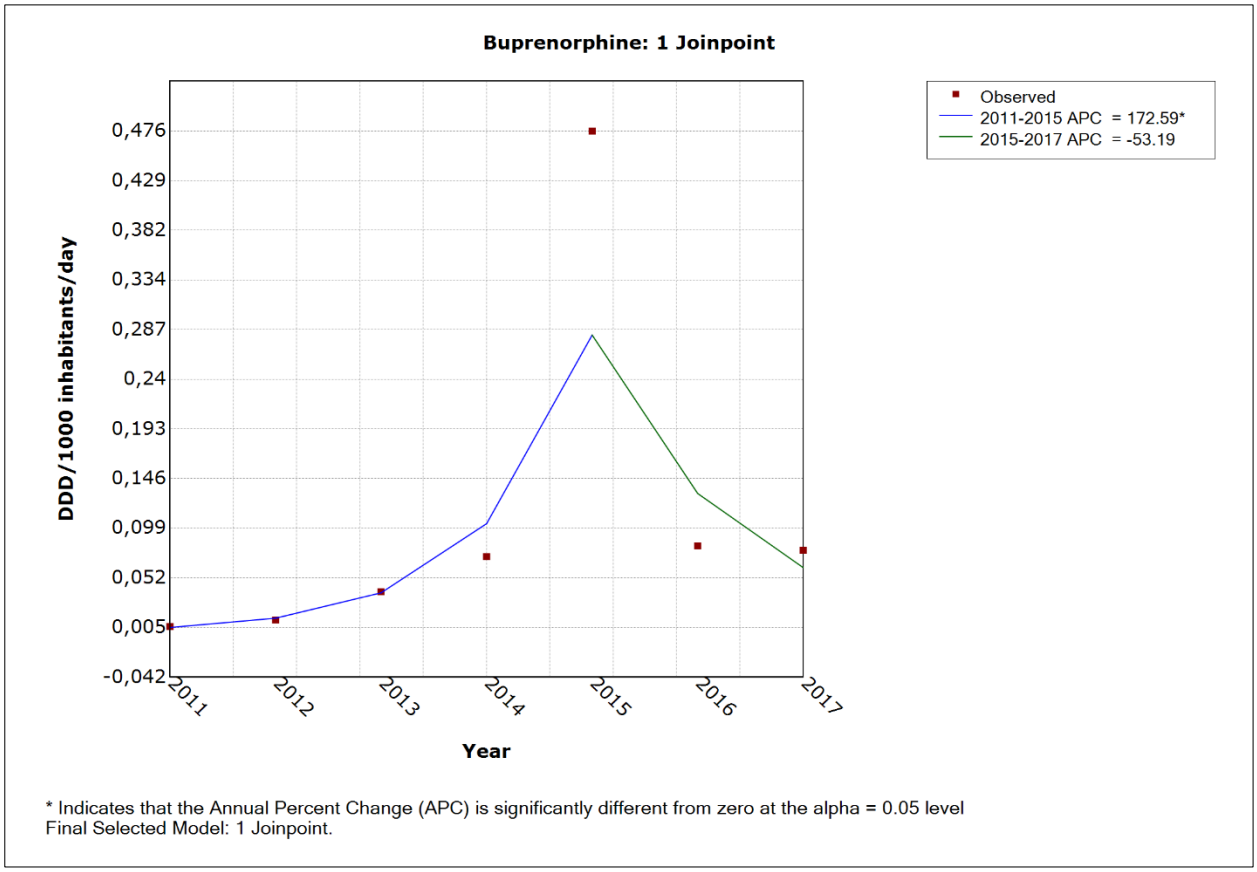

Figure 3-2: The DDD/1 000 inhabitants per day for buprenorphine from 2011 to 2017

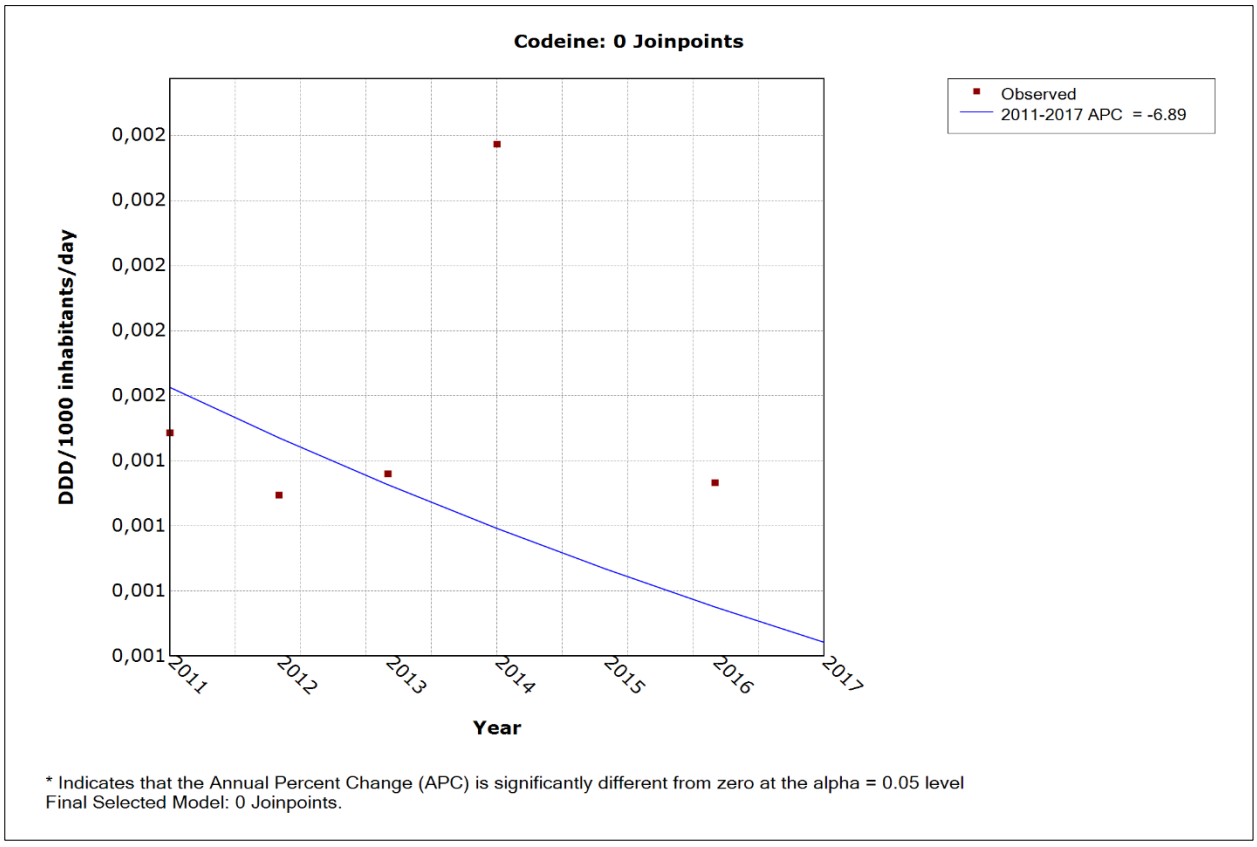

Figure 3-3: The DDD/1 000 inhabitants per day for codeine from 2011 to 2017

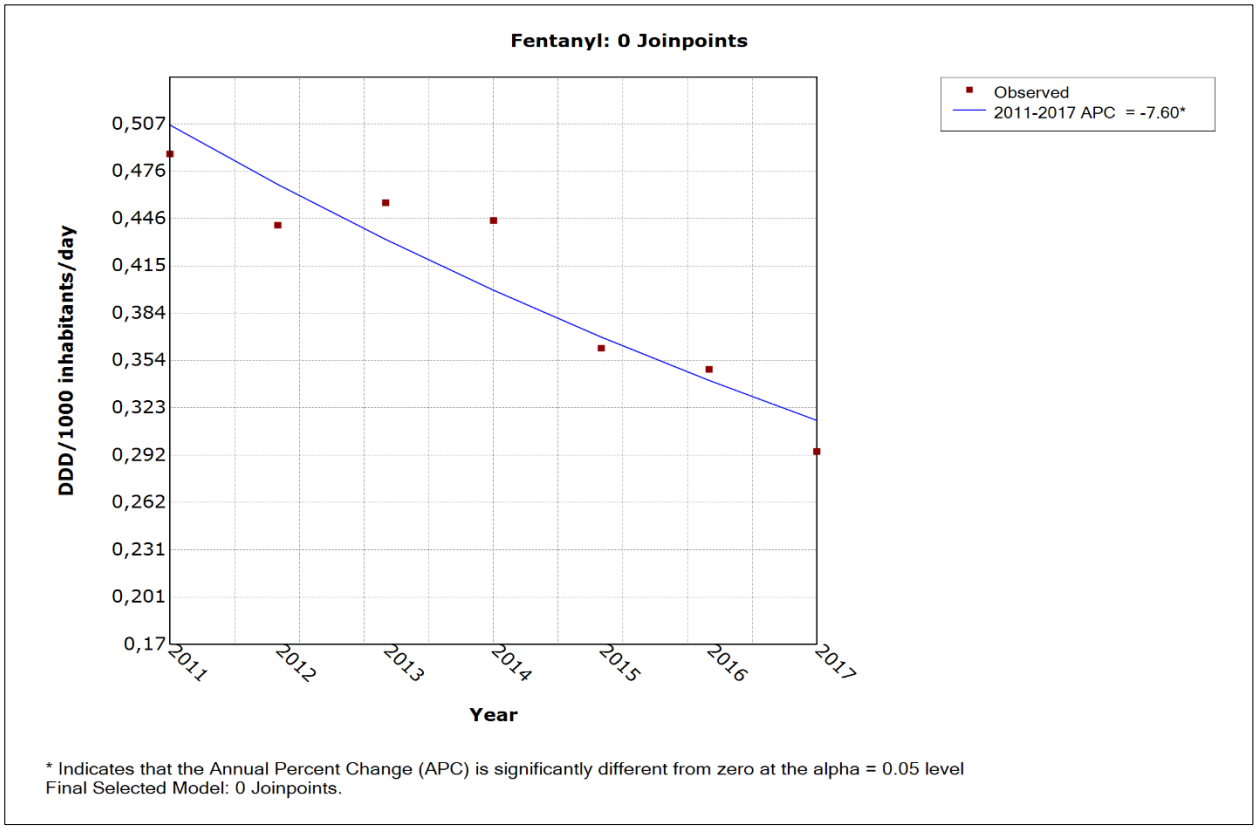

Figure 3-4: The DDD/1 000 inhabitants per day for fentanyl from 2011 to 2017

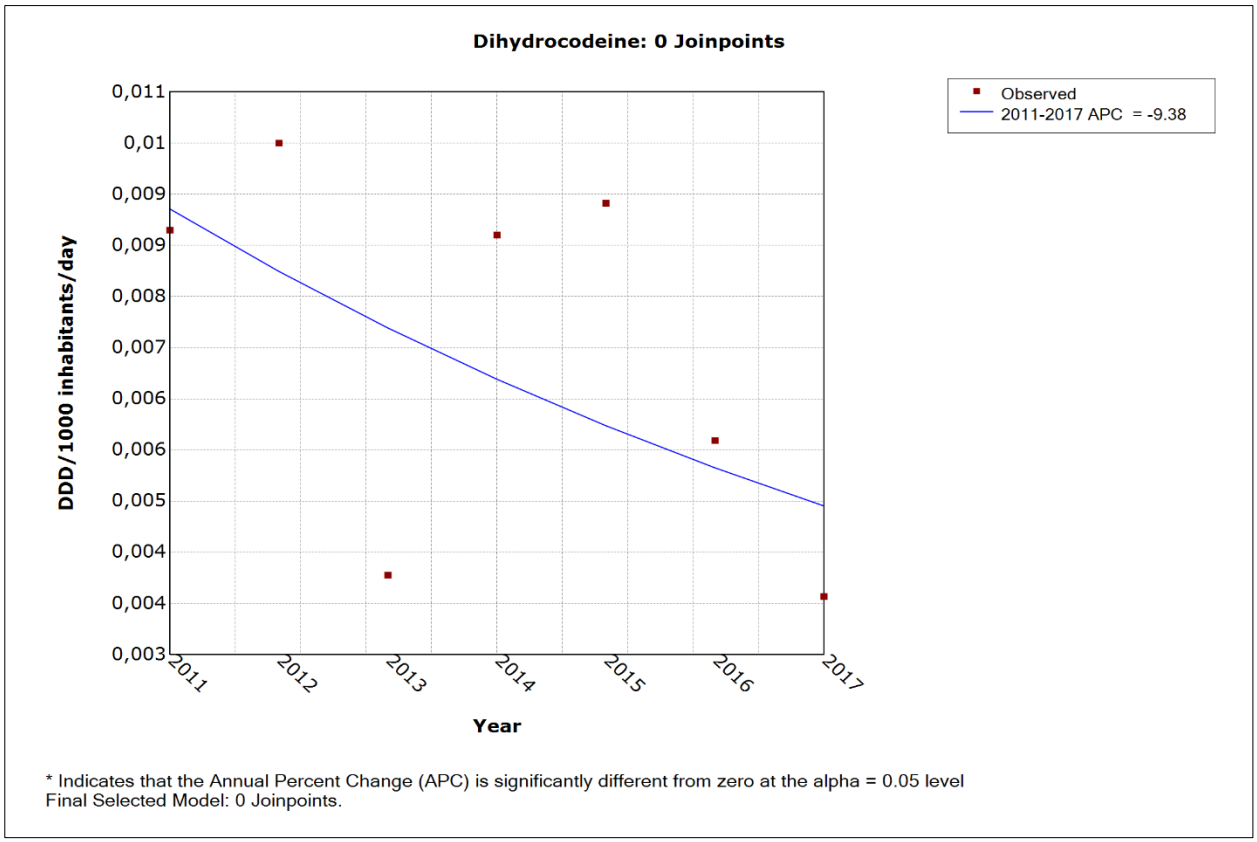

Figure 3-5: The DDD/1 000 inhabitants per day for dihydrocodeine from 2011 to 2017

