Drug Utilization Review of Analgesics in the Management of Pain in Accordance with the South African Standard Treatment Guidelines at a Hospital Level in Limpopo, South Africa.

BY:

RIKHOTSO MUHLURI ALVINAH (218044999)

Supervisor

Professor Varsha Bangalee

Co-supervisor

Professor Fatima Suleman

Date submitted: 1 December 2022

PREFACE

This dissertation is presented in manuscript format. The findings of the study are presented in chapter 3, as a manuscript as required by the regulations of the University of Kwazulu-Natal. This manuscript was submitted for publication to the *Journal of Hospital Practice.* The reference list is formatted according to the instructions for authors as required by the *Journal of Hospital Practice.* A complete reference list is included at the end of every chapter and according to the reference style of the University of Kwazulu-Natal.

The dissertation consists of four chapters as follows:

- Chapter 1: Provides an introduction to the study as well as the aims, objectives and a brief overview of the methodology.
- Chapter 2: Provides the literature background to the study.
- Chapter 3: Consists of the results, discussion and conclusion written in a manuscript format.
- Chapter 4: Provides the general conclusions, recommendations, limitations and strengths of the study.

ABSTRACT

Background

One of the aims of the National Drug Policy (NDP) of South Africa was to promote the rational use of medicines and to achieve this goal, the Essential Medicines Programme (formerly EMP), which included an Essential Medicines List (EML) and Standard Treatment Guidelines (STGs), was developed. The STGs offer guidance on the rational use of medicines for the most common conditions including pain management. A perceived marked increase in the use of tramadol for pain management requires that research be undertaken to confirm if there is use of tramadol outside of prescribed guidelines, and to determine the contributing factors for this.

Study aim

The overall aim of the research was to review the use of analgesics in the management of pain in terms of compliance with STGs by prescribers and to determine the cost implication of failure to follow STGs in pain management for the district hospital. Prescriber awareness and use of the guidelines for pain management and the associated cost implications of non-adherence to guidelines was also assessed. Finally the study sought to ascertain prescriber experience on the misuse of tramadol when treating patients for pain.

Methods

This was a quantitative study in which the records of patients admitted and being treated for chronic mild to moderate pain at a district hospital in Limpopo from the 1st of April to the 30th of September 2021 were reviewed to determine whether the Hospital Level Adults STG/EML (2019) was followed when patients commenced with treatment. An Excel spreadsheet was used to record patient demographics; diagnosis; pain medication prescribed; dosage regimen; prescriber post and prescriber compliance with recommended STG. The treatment regimens for pain that were captured included paracetamol; ibuprofen; and tramadol as single prescribed therapies as well as combinations of paracetamol and ibuprofen; paracetamol and tramadol; and a combination of all three, viz. paracetamol, ibuprofen and tramadol. The recorded prescriptions were assessed for compliance in terms of the stepwise process of pain management as outlined in the Hospital Level Adults STG/EML (2019). Descriptive statistics

and Excel were used for data analysis. The cost of analgesics was obtained from the Limpopo Province Pharmaceutical Depot (LPPD). A questionnaire was used to determine prescribers' awareness of STGs, compliance with guidelines for the management of chronic mild to moderate pain, and awareness of the cost implications of non-compliance among prescribers assigned to the general ward for the period of data collection. Full ethical approval was obtained before commencement with the study.

Results

A total of 224 prescriptions were recorded for the 6-month period. Patients initiated on paracetamol as first-line treatment for pain were 129 (57.5 %). Nineteen patients (8.5%) were initiated on tramadol and 54 patients (24 %) on paracetamol and tramadol. Patients initiated on paracetamol and ibuprofen were 12 (5.4%); those on ibuprofen were 3 (1.3%) and 7 (3%) were switched between pain regimens. The prescription compliance rate in terms of the stepwise process of pain management as outlined in the STGs/EML was 90.6% and 9.4% were non-compliant. The total cost for both compliant and non-compliant prescriptions was R1128,10. Compliance to STGs when prescribing analgesics as reported by prescribers was 33%. Half of the prescribers (50%) stated that they only follow guidelines occasionally. Only 33% followed STGs when prescribing tramadol although 83% stated that they prescribe paracetamol for pain. All prescribers had encountered tramadol misuse by patients but only 50% monitored patients after the medicine was prescribed. The study found that 67% of prescribers had poor knowledge of the cost implication associated with non-compliance to STG.