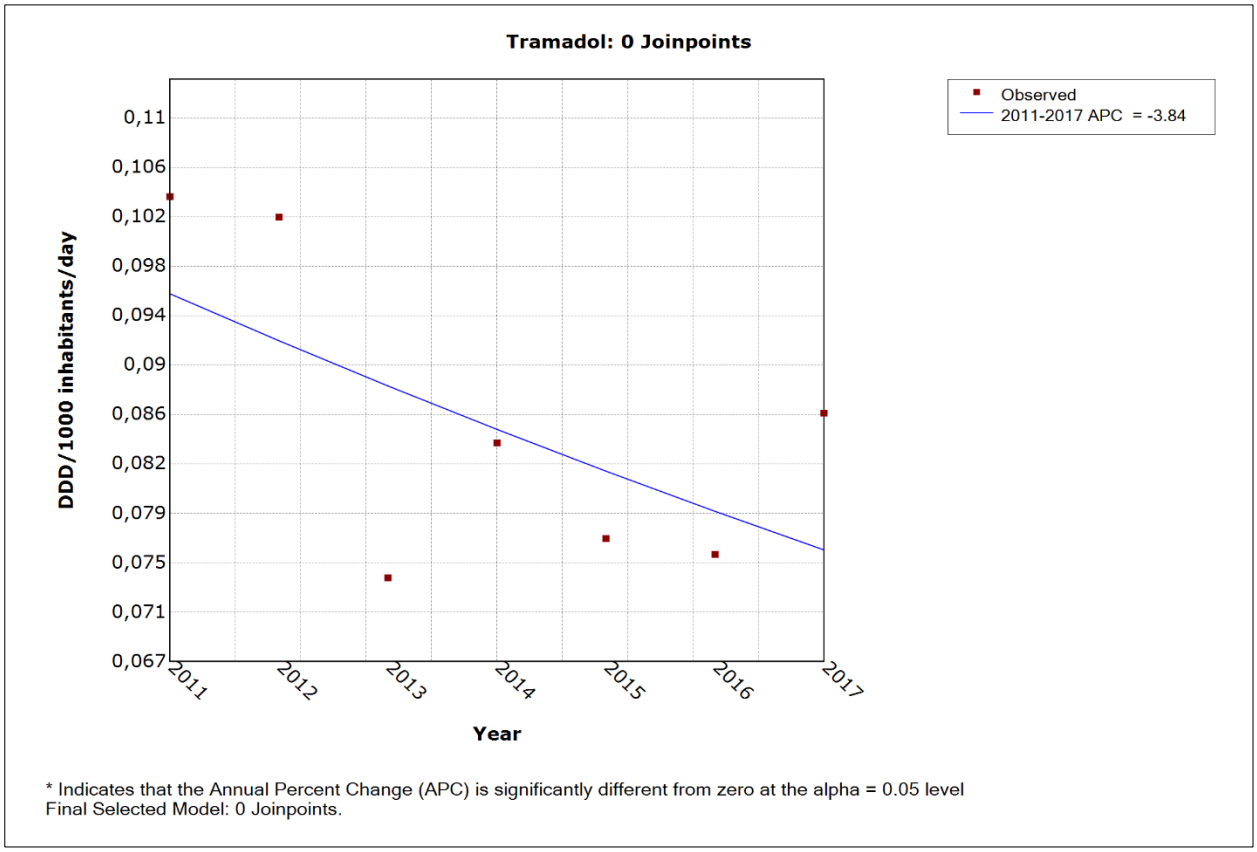

Figure 3-6: The DDD/1 000 inhabitants per day for tramadol from 2011 to 2017

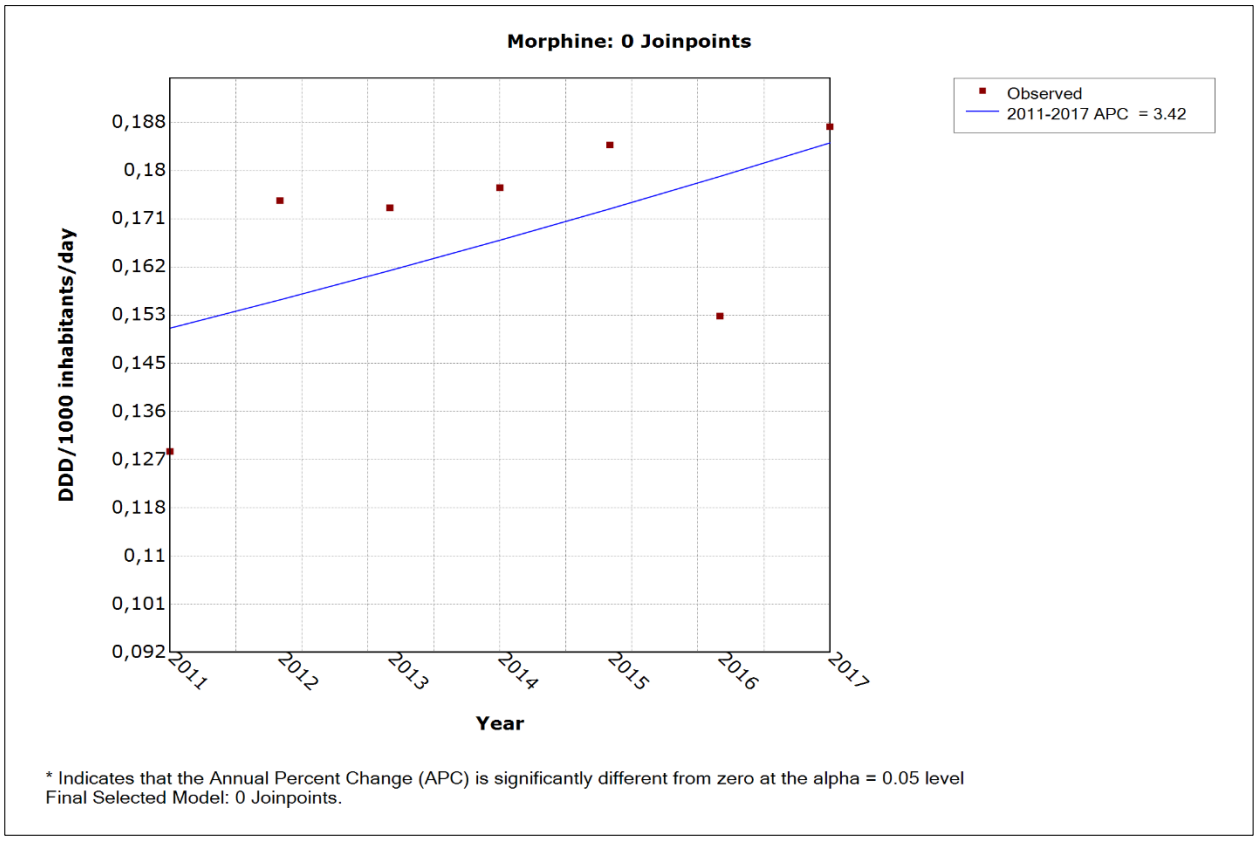

Figure 3-7: The DDD/1 000 inhabitants per day for morphine from 2011 to 2017

Figure 3-7 shows that the amount of morphine (mg) prescribed increased, with an AAPC of 3.4 (95 % CI: -2.5, 9.7) (p = 0.203) from 2011 to 2017.

Combination analgesics are frequently prescribed in South Africa, particularly those that contain paracetamol (acetaminophen) (Truter 2016a:207). There are several justifications for using combination analgesics; the combination of paracetamol and tramadol, in particular, has favourable pharmacodynamic features that combine the fast onset of paracetamol with the long-lasting effects of tramadol (Schug, 2006:S16). This combination provides higher immediate and long-lasting pain relief than either drug alone when used as a single-dose treatment for acute post-operative pain (Pergolizzi *et al*., 2012:331). According to Dhillon (2010:716), this combination effectively reduces pain in adult patients with migraine pain, severe diabetic peripheral neuropathy and acute, subacute or chronic musculoskeletal pain. According to Subedi *et al*. (2019:447), osteoarthritis, lower back pain and fibromyalgia can all be treated effectively over the long term with this combination. Additionally, the combination of paracetamol and tramadol has been found to cause no organ damage related to both selective and non-selective non-steroidal anti-inflammatory medications (Schug, 2006:S16). Based on the South African guideline for using chronic opioid therapy for CNCP (Raff *et al.,* 2014:82), tramadol is regarded as the first-line option for mild-to-moderate pain. In terms of treatment of cancer-related pain, tramadol is regarded as a Step II treatment on the analgesic ladder for neuropathic pain in the country (South African Cancer Pain Working Group, 2015:21). The higher use of tramadol in combination with paracetamol observed in the database is therefore not surprising.

Fentanyl is a high-potency opioid with exceptional potential for misuse (Prekupec *et al*., 2017:256). According to Socias *et al.* (2021), over-prescribing opioids with a high potential for abuse is the primary cause of the opioid overdose crises; however, the situation was worsened by the illegal manufacturing of fentanyl and related analogues, which then became the leading cause of opioid-poisoning fatalities. The opioid crisis led to changes in policies, guidelines and state laws (in the USA), subsequently affecting standard practices for opioid prescription, patient expectations and broader medical culture (Collins *et al*., 2019:97). Consequently, fentanyl prescribing has reduced over the past years. For example, in the USA, the use of fentanyl decreased by 18.4% in pharmacies and 12.2% in hospitals from 2016 to 2017 (Collins *et al*., 2019:100).

The current study indicates the increased prescribing of combination products comprising paracetamol plus codeine and meprobamate over the study period. From 2012 to 2017, this combination was the second most claimed pharmaceutical active ingredient. A previous study on prescribing meprobamate-containing combination analgesics in South Africa (Truter, 2016a:209) showed that about a third of patients received one or more meprobamate-containing analgesics in 2011. Since the early 1950s, meprobamate, a mild tranquiliser, has been used to treat insomnia

and anxiety disorders. It is a by-product of the muscle relaxant, the central active ingredient of which is known as “carisoprodol” (Gorodetsky, 2014:226). The risks associated with the drug exceed the benefits thereof. Meprobamate was subsequently placed under abuse control amendments to the Food, Drug and Cosmetic Act in December 1967, limiting the prescription duration and refills. It was withdrawn from the European market in 2012 (EMA, 2018) and from Canada in 2013 (Government of Canada, 2021).

The amount of morphine and buprenorphine (mg) prescribed both increased over the study period. When it comes to managing moderate to severe pain, whether it be acute or chronic, morphine is recognised as the first choice in the treatment of pain (Murphy *et al*., 2022:2).

3.4.3 Analysis based on chronic pain treatment groups

The results in this section pertain to the changes in prescribing patterns of prescribed opioid analgesics (medicine items) for chronic pain from 1 January 2011 to 31 December 2017, stratified into two treatment groups (i.e., cancer-related and CNCP treatment). The discussion in this section is based on the summary of information in Table 3-8.

3.4.3.1 Patient demographic characteristics and geographic location

The majority of patients who received at least one opioid analgesic during the study period received it in relation to cancer-related pain, reimbursed as oncology benefits. The number of patients receiving opioids for cancer-related pain, as a percentage of all those receiving at least one opioid analgesic, increased progressively from 90.0% (*N* = 2 499) of patients in 2011 to 98.2% (*N* = 5 636) of patients by 2017. According to a recent study by Finestone and Wishnia (2022), cancer is a major and growing public health problem in South Africa, estimated to be more than double in incidence from 2019 to 2023. This increase in incidence may be ascribed to the growing SA population and an ageing population.

Among the patients receiving opioids for cancer-related pain, more than half were female, increasing marginally from 51.5% (*N* = 2 149) in 2011 to 53.1% (*N* = 5 533) in 2017, corresponding to the decrease in the number of male patients over the study period. In contrast, among the patients receiving opioids for CNCP, the majority in 2011 was female (73.6%, *N* = 250), decreasing to 57.3% (*N* = 103) in 2017. Prescribing for male patients increased from 26.4% in 2011 to 42.7% in 2017.

The analysis by age group corresponded with the increase in the number of patients receiving opioids over the study period, in which the number of patients in age groups 3 and 4 (thus patients older than 66 years) receiving treatment for cancer-related pain increased from 45.8% (*N* = 2 249) in 2011 to 52.8% (*N* = 5 533) in 2017. There was a decline in the number of patients between the

ages of 58 and 75 years (age groups 2 and 3) receiving treatment for CNCP, whereas the number of patients older than 75 years increased from 32.4% (*N* = 250) in 2011 to 38.8% in 2017 (*N* = 103).

Analysis based on geographic location showed that most patients receiving opioids for cancer-related pain resided in Gauteng, followed by KwaZulu-Natal and the Western Cape. There were marginal changes in percentage over the study period, with a decline in the number of patients residing in the Eastern Cape, Gauteng and North West. There was a pronounced increase in the number of patients in the Free State who received opioids for CNCP, from 6.4% in 2011 (*N* = 250) to 13.6% (*N* = 103).

Table 3-8: General characteristics of patients receiving opioid analgesics per treatment group

	2011 *n* (%) (*N* = 2 499)	2012 *n* (%) (*N* = 3 079)	2013 *n* (%) (*N* = 2 954)	2014 *n* (%) (*N* = 3 951)	2015 *n* (%) (*N* = 3 871)	2016 *n* (%) (*N* = 3 998)	2017 *n* (%) (*N* = 5 636)
Cancer-related pain, *n* (%)	**2 249 (90.0)**	**2 875 (93.4)**	**2 843 (96.2)**	**3 833 (97.0)**	**3 786 (97.8)**	**3 906 (97.7)**	**5 533 (98.2)**
Gender							
Female	1 159 (51.5)	1 502 (52.2)	1 467 (51.6)	2 089 (54.5)	1 958 (51.7)	2 160 (55.3)	2 938 (53.1)
Male	1 090 (48.5)	1 373 (47.8)	1 376 (48.4)	1 744 (45.5)	1 828 (48.3)	1 746 (44.7)	2 595 (46.9)
Age groups (years)							
Age ≤57	624 (27.8)	879 (30.6)	795 (28.0)	1 020 (26.6)	1 044 (27.6)	1 047 (26.8)	1 448 (26.2)
57> Age ≤66	595 (26.5)	706 (24.6)	736 (25.9)	955 (24.9)	867 (22.9)	884 (22.6)	1 161 (21.0)
66> Age ≤75	519 (23.1)	702 (24.4)	771 (27.1)	1 049 (27.4)	1 063 (28.1)	1 112 (28.5)	1 410 (25.5)
Age >75	511 (22.7)	588 (20.5)	541 (19.0)	809 (21.1)	812 (21.5)	863 (22.1)	1 514 (27.4)
Province							
Eastern Cape	86 (3.8)	122 (4.2)	85 (3.0)	135 (3.5)	115 (3.0)	123 (3.2)	206 (3.7)
Free State	114 (5.1)	133 (4.6)	222 (7.8)	234 (6.1)	281 (7.4)	239 (6.1)	356 (6.4)
Gauteng	973 (43.3)	1 298 (45.2)	1 126 (39.6)	1 493 (39.0)	1 383 (36.5)	1 585 (40.6)	2 162 (39.1)
Kwazulu-Natal	465 (20.7)	536 (18.6)	639 (22.5)	971 (25.3)	951 (25.1)	912 (23.4)	1 167 (21.1)
Limpopo	27 (1.2)	51 (1.8)	58 (2.0)	69 (1.8)	49 (1.3)	55 (1.4)	79 (1.4)
Mpumalanga	57 (2.5)	108 (3.8)	103 (3.6)	138 (3.6)	154 (4.1)	131 (3.4)	190 (3.4)
North West	78 (3.5)	88 (3.1)	67 (2.4)	85 (2.2)	85 (2.3)	84 (2.2)	124 (2.2)
Northern Cape	22 (1.0)	31 (1.1)	42 (1.5)	62 (1.6)	64 (1.7)	75 (1.9)	97 (1.8)
Western Cape	417 (18.5)	484 (16.8)	494 (17.4)	635 (16.6)	684 (18.1)	702 (18.0)	1133 (20.5)
Not indicated	10 (0.4)	24 (0.8)	7 (0.3)	11 (0.3)	20 (0.5)	0	19 (0.3)

	2011 *n* (%) (*N* = 2 499)	2012 *n* (%) (*N* = 3 079)	2013 *n* (%) (*N* = 2 954)	2014 *n* (%) (*N* = 3 951)	2015 *n* (%) (*N* = 3 871)	2016 *n* (%) (*N* = 3 998)	2017 *n* (%) (*N* = 5 636)
Non-cancer-related pain, *n* (%)	**250 (10)**	**204 (6.6)**	**111 (3.8)**	**118 (3.0)**	**85 (2.2)**	**92 (2.3)**	**103 (1.8)**
Gender							
Female	184 (73.6)	140 (68.6)	72 (64.9)	69 (58.5)	50 (58.8)	64 (69.6)	59 (57.3)
Male	66 (26.4)	64 (31.4)	39 (35.1)	49 (41.5)	35 (41.2)	28 (30.4)	44 (42.7)
Age groups (years)							
Age ≤57	54 (21.6)	69 (33.8)	48 (43.2)	40 (33.9)	22 (25.9)	24 (26.1)	28 (27.2)
57> Age ≤66	56 (22.4)	42 (20.6)	21 (18.9)	34 (28.8)	32 (37.7)	36 (39.1)	20 (19.4)
66> Age ≤75	59 (23.6)	34 (16.7)	19 (17.1)	18 (15.3)	14 (16.5)	6 (6.5)	15 (14.6)
Age >75	81 (32.4)	59 (28.9)	23 (20.7)	26 (22.0)	17 (20.0)	26 (28.3)	40 (38.8)
Province							
Eastern Cape	14 (5.6)	9 (4.4)	8 (7.2)	4 (3.4)	3 (3.5)	1 (1.1)	4 (3.9)
Free State	16 (6.4)	11 (5.4)	9 (8.1)	8 (6.8)	4 (4.7)	5 (5.4)	14 (13.6)
Gauteng	117 (46.8)	101 (49.5)	54 (48.7)	53 (44.9)	47 (55.3)	46 (50.0)	48 (46.6)
Kwazulu-Natal	28 (11.2)	27 (13.2)	11 (9.9)	13 (11.0)	3 (3.5)	8 (8.7)	8 (7.8)
Limpopo	10 (4.0)	7 (3.4)	4 (3.6)	3 (2.5)	2 (2.4)	3 (3.3)	1 (1.0)
Mpumalanga	6 (2.4)	5 (2.5)	5 (4.5)	8 (6.8)	7 (8.2)	5 (5.4)	4 (3.9)
North West	5 (2.0)	10 (4.9)	10 (9.0)	6 (5.1)	6 (7.1)	3 (3.3)	2 (1.9)
Northern Cape	1 (0.4)	2 (1.0)	0	0	1 (1.2)	0	0
Western Cape	51 (20.4)	32 (25.7)	10 (9.0)	22 (18.6)	11 (12.9)	21 (22.8)	21 (20.4)
Not indicated	2 (0.8)	0	0	1 (0.9)	1 (1.2)	0	1 (1.0)

3.4.3.2 Analysis of the number of opioid analgesics, stratified by chronic pain treatment group

3.4.3.2.1 Analysis based on demographic characteristics of the chronic pain treatment groups

Table 3-8 shows that there was a steady increase in the number of opioid analgesic medicine items claimed for cancer-related pain from 81.9% (*N* = 5 797) in 2011 to 96.0% (*N* = 12 018) in 2017, corresponding to a decline in the number of opioid medicine items for CNCP from 18.1% (*N* = 1 049) in 2011 to 4.0% (*N* = 479) in 2017. Marginally more opioid analgesic medicine items were claimed for cancer-related pain for female than male patients over the seven years, with prevalence increasing from 52.9% (*N* = 5 797) in 2011 to 54.2% (*N* = 12 018) in 2017. Most opioid analgesic medicine items for CNCP were also for female patients, decreasing from 73.1% (*N* = 1 049) to 61.4% (*N* = 479) in 2017. The association between treatment groups and gender was statistically but not practically significant ($p < 0.001$, Cramér's $V < 0.2$).

Claims for opioid analgesics for cancer-related pain among patients below the age of 57 years and between 57 and 66 years decreased from 26.3% to 24.0% and 25.7% to 20.6% in 2011 (*N* = 5 797) and 2017 (*N* = 12 018) respectively. Opioid analgesic medicine item claims for patients between the ages of 66 and 75 years and those older than 75 years increased from 23.0% and 25.0% in 2011 to 27.0% and 28.4% in 2017, respectively. In contrast, as a percentage of the total number of medicine item claims in the study population each year, the claims of opioid analgesics for CNCP were similar in 2017 and 2011 at 21.9%. Claims for patients between the ages of 66 and 75 years decreased from 21.5% in 2011 (*N* = 5 797) to 14.8% in 2017 (*N* = 12 018). There was no practically significant association between age and treatment group ($p < 0.001$, Cramér's $V < 0.1$).

Between 30% and 50% of patients with cancer might feel moderate-to-severe pain, making pain one of the most prevalent symptoms linked to cancer (Van den Beuken-van Everdingen *et al*., 2016:1079). Although pain can manifest at any stage of the disease, it usually gets worse and more frequent as the cancer progresses (Pich, 2018). Because of their reliability, dependability, ease of titration, safety, and effectiveness for all types of pain, opioids are frequently used to treat cancer-related pain, namely somatic, visceral and neuropathic pain (Mercadante, 2022:1361). Opioids, therefore, play a pivotal role in managing pain in cancer patients and CNCP (Dzierżanowski & Ciałkowska-Rysz, 2017:775, Pisanu *et al*., 2019:1).

3.4.3.2.2 Analysis based on geographic characteristics of the chronic pain treatment groups

Over the treatment period from 2011–2017, opioid analgesic was highest in Gauteng, Kwa-Zulu-Natal and the Western Cape province (refer to Table 3-8). Table 3-9 furthermore shows that the number of claims for opioid analgesics for the treatment of cancer-related pain decreased in

Gauteng from 42.1% (*N* = 2 514) in 2011 to 39.4% (*N* = 11 539) in 2017, as well as in KwaZulu-Natal (21.6% vs 19.1%), Limpopo (1.8% vs 1.4%), and North West (2.9% vs 1.8%). In contrast, the number of claims for opioid analgesics for cancer-related pain increased from 2011 to 2017 respectively, in the Eastern Cape (3.1% vs 3.4%), Free State (5.7% vs 8.0%), Mpumalanga (2.2% vs 3.8%), Northern Cape (0.8% vs 1.3%) and the Western Cape (19.7% vs 21.5%).

As a percentage of the total number of opioid analgesics items claimed for treatment for CNCP in 2011 (*N* = 4 748) and 2017 (*N* = 11 539), increases were observed in the Free State (8.4% vs 15.0%) and Gauteng (40.9% vs 44.1%). A decrease was observed in the Eastern Cape (6.5% vs 5.9%), KwaZulu-Natal (11.5% vs 7.3%), Limpopo (3.8% vs 2.7%), Mpumalanga (3.3% vs 2.7%) and North West (3.7% vs 0.6%).

Table 3-9: Prescribed opioid analgesic medicine items related to cancer pain compared to non-cancer-related pain

	2011 *n* (%) (*N* = 5 797)	2012 *n* (%) (*N* = 6 423)	2013 *n* (%) (*N* = 6 330)	2014 *n* (%) (*N* = 8 486)	2015 *n* (%) (*N* = 8 228)	2016 *n* (%) (*N* = 8 404)	2017 *n* (%) (*N* = 12 018)
Cancer-related pain, *n* (%)#	**4 748 (81.9)**	**5 642 (87.8)**	**5 825 (92.0)**	**7 958 (93.8)**	**7 813 (95.0)**	**7 965 (94.8)**	**11 539 (96.0)**
Gender*							
Female	2 514 (52.9)	2 912 (51.6)	3 033 (52.1)	4 449 (55.9)	4 098 (52.5)	4 546 (57.1)	6 250 (54.2)
Male	2 234 (47.1)	2 730 (48.4)	2 792 (47.9)	3 509 (44.1)	3 715 (47.6)	3 419 (42.9)	5 289 (45.8)
Age group (yr), *n* (%)*							
Age ≤57	1 248 (26.3)	1 469 (26.0)	1 446 (24.8)	1 974 (24.8)	1 971 (25.2)	2 005 (25.2)	2 765 (24.0)
57> Age ≤66	1 220 (25.7)	1 414 (25.1)	1 518 (26.1)	1 892 (23.8)	1 851 (23.7)	1 793 (22.5)	2 379 (20.6)
66> Age ≤75	1 092 (23.0)	1 530 (27.1)	1 678 (28.8)	2 294 (28.8)	2 232 (28.6)	2 298 (28.9)	3 118 (27.0)
Age >75	1 188 (25.0)	1 229 (21.8)	1 183 (20.3)	1 798 (22.6)	1 759 (22.5)	1 869 (23.5)	3 277 (28.4)
Provinces*							
Eastern Cape	145 (3.1)	230 (4.1)	139 (2.4)	247 (3.1)	225 (2.9)	242 (3.0)	397 (3.4)
Free State	270 (5.7)	261 (4.6)	496 (8.5)	488 (6.1)	539 (6.9)	519 (6.5)	921 (8.0)
Gauteng	1 997 (42.1)	2 484 (44.0)	2 279 (39.1)	3 239 (40.7)	2 940 (37.6)	3 323 (41.7)	4 542 (39.4)
KwaZulu-Natal	1 025 (21.6)	1 073 (19.0)	1 216 (20.9)	1 967 (24.7)	1 930 (24.7)	1 729 (21.7)	2 204 (19.1)
Limpopo	86 (1.8)	90 (1.6)	94 (1.6)	155 (2.0)	82 (1.1)	107 (1.3)	158 (1.4)
Mpumalanga	103 (2.2)	177 (3.1)	219 (3.8)	291 (3.7)	320 (4.1)	288 (3.6)	441 (3.8)
North West	136 (2.9)	132 (2.3)	130 (0.5)	144 (1.8)	158 (2.0)	162 (2.0)	209 (1.8)
Northern Cape	38 (0.8)	45 (0.8)	78 (0.1)	146 (1.8)	113 (1.5)	135 (1.7)	149 (1.3)
Western Cape	935 (19.7)	1 112 (19.7)	1 167 (20.0)	1 266 (15.9)	1 480 (18.9)	1 460 (18.3)	2 479 (21.5)
Not indicated	13 (0.3)	38 (0.7)	7 (0.1)	15 (0.2)	26 (0.3)	0 (0.0)	39 (0.3)

	2011 *n* (%) (*N* = 5 797)	2012 *n* (%) (*N* = 6 423)	2013 *n* (%) (*N* = 6 330)	2014 *n* (%) (*N* = 8 486)	2015 *n* (%) (*N* = 8 228)	2016 *n* (%) (*N* = 8 404)	2017 *n* (%) (*N* = 12 018)
Non-cancer-related pain, *n* (%)#	**1 049 (18.1)**	**781 (12.2)**	**505 (8.0)**	**528 (6.2)**	**415 (5.0)**	**439 (5.2)**	**479 (4.0)**
Gender†							
Female	767 (73.1)	507 (64.9)	325 (64.4)	323 (61.2)	239 (57.6)	263 (59.9)	294 (61.4)
Male	282 (26.9)	274 (35.1)	108 (21.4)	205 (38.8)	176 (42.4)	176 (40.1)	186 (38.8)
Age group (yr), *n* (%)†							
Age ≤57	230 (21.9)	280 (35.9)	198 (39.2)	203 (38.5)	87 (21.0)	94 (21.4)	105 (21.9)
57> Age ≤66	216 (20.6)	195 (25.0)	111 (22.0)	122 (23.1)	182 (43.9)	183 (41.7)	121 (25.3)
66> Age ≤75	226 (21.5)	119 (15.2)	54 (10.7)	64 (12.1)	39 (9.4)	35 (8.0)	71 (14.8)
Age >75	377 (35.9)	187 (23.9)	142 (28.1)	139 (26.3)	107 (25.8)	127 (28.9)	182 (38.0)
Provinces†							
Eastern Cape	68 (6.5)	49 (6.3)	38 (7.5)	19 (3.6)	12 (2.9)	13 (3.0)	28 (5.9)
Free State	88 (8.4)	52 (6.7)	39 (7.7)	54 (10.2)	34 (8.2)	39 (8.9)	72 (15.0)
Gauteng	429 (40.9)	367 (47.0)	239 (47.3)	242 (45.8)	243 (58.6)	208 (47.4)	211 (44.1)
KwaZulu-Natal	116 (11.5)	110 (14.1)	41 (8.1)	66 (12.5)	24 (5.8)	43 (9.8)	35 (7.3)
Limpopo	40 (3.8)	38 (4.9)	16 (3.2)	6 (1.1)	12 (2.9)	18 (4.1)	13 (2.7)
Mpumalanga	35 (3.3)	32 (4.1)	22 (4.4)	36 (6.8)	18 (4.3)	34 (7.7)	13 (2.7)
North West	39 (3.7)	32 (4.1)	61 (12.1)	18 (3.4)	22 (5.3)	7 (1.6)	3 (0.6)
Northern Cape	5 (0.5)	4 (0.5)	0 (0.00)	0 (0.00)	3 (0.7)	0 (0.00)	0 (0.00)
Western Cape	223 (21.3)	97 (12.4)	49 (9.7)	78 (14.8)	46 (11.1)	77 (17.5)	103 (21.5)
Not indicated	6 (0.6)	0 (0.00)	0 (0.00)	9 (1.7)	1 (0.2)	-	1 (0.2)

#Percentage calculated using the total number of medicine items per study year in the dataset (Table 3-4) as the denominator. *Percentage calculated using the total number of opioid analgesics claimed for cancer-related pain per year, as the denominator. †Percentage calculated using the total number of opioid analgesics claimed for non-cancer-related pain per year, as the denominator

3.5 General analysis of opioid analgesic medicine items based on treatment duration and the relationship with depression

For this analysis, all treatment episodes were grouped into short-term (daily supply < 90 days) or long-term (total supply ≥ 90 days) duration. Treatment episodes were then analysed to determine the relationship between depression and opioid analgesic treatment duration, stratified by patient gender and age groups.

Overall, 23 910 treatment episodes were identified, of which most (85.5%, *N* = 23 910) were of short-term duration. No depression was identified in 80.9% (*N* = 23 910) of treatment episodes. Overall, the association between treatment duration and depression was statistically but not practically significant ($p < 0.0001$, Cramér's $V = 0.1997$).

Table 3-10 shows that for the short-term treatment episode group, there were more female than male patients, at 55.6% vs 44.4% (*N* = 20 448), respectively. Although there were more men and women without depression in the short-term duration group, there was no association between treatment duration and depression by gender ($p < 0.0001$, Cramér's $V = 0.1006$). Analysis based on age shows that most of the patients in the short-term treatment episode group were in age group 1, that is, patients aged ≤ 57 years, at 44.9% (*N* = 20 448). There was an equal number of patients with (22.6%) and without depression (22.4%) in this age group. There were no patients in age groups 2–4 in the short-term treatment episode group with depression. The relationship between short-term treatment duration and depression by age group was therefore statistically and practically significant ($p < 0.0001$, Cramér's $V = 0.5940$).

In the long-term treatment duration group, almost all the treatment episodes (99.7%, *N* = 3 462) were for patients without depression. More than half of long-term duration treatment episodes were for female patients (55.3%, *N* = 3 462) and patients in age groups 3 and 4, at 28.6% and 26.0% respectively. There was no association between long-term treatment duration and depression by gender ($p = 0.2661$, Cramér's $V = 0.0189$) or age group ($p = 0.3242$, Cramér's $V = 0.0317$).

Table 3-10: Association between depression and treatment duration, stratified by age and gender

	Short-term duration treatment episodes (*N* = 20 448)					**Long-term duration treatment episodes (*N* = 3 462)**				
	Total *n* (%)	**Without depression, *n* (%)**	**Depression, *n* (%)**	**p-value**	**Cramérs *V***	**Total *n* (%)**	**Without depression, *n* (%)**	**Depression, *n* (%)**	**p-value**	**Cramérs *V***
Treatment episodes	20 448 (100.0)	15 878 (77.6)	4 570 (22.4)			3 462 (100.0)	3 461 (99.7)	1 (0.03)		
Gender				<0.0001	0.1006				0.2661	0.0189
Female	11 370 (55.6)	8 403 (41.1)	2 967 (14.5)			1 914 (55.3)	1 914 (53.7)	0 (0.0)		
Male	9 078 (44.4)	7 475 (36.6)	1 603 (7.8)			1 548 (44.7)	1 547 (44.7)	1 (0.03)		
Age group, yr, *n* (%)				<0.0001	0.5940				0.3242	0.0317
Age ≤ 57	9 187 (44.9)	4 617 (22.6)	4 570 (22.4)			774 (22.4)	773 (22.3)	1 (0.03)		
57 > Age ≤ 66	3 696 (18.1)	3 696 (18.1)	0 (0.0)			797 (23.0)	797 (23.0)	0 (0.00)		
66 > Age ≤ 75	4 052 (19.8)	4 052 (19.8)	0 (0.00)			991 (28.6)	991 (28.6)	0 (0.00)		
Age >75	3 513 (17.2)	3 513 (17.2)	0 (0.0)			900 (26.0)	990 (26.0)	0 (0.00)		

Up to 54% of patients in developed countries with chronic pain might have comorbid depression (Feingold *et al.,* 2018:293). Previous studies have shown that patients with comorbid pain and depression are likely to be prescribed opioids (Batkis *et al.*, 2010:16; Bruffaerts *et al.,* 2015:43; Fischer *et al.,* 2016:332; Goesling *et al.,* 2015:1433; Rosoff *et al*., 2021:157; Scherrer *et al*., 2014:491; Scherrer *et al*., 2016:110). According to Scherrer *et al.* (2017:125), long-term use of prescribed opioids is associated with new depressive episodes among patients who use them for more than 90–180 days or more than 180 days (see section 1.7.1). In contrast to these international studies, the present study found that the majority of patients (80.9%, *N* = 23 910) did not have a diagnosis of depression during the study period. Among those with the diagnosis (*n* = 4 571), only one received long-term treatment with opioids. The association between depression and long-term treatment with opioids was therefore not significant.

According to Beebe and Utley (2011:e13), women are more likely than men to have depression and chronic pain concurrently. In contrast, the analysis of the present study showed that in contrast, only one male patient with depression received long-term opioid treatment. Among patients receiving short-term treatment, there were; however, there were more female than male patients, at 55.6% vs 44.4% (*N* = 20 448), respectively. The association between depression and gender in this treatment duration group was statistically but not practically significant.

3.6 Chapter summary

The findings and analysis from the study's empirical inquiry phase are presented in this chapter. When analysing the data collection, information from the PBM Company was taken into consideration from a broad perspective, with prescribed opioid analgesics stratified by chronic pain treatment groups and the relationship between depression and treatment duration and stratified by gender and age. The following (last) chapter concludes the study and contains the findings, any limitations, and suggestions for further research.

CHAPTER 4 CONCLUSIONS AND RECOMMENDATIONS

4.1 Introduction

Conclusions relating to the literature and the empirical goals listed in Chapter 1 are discussed in this chapter. The study's weaknesses, areas of strength and areas of concern are also listed, and suggestions are made for further research.

4.2 Literature objectives

The conclusions regarding the literature objectives (refer to section 1.3.2) are presented in paragraphs 4.2.1 to 4.2.5.

4.2.1 What pain, in particular, chronic pain, entails

This literature objective was achieved in sections 2.2 and 2.2.5. Chronic pain was explained by providing broad definitions of pain, related terminology and classifications of pain.

Pain was categorised according to its physiology, intensity, temporal features, the type of tissue affected and syndrome as follows (IASP, 2018):

- Pain physiology (nociceptive, neuropathic, inflammatory) is when the somatosensory nerve system, which includes the bones, joints and muscles, is damaged or afflicted by diseases to produce neuropathic pain (Giordano, 2006:1-2; Lehne, 2010:287; Mann & Carr, 2006:9). Neuropathic, functional and nociceptive pain are all forms of chronic pain that continue for more than three to six months (Fornasari, 2012:46). Neuropathic pain, which is intermittent and linked to peripheral nervous system damage or pathological alterations, develops in the central nervous system (CNS) (see section 2.2.1).

- Intensity (mild-moderate-severe; 0–10 numeric pain rating scale) was described as the intensity of pain which differs from one patient to the next over time, depending on the individual. Patients can describe pain differently due to some pathological condition (e.g., on a scale of 0 to 10, where 0 signifies no pain and 10 is the worst pain). Chronic non-cancer pain, in particular, ranges from mild to moderate to severe (see section 2.2.2).

- The type of tissues affected by pain, such as skin, muscles, viscera, joints, tendons and bones, are described as nerves that are compressed or pain signals that are processed improperly. Neuropathic pain affects the brain and spinal cord. The peripheral CNS and any process that damages nerves, such as metabolic, traumatic, infectious, ischemic, toxic or immune-mediated pathological diseases, might be affected by neuropathic pain. Visceral

pain, often referred to as “deep somatic pain”, affects internal organs such as the liver, pancreas, pleura and peritoneum. In contrast, nociceptive pain, also known as “deep somatic pain”, affects the bones, joints, muscles and connective tissue (see section 2.2.3).

- Syndromes such as cancer, fibromyalgia, migraine, and others are when cancer patients might experience neuropathic pain due to tumour-associated neural compression, directly or indirectly, as a result of cancer treatment, such as surgery or chemotherapy or concurrently with non-cancer-related neuropathic pain. The pain associated with fibromyalgia syndrome includes afferent enhancement of peripheral stimuli, particularly of the nociceptive variety, as well as other neuropathic symptoms such as exhaustion and changes in cognition and mood. Migraine is the most common chronic headache. It occurs mostly during middle age and is less reported in teenagers and patients older than 60 years. It is caused by psychosocial stress, depression, anxiety, inadequate or too much sleep, strong smells, atmospheric pressure and humoral factors such as abnormal blood glucose and gonadotrophic hormones (Bartleson & Cutrer, 2012:38) (see section 2.2.4).

- Pain based on time course/duration was described as acute pain that follows once injured and does not last long, typically for less than 30 days, whereas chronic pain can start as acute pain and endure for a long time or recur due to the persistence of noxious stimuli or the recurring worsening of an injury (see section 2.2.5).

Chronic pain is defined as ongoing or recurrent pain that lasts throughout the typical recovery period following an event or illness, that is, beyond three months (see section 2.2.5).

Chronic pain has been categorised by the WHO (2012) as follows: (1) chronic primary pain affecting one or more anatomical parts of the body; (2) chronic cancer pain; (3) chronic posttraumatic and postsurgical pain, which occurs in three months after surgery or tissue injury, including tissue trauma or burns; (4) chronic neuropathic pain, which is caused by a disease of the somatosensory nervous system; (5) chronic headache and orofacial pain occurring 50% of the days during three months; (6) chronic visceral pain is pain which originates in the internal organs in the head and neck regions, and abdominal, thoracic and pelvic cavities; and (7) chronic musculoskeletal pain arising as part of a disease process directly affecting bone(s), joint(s), muscle(s), or related soft tissue(s) (see section 2.2.5).

Literature has shown neuropathic, functional and nociceptive pain are all forms of chronic pain that continue for more than three months (Fornasari, 2012:46).

The mechanism action for chronic pain is the process known as sensitisation which can be classified into peripheral sensitisation and central sensitisation (Isa & Chetty, 2022:11). Peripheral sensitisation is a result of tissue injury and inflammation, which causes changes in the nerves (Isa

& Chetty, 2022:11). Inflammation occurs after nerve damage within the periphery, which results in the release of a host of endogenous inflammatory mediators, including serotonin, bradykinin, substance P, histamine, ATP, PGE2, thromboxanes, leukotrienes, endocannabinoids, NGF, cytokines (IL6, IL1β, TNFα), chemokines and CGRP (Isa & Chetty, 2022:11). Peripheral sensitisation involves a shift in the activation threshold of nociceptors and an increase of voltage-gated sodium channels (Scholz, 2014:O15). Central sensitisation is a process of dorsal horn neurons reacting to the rising input with heightened excitability (Scholz, 2014:O15). Increased depolarisation leads to the recruitment of N-methyl-D-aspartate (NMDA)-type glutamate receptors. The NMDA and neuropeptide receptor activation produces a sharp increase in intracellular calcium, triggering signalling pathways and gene expression changes that promote a long-term shift in the activity of nociceptive circuits (see section 2.3).

The literature reviewed in section 2.4 indicated the prevalence of chronic pain. It can be concluded from this section that chronic pain is among the most prevalent debilitating conditions worldwide. The prevalence of chronic pain is high in low- and middle-income groups. Chronic pain, such as lower back pain, rheumatoid arthritis, fibromyalgia and migraine, affects people in both developed and developing countries and is more prevalent among patients 65 years or older. Chronic pain is more prevalent among women than among their male counterparts. Lower back pain is more prevalent in pregnant women than in non-pregnant women. Headaches are more common among individuals with depression or anxiety disorders than patients without neuropsychiatric disorders.

Chronic pain, in particular, CNCP, can be managed holistically using non-pharmacological and pharmacological methods. The literature reviewed in section 2.6 indicates the following non-pharmacological methods of treating pain, namely: 1) physical medicine is used to treat conditions such as headaches, including migraine, lower back pain and fibromyalgia (De Goffau *et al.,* 2017:615; Toldo *et al.,* 2017:509); 2) behavioural therapy, which is focused on the patient's environmental, behavioural and mental state this method assists patients with relaxation, problem-solving and controlled-breathing exercises; and 3) neuromodulation therapy, which is a technology that is used to directly activate nerves by delivering electrical or pharmaceutical agents to the targeted area of pain, thereby interrupting the pain signal at the point of stimulation, thus stopping the pain from reaching the brain. In addition, Interventional therapy, a procedure in which injections are inserted through the skin and directed to the site of pain using an imaging technique, and after that inserting medicine, is a feasible therapy option for individuals who did not react to conservative treatment, providing pain relief for up to three months. Surgical treatment or lumbar total disk replacement can be used to alleviate lower back discomfort brought on by degenerative disc degeneration (see section 2.5).

Chronic non-cancer pain can be treated by various classes of medicines, such as NSAIDs, antidepressants, anti-epileptics and opioid analgesics (see section 2.5.6).

4.2.2 The role of opioid analgesics in chronic pain treatment

The literature on the role of opioid analgesics in the treatment of chronic pain was reviewed in section 2.6. It can be concluded that opioid analgesics are used in the treatment of mild, moderate and severe pain management when other analgesics are not able to provide pain relief.

Opioid analgesics can be either natural or synthetic. They are classified into two groups: weak opioids and potent opioid analgesics (Ward, 2015:11). Weak opioids are used to treat mild to moderate pain and produce fewer analgesic effects, such as respiratory depression and sedation (Asturias-Arribas *et al.,* 2014:315) than the strong opioids which are used to treat severe pain, such as postoperative pain, terminal cancer and pain after trauma or injury (Gatoulis *et al.,* 2012:139; Kashkin *et al.,* 2018:91).

4.2.3 Opioids as a pharmacological group of pain medication

Opioids are divided into groups based on their mechanism of action: mu-agonists, partial agonists and mixed agonist-antagonists (Ward, 2015:11). Mu-agonists bind to mu-opioid receptors found in the brain stem, ventricles and medial thalamus (Trescot, 2016:45). Examples of mu-opioid agonists are codeine, dihydrocodeine and tramadol (Trescot, 2016:45). Agonist-antagonists bind to the kappa-opioid receptors, which are found in the limbic system, brain stem and spinal cord. Examples are pethidine, hydromorphone, oxycodone and morphine (Trescot, 2016:46; Ward, 2015:12). Partial agonists, such as buprenorphine and methadone, have limited use as an analgesic and are used for patients with opioid addiction (Gonzalez-Saiz *et al.,* 2017:127; Haasen *et al.,* 2017:23; Haber *et al.,* 2017:132; Tsai & Huang, 2017:46).

The drug-drug interactions involving opioid analgesics were listed in section 2.6.5. A total of 86% of the drug-drug interactions occur in the liver through the cytochrome (CYP) 450 enzyme (Ranchon *et al.*, 2015:190). Furthermore, opioid analgesics have acute effects associated with single or continuous use for a short period, namely temporary constipation, loss of appetite, decreased body temperature and urinary retention. Tolerance and weight loss are chronic effects of the continuous use of opioid analgesics for an extended period (Khademi *et al.,* 2016:872). Other side effects associated with the use of opioids are nausea, vomiting, respiratory depression and sedation (Benyamin *et al.,* 2008:S106; Porreca & Ossipov, 2009:655; Shang & Filizola, 2015:206). A more severe side effect associated with increased usage of opioids is a hormonal change (Taylor & Erb, 2016:23). Opioid analgesic use may increase pain sensitivity (hyperalgesia) (Arout *et al.*, 2015:465). In individuals receiving replacement therapy for opioid dependence, methadone in therapeutic doses can potentially cause ventricular arrhythmias, including *Torsades de Pointes* tachycardia, which can result in sudden cardiac death (Lusetti *et al.,* 2016:80) (see section 2.6.4). Opioids such as codeine and tramadol should be used cautiously

because some patients with poor metabolisms might be at high risk due to high systemic concentrations of active ingredients (Brennan, 2012:S16).

4.2.4 Regulatory policies and guidelines on opioid prescribing worldwide

It is evident from the literature that guidelines for treating chronic pain are well-established in the USA, UK, Canada and South Africa, with similar methods for managing chronic non-cancer pain. The guidelines indicate that opioids are not recommended as first-line treatment for CNCP (Chueng *et al*., 2014:401); however, should doctors decide to use them, close monitoring of patients is required for non-responsiveness, adverse effects or abnormal behaviour. Buprenorphine and methadone are regulated under the International Regulatory Framework, according to which nations have to comply with international regulations, such as the Convention on Narcotic Drugs, 1961 (as revised in the 1972 protocol) and the Convention on Psychotropic Substances, 1971 (Dowell *et al.*, 2016:1-49; WHO, 2008a) (see section 2.8).

The USA guidelines recommend starting with modest doses when beginning therapy on opioids for maintenance therapy to minimise problems and side effects, particularly when opioid treatment is paired with other modalities such as interventional procedures (see Table 2-6). In Canada, the guidelines strongly recommend non-pharmacological therapy in addition to a non-opioid approach to pharmacotherapy (NOUGG, 2017:15). When patients with CNCP do not respond to this approach, the following steps should be followed: 1) “For patients beginning long-term opioid treatment, the recommendation is to restrict prescribed opioid doses to less than 90 mg of morphine equivalents daily; 2) For patients currently using opioids with persistent pain and/or problematic adverse effects, rotation to other opioids of the same dosage form is recommended; and 3) For patients currently using 90 mg morphine equivalents of opioids per day or more, tapering opioids to the lowest effective dose and considering discontinuation of opioids is also recommended. A formal multidisciplinary programme involving different healthcare professionals is recommended for patients using opioids and experiencing serious challenges in tapering opioids.” The guidelines in the UK favour patient history assessment, including a biopsychosocial assessment, identifying the type of pain, namely neuropathic/nociceptive/mixed and the severity of the pain and functional impact on patients with CNCP to assist in the selection of treatment options. Self-support programmes are recommended at an early stage of pain conditions, whereby healthcare professionals identify local service points to assist the patient with their journey during pain management. Patients using analgesics are evaluated once a year or if their pharmaceutical regimen, pain syndrome or underlying comorbidities change (see section 2.8).

The international guidelines from the USA, Canada and the UK were used to compile the South African guidelines. Opioid analgesics are not recommended as the first-line treatment but are included when the first-line has failed (Raff *et al.,* 2014:81). Medicines and devices in South Africa

are regulated by SAHPRA, as stipulated in the *Medicines and Related Substances Control Act* 101 of 1965. This body aims to ensure that all registered and non-registered medicines comply with all safety, quality and efficacy requirements. Narcotic analgesics are classified as Schedule 6 medicines in South Africa, meaning they are highly controlled and are not easily accessible to the general public Combination analgesics containing codeine or norcodeine containingare regulated in terms of Schedule 2 and Schedule 3 to the Medicines Act, whereas the combination of codeine and meprobamate, and tramadol are classified as Schedule 5 medicines.These types of medicines are controlled by the process of purchasing, manufacturing, handling and dispensing opioids, as stipulated in the *Medicines and Related Substances Control Act* 101 of 1965.

4.2.5 Opioid prescribing patterns internationally and locally

Opioid prescribing patterns worldwide were outlined in Section 2.8 of the literature review. It was found that the prescribing of opioids by doctors in several specialities worldwide has increased over the years. According to Davis *et al.* (2019:166), opioid prescribing in the USA increased by 300% from 1999 to 2015. A study by Miller *et al.* (2020:405) showed that 36.9% of patients aged 20–30- years received prescribed opioids compared to 14.7% of patients below the age of 20 years, with the percentage of opioid prescriptions increasing with age by decade. More than half (57.1%) of these patients were female (Miller *et al.,* 2020:405). Opioids are prescribed mainly for acute postoperative pain for women post-caesarean section (Badreldin *et al.*, 2018:103e1; Bateman *et al.*, 2016:353.e1).

The USA is the leading country in the consumption of opioids among the developed countries, with consumption levels being 43 879 defined daily doses (DDD) per million inhabitants per day in the year 2011 to 2013, followed by Canada with 23 352 defined daily doses (DDD) per million inhabitants per day and Germany, with 22 941 defined daily doses (DDD) per million inhabitants per day in the same years, respectively (Bedard *et al.*, 2017:3676; OECD, 2019).

4.2.6 The association between the regular use of prescribed opioids in patients with chronic pain and psychiatric conditions

Section 2.7 in the literature review covered chronic pain and its associated comorbid conditions, such as neurocognitive alterations, anxiety, insomnia and depression. It can be concluded that patients with chronic pain present with higher rates of depression and anxiety than patients who do not have chronic pain (Ahn *et al.,* 2017:1230; Alavi *et al.,* 2016:4; Alev *et al*., 2017:200; Apfelbacher *et al.,* 2017:49-50; Rajmohan & Kumar, 2013:146; Scherrer *et al.,* 2017:125; Scherrer *et al*., 2016:110-111; Scherrer *et al.,* 2014:491; Smith *et al.,* 2015:73-74).

Depression is characterised by medically unexplained somatic complaints such as back pain, abdominal pain and headaches (Birgenheir *et al.,* 2013:480). Patients with depression might be

misdiagnosed as having somatic symptoms and are prone to be prescribed opioid medications, and these patients might be be using opioid analgesics in high doses, which may lead to unwanted effects, including death (Batkis *et al.,* 2010:16; Dobscha, 2013:1447; Fischer *et al.*, 2016:332; Scheidt *et al.,* 2013:160; Scherrer *et al.*, 2014:491; Scherrer *et al.,* 2016:110).

More attention has been given to depression as a comorbid disease than other psychiatric disorders (Mehraban *et al.*, 2014:203). There is a high prevalence of depression in patients suffering from chronic pain, ranging from 31–40%, and it is proportionately higher among women than men (Munce & Stewart, 2007:394-395; Siebenhuener *et al.,* 2017:6).

It is evident from the literature that chronic pain, in particular headaches, is a leading cause of stress, which negatively induces psychological or physical distress; for example, personnel working in trauma centres might be at increased risk of several mental disorders (Munce & Stewart, 2007:394-395; Siebenhuener *et al.,* 2017:6). Chronic pain in the spine is more common in patients with bipolar disorder compared to the general population (Birgenheir *et al*., 2013:480).

4.3 Conclusions based on findings from the empirical investigation

These sections present the conclusions drawn from the empirical inquiry per the relevant objectives stipulated in section 1.3.2.

4.3.1 General analyses of the central database

In this study, the central database of a South African PBM was used as a data source. An analysis of patients' demographic profiles and geographic locations was performed first to put the results of the empirical investigation into context.

It was observed that this database which is connected to all pharmacies and 98% of all dispensing doctors in South Africa (see section 1.5.2), represented about 10% of the private healthcare sector in the country in 2011, increasing their market share to about 12% in 2017 (see section 3.3.1). The demographic profile of patients on the central database (i.e., age and gender) and geographic location were similar to the profile of beneficiaries covered by medical aid schemes registered in South Africa in terms of the Medical Schemes Act (131 of 1998) from 2011 to 2017, for instance, the majority of patients were below the age of 57 years, female and residing in Gauteng, Western Cape and KwaZulu-Natal (CMS, 2020).

An elementary analysis was performed on the number of prescribed medicine items captured on the central database from 2011 to 2017, stratified by age, gender and geographic area to serve as a baseline for comparison. The following conclusions were drawn from the empirical inquiry described in section 3.3.2:

- It was found that more than half of medicine items claimed annually were for female patients, with prescribing declining marginally by 1.7% from 58.2% (*N* = 18 099 133) in 2011 to 56.5% (*N* = 20 236 841) in 2017 (see section 3.3.2.1). The higher proportion of medicine items claimed for female patients can be ascribed to the higher proportion of women in the central database. However, the decline in the total number of medicine items claimed for women from 2011 to 2017 cannot be explained by the number of patients, as this proportion remained relatively stagnant over the study period. Prescription claim rates per patient are, in general, often greater for female patients than for male patients (Orlando *et al*., 2020:6) (see section 3.3.2.1).
- Analysis based on age group showed that most medicine items were claimed for patients in age group 1 (i.e., patients below the age of 57 years). However, Tables 3-1 and 3-2 show that, proportionally, more medicine items were claimed over the study period for patients above 75 years compared to those below the age of 57 years. For example, in 2011, 56.4% (*N* = 18 099 133) of medicine items were claimed for patients below the age of 57 years, who represented 76.8% (*N* = 864 962) of the population in the age group. In comparison, 6.2% of the population were in age group 4 (patients older than 75 years), whereas 14.2% of medicine items were claimed for this age group. Older persons are more likely to use many prescription drugs than younger adults. According to a report by the Kaiser Family Foundation (Kirzinger *et al*., 2019), adults 65 years and older report taking prescription medication in about nine out of 10 (89%) cases. In contrast, three-fourths of those aged 50 to 64 years, 50% of people aged 30–49 years, and 40% of people aged 18 to 29 years report using prescription medicines. Therefore, the higher use of medicine items observed in the database is unsurprising (see section 3.3.2.2).
- Analysis based on geographic location (see section 3.3.2.3) showed that most medicine items were claimed in Gauteng, decreasing in prescribing prevalence from 41.0% (*N* = 18 099 133) in 2011 to 37.0% (*N* = 20 236 841) in 2017, alongside the decrease observed in the number of patients in the province (see Table 3-1). An increasing prescribing trend was observed for the Northern Cape (from 1.8% in 2011 to 2.9% in 2017) and the Western Cape (15.9% vs 21.7%), compared to decreases in the other provinces from 2011 to 2017.

4.3.2 General opioid analgesic prescribing trends and patterns 2011–2017

The analysis first focussed on the general description of the demographic profile and geographic location of patients who received at least one opioid analgesic (claimed from chronic, oncology or prescribed minimum benefits) during the study period in the context of the central database, whereafter opioid analgesic prescribing was analysed stratified on gender, age group and geographic location. Hereafter, the analysis focused on the prescribing patterns of prescribed

opioid analgesics stratified by the top 10 active pharmaceutical ingredients claimed, the DDD/1 000 inhabitants per day and the type of chronic pain treatment. The following conclusions were drawn from the empirical inquiry described in section 3.4:

- As a percentage of the total number of patients in the central database (see Table 3-1), those who received at least one opioid analgesic (claimed from chronic, oncology or prescribed minimum benefits) during the years under study increased marginally from 0.3% (*N* = 864 962) in 2011 to 0.5% (*N* = 1 103 167) in 2017. Alongside this increase in the number of patients, an increase in the number of opioid analgesics claimed during the years under study from 0.03% (*N* = 18 099 133) in 2011 to 0.06% (*N* = 20 236 841) in 2017 (Table 3-4) was observed. A mean of 1.16 ± 0.46 (95% CI: 1.15, 1.17) opioid analgesic medicine items were prescribed per prescription over the study period. Although there were fluctuations in the mean number of opioid analgesics per patient between the years under study, these differences were not statistically or practically significant. This finding agrees with a recent study by Jayawardana *et al*. (2021:3), indicating a significantly lower opioid consumption rate in upper-middle-income and low-to-middle-income nations compared to other high-income nations, in addition to a slight increase in consumption opposed to a global decrease between 2009 and 2019.
- More female than male patients received at least one claim for an opioid analgesic during the study period (see section 3.4.1; Table 3-3), mirroring the gender distribution from the central database. The male-to-female ratio per year remained relatively stagnant over the seven years. Despite the 2.2% decrease in the total number of medicine items claimed for female patients from 2011 to 2017, there were more opioid analgesic claims in total for them over the study years (see Table 3-4). Literature has established that female patients consume and receive opioid prescriptions more frequently from doctors than their male counterparts (Foy *et al.,* 2016:4; Muench *et al*., 2020:6; Pisanu *et al*., 2019:2; Serdarevic *et al*., 2017:243; Suvada *et al*., 2022:3-4). This might be ascribed to differences in pain sensitivity and pain tolerance between the sexes, with women more prone to chronic pain-causing diseases (LeResche *et al*., 2015:632; Pisanu *et al*., 2019:2), such as fibromyalgia, migraines and osteoarthritis (Darnall *et al*., 2012:1182; Pisanu *et al*., 2019:2).
- Patients in age groups 1 and 2 (i.e., patients below the age of 66 years) decreased by 6.1% from 2011 (*N* = 2 499) to 2017 (*N* = 5 636), corresponding to the increase in those older than 66 years of age (see Table 3-3). The total number of opioid analgesic items claimed for age groups 1 and 2 decreased by 5.6% from 50.3% in 2011 (*N* = 5 797) to 44.7% in 2017 (*N* = 12 018). The differences between the age groups in the present study are consistent with Foy *et al*. (2016:6) and Weesie *et al*. (2020), showing that older patients above 65 years are more likely than younger patients to receive opioids. Fayaz

et al. (2016) attribute this to chronic pain becoming more prevalent with advancing age, affecting up to 62% of people over 75 years.

- Based on geographic location, most patients receiving at least one opioid analgesic during the study period resided in Gauteng, Western Cape and KwaZulu-Natal, similar to distribution trends observed in the central database. As a percentage of the number of patients per province (i.e., using the number of patients on the central database per province as the denominator, Table 3-1), however, there were proportionally more patients from KwaZulu-Natal in this population than in the other provinces, doubling in prevalence from 0.5% (*N* = 109 150) in 2011 to 1.0% (*N* = 120 411) in 2017. Following the pattern in patient distribution, most opioid analgesic medicine items were claimed in Gauteng, followed by the Western Cape and KwaZulu-Natal. Table 3-4 shows that the mean number of opioid analgesics per prescription increased marginally in Gauteng, Limpopo, Mpumalanga, North West and Western Cape provinces, in contrast to decreased items per prescription for the Free State and KwaZulu-Natal. However, the mean differences were insignificant ($d < 0.2$).
- Although up to six different APIs were prescribed per prescription over the study period, more than 85% of prescriptions for patients in the study population contained only one API (see Table 3-5, section 3.4.2.4). The combination product of tramadol and paracetamol was the most prescribed product over the study period, decreasing by 2.0% from 2011 to 2017. This observation may be explained by the SA guideline for chronic opioid therapy for non-cancer pain (Raff *et al*., 2014:82), recommending tramadol as the first-line option for treating mild-to-moderate non-cancer pain (see section 2.8.4). Fentanyl (14.6%, *N* = 5 133), the second most claimed API in 2011, declined by more than 10% over the study period. From 2012 to 2017, the second position on the top 10 list was replaced by a combination product comprising paracetamol/codeine/meprobamate, increasing in prescribing prevalence by almost 5%. Meprobamate is still a Schedule 5 medicine in South Africa (Medicines and Related Substances Control Amendment Act 59 of 2002) despite efforts by the SAPHRA (previously known as the Medicines Control Council (MCC)) late 2013 to re-schedule the medicine to Schedule 6 in South Africa (Hela, cited by Truter, 2016a:207). Because of its risk-benefit profile, meprobamate was placed under abuse control amendments to the Food, Drug and Cosmetic Act in December 1967, limiting the prescription duration and refills. The South African guideline for the management of pain is aligned with four international guidelines to increase awareness about the risks associated with opioid use, stricter regulations on opioid prescribing, and efforts to curb the opioid epidemic in recent years by the Centers for Disease Control and Prevention (CDC, 2017) and United States Food and Drug Administration (FDA, 2019).

- Although the number of prescriptions containing morphine decreased by 5.0% over the study period, an increase in morphine prescribed in milligrammes was observed in terms of dose, as measured by the DDD/1 000 inhabitants/day. Morphine is the most commonly used opioid for severe cancer-related pain (Caraceni *et al*., 2021:e59). Therefore, these observations may be explained by the analysis performed based on treatment groups (i.e., cancer-related and CNCP-related treatment) (see below) that showed that the majority of patients who received at least one opioid analgesic during the study period received it in relation to cancer-related pain. Morphine is also advocated as the preferred second-line option for mild-to-moderate CNCP and as a first-line option for severe pain in South Africa (Raff *et al*., 2014:82). Analysis based on pain severity was not possible because of a lack of clinical data on the database. The joinpoint analysis (Figure 3-2) showed that although the number of medicine items containing buprenorphine increased over the study period, the prescribed doses peaked in 2015 and then declined. Buprenorphine is, similar to morphine, recommended as the preferred second-line option for mild-to-moderate CNCP and as a first-line option for severe pain in South Africa (Raff *et al*., 2014:82) (see section 2.8.4.
- Analysis stratified by chronic pain treatment groups showed that more than 90% of patients who received at least one opioid analgesic during 2011 received it in relation to cancer-related pain, increasing progressively by 8.2% to 98.2% in the year 2017. This observation was expected considering the recent prediction in incidence made by Finestone and Wishnia (2022) (see section 3.4.3.1). Claims for opioid analgesic medicine items for these patients, however, increased by more than 14% from 2011 to 2017 (see Table 3-9). Although it was not possible to investigate the association between opioid consumption and cancer staging because of a lack of clinical data on the database, the increase in opioid prescribing may be ascribed to cancer pain intensifying with disease progression, as was noted by Pich (2018), in addition to an ageing population (Finestone & Wishnia, 2022). In accordance with the findings by Finestone and Wishnia (2022), a 7% increase was observed in the number of patients older than 66 years receiving opioid analgesic medicine items for cancer-related pain. Opioid analgesic medicine item claims for patients older than 66 years increased by 4% from 23.0% (*n* = 1 092) in 2011 to 27.0% (*n* = 3 118) in 2017 (see Table 3-9). In comparison, claims for CNCP treatment in the same age group decreased by 6.7% from 21.5 % (*n* = 226) in 2011 to 14.8% (*n* = 71) in 2017. The results have shown that there was an increase in the use of opioids in patients with cancer-related pain and a decrease in the use of opioids in CNCP (see section 3.4.3.2).
- As a percentage of the total number of medicine item claims in the study population each year, the claims of opioid analgesics for CNCP were similar in 2011 and 2017 at 21.9%.

In contrast to the population of patients receiving opioids for cancer-related pain, where just more than half were female, almost 74% of patients receiving opioids for CNCP in 2011 were female. There was, however, a 16.3% decrease to 57.3% (*N* = 103) in 2017, with a subsequent equal increase in the number of male patients in this population. Most opioid analgesic medicine items claimed for CNCP were also for female patients, decreasing from 73.1% (*N* = 1 049) to 61.4% (*N* = 479) in 2017. Despite these changes, there was no practically significant association between chronic pain treatment groups and gender (see section 3.4.3.2.1).

- There was a decline in the number of patients between the ages of 58 and 75 years (age groups 2 and 3) receiving treatment for CNCP, whereas the number of patients 57 years and younger and those older than 75 years increased from 2011 to 2017 by 5.6% and 6.4% respectively. Advanced age is a risk factor for chronic pain (Domenichiello & Ramsden, 2019:284).
- Geographic location analysis showed that most patients receiving opioids for cancer-related pain resided in Gauteng, followed by KwaZulu-Natal and the Western Cape. There were marginal changes in percentage over the study period, with a decline in the number of patients residing in the Eastern Cape, Gauteng and North West. There was a 7.2% increase in the number of patients in the Free State who received opioids for CNCP from 2011 to 2017. Over the treatment period from 2011–2017, opioid analgesic was highest in Gauteng, Kwa-Zulu-Natal and the Western Cape province (refer to Table 3-8). Table 3-9 furthermore shows that the number of claims for opioid analgesics for the treatment of cancer-related pain decreased in Gauteng from 42.1% (*N* = 2 514) in 2011 to 39.4% (*N* = 11 539) in 2017, as well as in KwaZulu-Natal (21.6% vs 19.1%), Limpopo (1.8% vs 1.4%), and North West (2.9% vs 1.8%). In contrast, the number of claims for opioid analgesics for cancer-related pain increased from 2011 to 2017 respectively, in the Eastern Cape (3.1% vs 3.4%), Free State (5.7% vs 8.0%), Mpumalanga (2.2% vs 3.8%), Northern Cape (0.8% vs 1.3%) and the Western Cape (19.7% vs 21.5%).

4.3.3 The relationship between opioid analgesic treatment duration and depression

For this analysis, all treatment episodes with specific opioid analgesics claimed between 2011 and 2017 were grouped into either short-term (daily supply < 90 days) or long-term duration (total supply ≥ 90 days). Treatment episodes were then analysed to determine the relationship between depression and opioid analgesic treatment duration, stratified by patient gender and age group. The following conclusions were drawn from the empirical inquiry described in section 3.5:

- Overall, 23 910 treatment episodes with opioid analgesics were identified from 2011 to 2017. Most treatment episodes (85.5%, *N* = 23 910) were short-term. No depression was

identified in 80.9% (*N* = 23 910) of treatment episodes. In the long-term treatment duration group, almost all the treatment episodes (99.7%, *N* = 3 462) were for patients without depression. Overall, the study failed to establish an association between treatment duration, both short- and long-term) and depression ($p < 0.0001$, Cramér's $V < 0.2$). The outcome of this study is therefore in contrast to international findings, which indicate an association between treatment duration and depression in patients with chronic non-cancer (refer to sections 2.7.1 and 3.5).

- Stratification by gender showed that there were slightly more female than male patients in both short- and long-term duration groups (female-to-male ratio of 1:1.2 for the long-term duration groups vs 1:1.3 for the short-term duration group). Only about 22% (*N* = 20 448) of short-term duration treatment episodes were identified for patients with coexisting depression ($p < 0.0001$, Cramér's $V = 0.1006$), compared to 0.03% (*N* = 3 462) in the long-term duration group ($p = 0.2661$, Cramér's $V = 0.0189$). The study, therefore, also failed to establish an association between depression and treatment duration stratified by gender, in contrast to findings by Beebe and Utley (2011:e13), showing that women are more likely than men to have depression and chronic pain concurrently.
- Different rates of opioid use have been observed in age groups, with older age groups being the most prevalent users of opioids (Ramírez-Maestre *et al*., 2020). Analysis stratified by age group in the present study showed that in contrast to the study by Ramírez-Maestre *et al*. most patients in the short-term treatment duration group were in age group 1, patients aged ≤ 57 years, at 44.9% (*N* = 20 448). There was an equal number of patients with (22.6%) and without depression (22.4%) in this treatment group. It was therefore determined that there was a statistically and practically significant association between short-term treatment duration and depression in patients below the age of 57 years ($p < 0.0001$, Cramér's $V = 0.5940$). In the long-term treatment duration group, only one patient aged ≤ 57 years had depression. No patients older than 57 years who received opioid analgesic treatment had coexisting depression. There was no association between depression and long-term treatment duration with opioid analgesics by age group ($p = 0.3242$, Cramér's $V = 0.0317$).

4.4 Study strengths and limitations

Although the data used were obtained from one PBM only, meaning that it is not representative of the entire private healthcare sector in South Africa (or the broader South African population), it did mirror the demographic profile of patients and geographic location of beneficiaries covered by medical aid schemes registered in South Africa in terms of the Medical Schemes Act (131 of 1998) from 2011 to 2017. The PBM's database, however, only included claims that were reimbursed. Patients paying out-of-pocket for medication were thus not considered. The analysis

in the present study focussed on claims reimbursed from chronic, PMB and oncology benefits; therefore, no claims paid from acute and OTC benefits are included in this analysis. Injections and suppositories were also excluded (see section 1.5.3). The prescribing prevalence presented in this study is, therefore, an underestimate of opioid consumption in the South African private healthcare sector but does provide baseline information for further analyses.

Because of a lack of patient-identifying information on the database, such as an address, the prescriber's practice's postal codes were used as a proxy for geographic location. Prescribers, especially oncologists, might be in a different area than the beneficiaries' residence. However, it was assumed that the patient would receive treatment in the same province they reside.

4.5 Recommendations

This research project will help increase the understanding of pain management for chronic patients in the South African private healthcare sector. Recommendations for proposed future research projects include the following:

- Future researchers could include claims reimbursed from acute and OTC benefits, injections, and suppositories to determine the extent of opioid use on the PBM company's database. Wholesale data can also be used to determine the volume of opioid analgesics sold in South Africa.
- Opioid analgesic prescribing patterns should be analysed, considering the co-prescribed pharmacological drug classes and accompanying disease profiles to determine possible causes for observed trends.
- The increase in prescribing meprobamate-containing products in the private healthcare sector should be further investigated.

4.6 Chapter summary

By relating the precise goals of the study to the outcomes, this chapter brought the dissertation to a close. As well as identifying the restrictions, suggestions for further research were given. As a result, all study goals were accomplished.

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ANNEXURE A STUDIES DOCUMENTING OPIOID CONSUMPTION AND PRESCRIBING (2018–2022)

Authors	Study inception period	Study setting/ Country	Study design and data source	Study population and sample size (*N*)	Measurements	Key findings/results extracts
Dave and Falcone (2022)	19 Jun 2020–1 Dec 2020	USA	Cross-sectional online survey	*N* = 82 Oculofacial plastic surgeons	Trends in opioid prescriptions among oculofacial plastic surgeons (OPS) after common oculoplastic surgeries	The two most popular opioid drugs are tramadol (21%) and hydrocodone-acetaminophen (35%, *N* = 82). The latter generation which are ophthalmologists is 4.9 times more likely to prescribe opioids overall when compared to OPS who completed their training before 1990 (16%) and those who did their training from 1991 to 2000 (12%) ([95% CI: 1.3, 15.4], *p* = .01). Additionally, compared to OPS working in the northeast of the country, those working in the southeast are 4.2 times more likely to prescribe opioids in general ([95% CI: 1.4, 12.8], *p* =.02).
Dias *et al.* (2022)	2014–2019	Mount Sinai Hospital	Retrospective; Mount Sinai Institutional Data Warehouse data	*N* = 5 874 non-geriatric (18–64 years) and 3,306 geriatrics patients (> 65 years) who underwent laparoscopic chole-cystectomy, laparoscopic colectomy, open colectomy, laparoscopic	Changes in postoperative opioid prescriptions Milligrammes (mg) of oxycodone for standardisation	A perioperative opioid prescription was written for 5 169 (88%) non-geriatric patients and 2 692 (81.4%) elderly patients. Patients in their advanced years were less likely to be prescribed an opioid (*p* = 0.0001). The number of opioids prescribed to the elderly population dropped yearly between 2016 and 2019 (*p* = 0.0001). When compared to patients 85 and above. Patients aged 65 to 74 received significantly greater dosages (*p* = 0.0001).

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				inguinal hernia repair, open inguinal hernia repair, laparoscopic ventral hernia repair and open ventral hernia repair		
Ju *et al*. (2022)	2015–2019	66 countries /regions; USA	IQVIA-Multinational Integrated Data Analysis System (MIDAS) database	Retail sector sales and hospitals	Opioid analgesic sales data were used as a proxy for the consumption of the medicine by patients	Overall sales of opioid analgesics went from 27.52 MME per 1 000/day (16.63-45.54) in 2015 to 29.51 MME per 1 000/day (17.85–48.79) in 2019 (difference per year 396%, 95% CI 0.26 to 7.80). Sales decreased annually in North America (-12.84%; 95% CI: -15.34 to -10.27) and Oceania (-2.96%; -4.20 to -170); increased in South America (28.69%; 7–18 to 54.53); Eastern Europe (7.68%; 3.99 to 11.49); Asia (5.74%; 061 to 11.14); and western and central Europe (1.64%; 052 to 278); and remained the same. The global patterns of opioid usage were linked to the Human Development Index at the country level (p = 0040), the cancer death rate outside of leukaemia (p = 00072) and geography (p < 00001).
Gentle *et al*. (2022)	Mar. 2019–Mar. 2021	USA	Abdominal Core Health Quality Collaborative for demographics, perioperative details and	*N* = 490 LIHR patients	Rate of patient-requested opioid refills and associated factors after laparoscopic inguinal hernia repair (LIHR)	Median number of opioid tablets prescribed: 12 (10–5). Patients who requested refills were younger (55 years [IQR 37 to 61] vs. 62 years [IQR 36.8 to 61], p = 0.012) and more likely to have undergone

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			patient-reported opioid usage			transabdominal preperitoneal repair (75% vs. 26.4%, $p = 0.001$), more likely to have had a scrotal component (30% vs. 11%, $p = 0.022$) and more likely to have had permanent tacks used. Patients who asked for refills were not given statistically different doses of morphine equivalents when they were discharged (112 mg [IQR 73.1 to 122] vs. 75 mg [IQR 67.5 to 112], $p = 0.143$). 289 patients (or 59%) had the option to report using opioids. Following surgery, 87% of patients took no more than 10 opioid tablets and 67% used no more than four. In spite of high-income levels and cancer mortality rates, opioid analgesic use in the 17 countries and regions in the lowest consumption quartile in 2019 ranged from 001 MME per 1 000/day to 540 MME per 1 000/day.
Gomes *et al*. (2022)	July 2014–August 2020	66 countries and jurisdictions, USA	Retrospective cross-sectional; IQVIA's MIDAS database	Retail pharmacy opioid sales from 66 jurisdictions in developed and developing economies. National retail prescription opioid sales data	Rate of opioid units purchased per 1 000 population; Relative change in international opioid purchasing rates	In the five years prior to the pandemic, opioid purchase rates decreased in industrialised economies by 23.8% (95CI 34.7% to 3.6%) but increased in underdeveloped economies by 15.2% (95% CI 4.6%-35.6%). In developing (10.9 units/1 000 population increase; $p = 0.0001$)

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						and developed (145.5 units/1,000 population; $p = 0.0001$) economies, the rate of opioid purchases spiked briefly in March 2020. This spike was quickly followed by a drop in opioid purchases of a comparable magnitude in April and May 2020 (14.8 and 171.8 units/1000 population in developing and developed economies, respectively; $p = <0.0001$).
Hadlandsmyth *et al*. (2022)	2018	USA	National administrative data from the United States Veteran's Affairs (Corporate Data Warehouse	*N* = 191 283 Cohort of outpatients with acute pain presentations and no more than minimal opioid use in the prior year	Days between the first dispensed prescription and index date; The supply days dispensed at first prescription; The type of opioid dispensed at first prescription, classified as schedule II (CII) versus non-CII products (tramadol or codeine–acetaminophen combinations); The estimated daily dose of the first prescription in morphine milligram equivalents (MMEs) The number of prescriptions dispensed in the 30-day period	LCA classifications were found among the 27 890 people who received their first opioid prescription by looking at the first supply day, the total days dispensed over the course of the first 30 days, the opioid type, the dosage and the number of prescriptions written over those first 30 days. Class 1 in the three-class paradigm stood for an immediate, low-dose, brief supply; class 2 for delayed, low-dose, longer-duration prescriptions; and class 3 for delayed, high-dose, moderate-duration prescriptions. Adjusted relative risk ratios for progression to long-term opioid use in the subsequent year were 3.33 (95% CI: 2.71-4.10) for class 1 (absolute risk 1.1%); 7.76 (95% CI: 6.69-8.99) for class 2 (3.1%); and 6.81 (95% CI: 5.72-8.12) for class 3 (2.4%) compared to patients who did not

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						receive an acute opioid prescription (0.3%).
Nechuta *et al*. 2022	2013–2016	Tennessee	Population-based cohort; State-wide Prescription drug monitoring programs and birth certificate data	*N* = 311 217 live singleton births with prescription history from 90 days before pregnancy to birth.	Patterns of prescription opioid during pregnancy overall by maternal characteristics and year.	14.1% of pregnant women used prescription opioid analgesics and 1.6% used buprenorphine for medication-assisted therapy. From 16.6% in 2013 to 11.8% in 2016, fewer people used opioid analgesics (*p* trend 0.001). 25% were utilised for > 7 days, while 9.7% were used for > 30 days ' supply. Hydrocodone (9.3%), codeine (3.4%) and oxycodone (2.9%) were the most widely used kinds. Poorer levels of education, lower income, pre-pregnancy obesity and smoking during pregnancy were found to increase the likelihood of using both opioids and opioid analgesics in adjusted models.
Ponizovsky *et al.* (2018)	2009–2016	Israel	National database from Israel ministry of Health's Pharmaceutical Administrative	Data was collected from national database maintained by the ministry of Health's pharmaceutical administration	Patterns of five prescription opioids (fentanyl, methadone, morphine, oxycodone & pethidine)	Five of the prescribed opioids increased by 68%, from 3.40 DDD/1 000 inhabitants/day in 2009 to 5.72 DDD/1 000 inhabitants/day in 2016. This trend resulted mostly from increases in oxycodone consumption from 0.50 DDD/1 000 inhabitants/day to 2.03 DDD/1 000 inhabitants/day (namely, 4-fold) and in fentanyl consumption from 1.09 DDD/1 000 inhabitants/day to 2.33 DDD/1 000 inhabitants/day (about 2-fold). The use of the three

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						remaining opioids decreased substantially as follows: pethidine from 0.03 DDD/1 000/day in 2009 to 0.007 DDD/1 000 inhabitants/day in 2016 (−67%), methadone from 1.61 DDD/1 000 inhabitants/day to 1.20 DDD/1 000 inhabitants/day (−25%), and morphine from 0.17 DDD/1 000 inhabitants/day to 0.15 DDD/ 1 000 inhabitants/day (−12%).
Rueter *et al*. (2022)	2014–2016	France	Retrospective cohort	*N* = 4 704 Cancer outpatients, who died between 2014 and 2016	Prevalence and timing of weak and strong opioid analgesic prescriptions in cancer outpatients during their last year of life	During their final year of life, 63.8% of patients had at least one weak or strong opioid analgesic prescribed to them and dispensed; of these, 2 458 (52.3%) received one weak opioid analgesic (tramadol as a single ingredient accounted for 25.9%) and 1 733 (36.8%) received one strong opioid analgesic (fentanyl 21.6%). For any strong opioid, the median time between the initial prescription and mortality was 18 weeks (interquartile range: 8–38) and for light opioids it was 33 weeks (interquartile range: 20-47). 1 229 (50%) patients who were weak opioid users had received 1 weak opioid analgesic dispensation in the year *N* = 2 before death. Strong opioid users included 986 (56.1%) and 381 (21.9%%) patients who had obtained one weak opioid analgesic prescription during the

Authors	Study inception period	Study setting/ Country	Study design and data source	Study population and sample size (*N*)	Measurements	Key findings/results extracts
						year *N* = 2 before death. Compared to patients with an inpatient death, patients with an outpatient death had a higher likelihood of a late strong opioid beginning. For patients with an inpatient death, late strong opioid initiation (18 weeks prior to death) was significantly associated with fewer hospital days and prior weak opioid exposure; for patients with an outpatient death, it was significantly associated with older age, social, prior weak opioid exposure and a prescription initiation by a general practitioner.
Ryu and Viet (2022)	1 Jan 2011–31 Dec 2021	Loma Linda Oral and Maxillofacial Surgery Clinic.	Cross-sectional	4 149 patients who underwent dentoalveolar procedures with either IV general anaesthesia or IV sedation	Opioid prescribing patterns by oral and maxillofacial surgeons after dentoalveolar surgery after dentoalveolar surgery had changed. (MME)	MME decreased significantly in four treatment groups from 2017 to 2021 (compared to 2011 to 2016): wisdom teeth extraction (20.5 vs. 7.9, $p = 0.001$; multiple teeth extraction (21.6 vs. 8.9, $p = 0.001$; implant placement (22.5 vs. 12.9, $p = 0.001$; preprosthetic surgery (28.0 vs. 11.2, $p = 0.037$); multiple teeth extraction (21.6 vs. 8.9, $p = 0.001$; and multiple teeth extraction (2 MMEs were found to statistically significantly decline from 2011 to 2016 to 2017 to 2021 in the therapy groups receiving implants, multiple teeth extraction and wisdom teeth extraction (unstandardised coefficient: -12.6, -12.6 and -9.77 respectively; all $p = 0.001$). Although it was not statistically

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						significant (p = 0.059), the trend toward a decline in MME was also present in preprosthetic surgery (unstandardised coefficient: -14.8).
Van Brug *et al*. (2022)	2013–2018	The Netherlands	2 national databases: Dutch Foundation for Pharmaceutical Statistics, which provides national coverage of medication prescriptions, was linked to the Dutch Arthroplasty Register, which records arthroplasty procedures	48 051 primary knee arthroplasty (Kas), 53 964 primary hip arthroplasty (Has), 3 540 revision KAs and 4 118 HAs	Number of defined daily dosages (DDD) and MME per person/ year (PY), stratified for primary and revision arthroplasty. Among subgroups for age (< 75; ≥ 75 years) and sex for primary osteoarthritis arthroplasties, prescription rates stratified for opioid type (weak/strong) and prevalent preoperative opioid prescriptions (yes/no)	After receiving primary KA, 58% of patients were prescribed one opioid during the first year in, 2013, and 89% in 2018. These figures climbed from 38% to 75% for main HA. The prescription rates in KAs rose from 13.1 DDD/PY to 14.4 DDD/PY, with oxycodone prescriptions accounting for the majority of the rise (2.9 DDD/PY to 7.3 DDD/PY), while tramadol prescriptions fell (7.3 DDD/PY to 4.6 DDD/PY). The amount of MME/PY also rose from 888 to 1 224. Both revision arthroplasties and HA underwent comparable modifications. No matter the joint, the prescription for opioid drugs grew with time, peaking in populations with prior opioid prescriptions, while weak opioid prescriptions declined.
Wampole *et al*. (2022)	1 Dec 2014–31 May 2019	Maine Medical Centre, Portland, Maine	Retrospective cohort	*N* = 2 975 adult patients admitted to the 32-bed medical, trauma/surgical, and neurologic ICUs	Pre- and posthospital opioid utilisation	After receiving primary KA, 58% of patients were prescribed one opioid during the first year, in 2013, and 89% in 2018. These figures climbed from 38% to 75% for main HA. The prescription rates in KAs rose from 13.1 DDD/PY to 14.4 DDD/PY, with oxycodone prescriptions accounting for the majority of the rise (2.9

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						DDD/PY to 7.3 DDD/PY), while tramadol prescriptions fell (7.3 DDD/PY to 4.6 DDD/PY). The amount of MME/PY also rose from 888 to 1 224. Both revision arthroplasties and HA underwent comparable modifications. No matter the joint, the prescription for opioid drugs grew with time, peaking in populations with prior opioid prescriptions, while weak opioid prescriptions declined.
Jayawardana *et al*. (2021)	2009–2019	Global consumption (76 countries)	Longitudinal, multicounty IQVIA MIDAS data	Sales data in hospital and retail settings obtained quarterly for 76 countries	Country-level consumption trends in MMEs	The global opioid consumption rate decreased from 216 to 151 MMEs per 1 000 people per day (MID), with the US and Germany having the lowest consumption rates. Consumption rates increased overall in HICs by a median 366 MID (IQR, -75 -1245), with significant regional variation. In comparison to HICs (345 1 MID), median consumption rates were lower in UMICs (23.6 MID) and LMICs (8.3 MID), and they increased by a median of 10.4 MID and 3.7 MID respectively from 2009 to 2019. In UMICs, consumption rates were correlated with trade (1 359, 13–258) and income (coefficient 1 884, 95% confidence interval 38–339) while in LMICs they were correlated with physician density (195, 12–27). The study period saw an increase in the rate

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						of tramadol usage, which made up a sizeable fraction of the total opioid volume ingested across all country-income categories. The rate of tramadol usage increased which made up a sizeable fraction of the total opioid volume ingested across all country-income categories.
Ellenbogen and Segal (2020:76-83)	1 Jan 2013–31 Dec 2016	Centers for Medicare and Medicaid Services, Baltimore	Serial cross-sectional analysis of prescription claims database	*N* = 36 999 generalist physicians prescribing opioids	Differences in opioid prescribing among generalist physicians, nurse practitioners and physician assistants Prescribers with two different practice settings defaulted to hospital medicine primarily and urgent care/walk-in clinic secondarily)	Compared to doctors and nurse practitioners, physician assistants' opioid prescriptions varied more. Between these four years. There were 660 claims for physicians, 755 for nurse practitioners and 812 for physician assistants.
Hurtado *et al*. (2020)	1 Jan 2010–31 Dec 2018	Valencia, Spain	Population-based, cross-sectional	Spanish population with more than 4.2 million inhabitants aged 18 years and older	Trends in opioid use: volume of prescriptions, dosage and number of patients treated Number of prescriptions, prescription rate per 100 inhabitants, dosage per capita (morphine mg equivalents, MME/c) and volume of patients treated	2 107 756 distinct patients received more than 35 million total treatments over the study period. The overall MME/c showed approximately a threefold increase and the number of treatments each year nearly doubled. When compared to 2017, fentanyl's MME/c more than tripled, making up 34.4% of all MME/c in 2018. When compared to tapentadol, which was introduced in 2011, oxycodone MME/c exhibited a 10-fold rise. From 335 379 in 2010 to

Authors	Study inception period	Study setting/ Country	Study design and data source	Study population and sample size (*N*)	Measurements	Key findings/results extracts
						722 838 in 2018, the number of patients obtaining at least one opioid prescription each year more than doubled.
Kiang *et al*. (2020)	2013–2017	National private insurer covering all 50 USA states and Washington DC	Retrospective, observational; Optum Clinformatics Data Mart Database	An annual average of 669 495 providers prescribing 8.9 million opioid prescriptions to 3.9 million patients from 2003 through 2017	Distribution and patterns of opioid prescribing; Standardised doses of opioids in MMEs and number of opioid prescriptions	49% of all opioid doses and 27% of all opioid prescriptions were written in 2017 by the top 1% of healthcare professionals. Absolute numbers show that the top 1% of doctors prescribed 748 000 MMEs on average, which is over 1 000 times more than the middle 1%. At least 50% of all providers who were in the top 1% in a given year were also in the top 1% in the years after that. The top 1% of providers wrote over two-fifths of all prescriptions, over four-fifths of which were for more than seven days and more than 50 MMEs per day. The prescriptions written by the bottom 99% of physicians, however, were below these standards, with 86% of them calling for fewer than 50 MMEs per day and 71% for fewer than seven days. Over time, both high opioid prescription rates from providers and high opioid use rates among patients persisted; more than half of both appeared in years close to one another.
Zin (2020)	2005–2014	Five Southeast Asian	Retrospective cross-sectional;	Data of all available strong opioids (morphine,	The total annual consumption with and without methadone	Malaysia had the highest increase in the use of the five powerful opioids (993.18%), followed by

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		countries (Malaysia, Singapore, Indonesia, Thailand and Vietnam).	Pain and Policy Studies Group data.	oxycodone, fentanyl, pethidine, and methadone)	DDD/1 000 inhabitants/day	Indonesia (530.34%), Vietnam (170.17%), Singapore (116.16%) and Thailand (104.66%). The consumption of all powerful opioids was highest in Malaysia (11.2 DDD/ 1 000 people/day), mostly methadone. The two countries where fentanyl was most commonly used were Malaysia and Singapore, but oxycodone use increased there the most. While morphine was mainly used in Thailand and Vietnam, fentanyl was also widely used in Indonesia.
Chen *et al*. (2019)	2003–2014	USA	Cohort; Truven MarketScan, US commercial claims database	Patients with rheumatoid arthritis (RA) (*N* = 181 710), systemic lupus erythematosus (SLE) (*N* = 45 834, psoriatic arthritis (PsA) (*N* = 30 307) and ankylosing spondylitis (AS) (7 686), each matched by age and sex with patients with hypertension (HTN)	Long-term opioid prescription use	Patients with AS made up the highest percentage of patients who received long-term opioid prescriptions, as well as other opioid prescribing measures. As opposed to HTN, AS had the highest risk of receiving long-term opioid prescriptions (RR 2.73, 95% CI 2.60 to 2.87) while the rates for RA, PsA, and SLE were 2.21 (2.16 to 2.25) and 1.94 (1.87 to 2.00) respectively.
Nissen *et al*. 2019	1 Jan 1999–31 Dec 2017	Denmark	Longitudinal; Danish Health Data Authority,	Nationwide sales data on opioid sales	Utilisation trends in age groups for the four opioids with the highest use.	Tramadol (46.1), codeine and combination products (12.4 for codeine, 3.7 for codeine and acetylsalicylic acid and 4.2 for

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					DDD/1 000/day, oral morphine equivalents/1 000/day packages dispensed/year). person-based metric (users/1 000/year).	codeine and paracetamol). Morphine (17.0) and oxycodone were the four opioids chosen based on users/1 000/year (12.1). With the exception of codeine and combination drugs, overall utilisation as measured by volume and person metrics increased. With advancing age, tramadol doses or strength rose, but less so. For all age groups, oxycodone doses or strength reduced, but for the group of people under 80 years old, they remained largely stable.
Rosner *et al*. (2019)	1985–2016	Germany	Systematic review	Yield: 19 relevant articles.	Prevalence of opioid prescribing	Over time, Germany has seen an increase in the number of individuals with opioid prescriptions and defined daily opioid doses per receiver. Patients with non-cancer pain received the bulk of opioid prescriptions. Older persons, women and Germany's northern region had higher rates of opioid use. Despite not being the first-line option for illnesses with chronic pain, fentanyl was found to be the strongest opioid that was most frequently prescribed in outpatient settings in Germany. None of the more recent research, but every piece of data produced before 2000, suggested that opioids were a poor choice for treating pain. In

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						Germany, there were no indications of an ongoing opioid pandemic.
Schwartz *et al*. (2018)		USA	Cross-sectional survey.	Otolaryngologist members of the American Academy of Otolaryngology–Head and Neck Surgery (*N* = 596 respondents)	Opioid prescribing patterns for the treatment of postoperative pain for common otolaryngologic surgeries	Adults are most likely to take oxycodone-acetaminophen (39%), followed by hydrocodone-acetaminophen (73%). Acetaminophen is the most popular pain reliever for children (67%), followed by nonsteroidal anti-inflammatory medications (65%). Overall, the number of opioid doses ordered for each surgery varied greatly, ranging from 0 to more than 60 doses. Mean opioid prescriptions were highest (37 tablets) for tonsillectomy and lowest (direct laryngoscopy) for that procedure (5.3 tablets).
Badreldin *et al*. (2018)	1 Dec. 2015–30 Nov. 2016	USA	Retrospective cohort	Opioid-naïve women hospitalised for delivery at a single, high-volume tertiary care centre (*N* = 12 326 women)	Opioid prescribing at postpartum hospital discharge in oral MMEs	30.4% and 86.7%, respectively, of 9 038 and 3 288 post-Caesarean deliveries of women, received an opioid prescription upon discharge was 200 (interquartile range: 120–300) following vaginal and 300 (interquartile range: 200–300) following cesarean delivery, the median number of MMEs given to women getting discharge opioid prescriptions was 200 (interquartile range: 120-300). The final hospital day saw 0 MMEs used by nearly half (45.7%) of women postvaginal delivery and 18.5% of women post-Caesarean delivery who were given

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						an opioid prescription. People who reported a pain score of 0 out of 10 and people who reported a pain score of >0 out of 10 right before discharge received the same dose of opioids. Women who had Caesarean deliveries received the same amount of morphine milligrammes.

ANNEXURE B ETHICS APPROVAL

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ETHICS APPROVAL CERTIFICATE OF STUDY

Based on approval by **Health Research Ethics Committee (HREC)** on **12/10/2016** after being reviewed at the meeting held on **16/08/2016**, the North-West University Institutional Research Ethics Regulatory Committee (NWU-IRERC) hereby **approves** your study as indicated below. This implies that the NWU-IRERC grants its permission that provided the special conditions specified below are met and pending any other authorisation that may be necessary, the study may be initiated, using the ethics number below.

Study title: Medicine prescribing patterns in a section of the private health sector utilising data from a Pharmaceutical Benefit Management company in South Africa.

Sub-study title: Opioid prescribing trends and patterns in the South African private Health sector, 2010-2015.

Study Leader/Supervisor: Dr JR Burger
Student: J Chauke

Ethics number:

N	W	U	-	0	0	1	7	9	-	1	4	-	A	1
Institution				Study Number						Year			Status	

Status: S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation

Application Type: Sub-study
Commencement date: 2016-10-12 **Risk:** Minimal

Continuation of the study is dependent on receipt of the annual (or as otherwise stipulated) monitoring report and the concomitant issuing of a letter of continuation up to a maximum period of three years.

Special conditions of the approval (if applicable):

- Translation of the informed consent document to the languages applicable to the study participants should be submitted to the HREC (if applicable).
- Any research at governmental or private institutions, permission must still be obtained from relevant authorities and provided to the HREC. Ethics approval is required BEFORE approval can be obtained from these authorities.

General conditions:

While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, please note the following:

- *The study leader (principle investigator) must report in the prescribed format to the NWU-IRERC via HREC:*
  - *annually (or as otherwise requested) on the monitoring of the study, and upon completion of the study*
  - *without any delay in case of any adverse event or incident (or any matter that interrupts sound ethical principles) during the course of the study.*
- *Annually a number of studies may be randomly selected for an external audit.*
- *The approval applies strictly to the proposal as stipulated in the application form. Would any changes to the proposal be deemed necessary during the course of the study, the study leader must apply for approval of these amendments at the HREC, prior to implementation. Would there be deviated from the study proposal without the necessary approval of such amendments, the ethics approval is immediately and automatically forfeited.*
- *The date of approval indicates the first date that the study may be started.*
- *In the interest of ethical responsibility the NWU-IRERC and HREC retains the right to:*
  - *request access to any information or data at any time during the course or after completion of the study;*
  - *to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process.*
  - *withdraw or postpone approval if:*
    - *any unethical principles or practices of the study are revealed or suspected,*
    - *it becomes apparent that any relevant information was withheld from the HREC or that information has been false or misrepresented,*
    - *the required amendments, annual (or otherwise stipulated) report and reporting of adverse events or incidents was not done in a timely manner and accurately,*
    - *new institutional rules, national legislation or international conventions deem it necessary.*
- *HREC can be contacted for further information or any report templates via Ethics-HRECApply@nwu.ac.za or 018 299 1206.*

The IRERC would like to remain at your service as scientist and researcher, and wishes you well with your study. Please do not hesitate to contact the IRERC or HREC for any further enquiries or requests for assistance.

Yours sincerely

Prof LA Du Plessis
Digitally signed by Prof LA Du Plessis
Date: 2016.10.14 07:51:35 +02'00'

Prof Linda du Plessis
Chair NWU Institutional Research Ethics Regulatory Committee (IRERC)