Conclusion

This study has identified that there is a prescription compliance rate of 90.6% among prescribers in prescribing analgesics according to the STG/EML. There is however still room for improvement because non-compliance to guidelines has cost implications. In the South African setting where there are resource constraints, compliance is critical for the purpose of efficient use of health care resources. There is also a need for educating prescribers on the importance of compliance to guidelines.

Keywords: Drug utilization review, paracetamol, tramadol, standard treatment guidelines, pain management.

DECLARATION 1 - PLAGIARISM

I, Muhluri Alvinah Rikhotso, declare that:

1. The research reported in this thesis, except where otherwise indicated, is my original work.
2. The work described in this thesis has not previously been submitted to UKZN or other tertiary institutions for purposes of obtaining an academic qualification, whether by myself or any other party.
3. This thesis does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written resources have been quoted, then:
    a) Their words have been re-written but the general information attributed to them has been referenced.
    b) Where their exact words have been used, then their writing has been placed inside quotation marks and referenced.
4. This thesis does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source is detailed in the thesis and the reference sections.

Signed: [redacted] Date: 22 February 2023

This is to certify that the contents of this thesis are the original work of Ms. Rikhotso Muhluri Alvinah and as the candidate's supervisor, I have approved this thesis for submission.

Signed:
Name: Prof. Varsha Bangalee Date: 22 February 2023

Signed:
Name: Prof. Fatima Suleman Date: 22February 2023

DECLARATION 2 – ETHICAL APPROVAL

Ethical approval for the study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu Natal (BREC/00001488/2020) – (Annexure 1) and the Limpopo Department of Health (REF: LP_2020_12_007) – (Annexure 2).

DECLARATION 3 – MANUSCRIPT PUBLICATION

1. My contribution to the project was as follows:

Rikhotso Muhluri: Author - I contributed to the project by performing all literature reviews, data and statistical analyses, interpretation of the results as well as manuscript preparation and writing of the dissertation.

2. The contributions of others to the project was as follows:

Professor Varsha Bangalee: Supervisor – Conceptualization of the study, data validation, editing of the dissertation and manuscript.

Professor Fatima Suleman: Co-supervisor — Conceptualization of the study, data analyses; data validation, editing of the dissertation and manuscript.

DEDICATION

I’m grateful to God for strengthening me through this journey. I dedicate this thesis to my children, Unarine and Oritonda.

ACKNOWLEDGEMENTS

I would like to acknowledge my research supervisor Prof. Varsha Bangalee for her continuous assistance, guidance, remarks and engagement throughout the development of this thesis. I am truly grateful for the time you dedicated to me and your words of encouragement.

I would also like to offer my gratitude to my co-supervisor Prof. Fatima Suleman, for her time and effort in guiding this thesis.

I thank my parents and siblings for their continuous support and confidence in me.

I also acknowledge my husband for walking this journey with me and for always motivating me.

LIST OF ACRONYMS AND ABBREVIATIONS

BREC	Biomedical Research Ethics Committee
CAP	Community-acquired pneumonia
CSD	Community Service doctors
DOT	Directly Observed Therapy
EML	Essential Medicines List
HAART	Highly Active Antiretroviral Therapy
MO	Medical Officer
NDoH	National Department of health
NDP	National Drug Policy
NSAIDs	Non-steroidal anti-inflammatory drugs
PEG	Pain, Enjoyment and General Activity
PTC	Pharmacy and Therapeutics Committee
STGs	Standard Treatment Guidelines
TB	Tuberculosis
US	United States
WHO	World Health Organization

TABLE OF CONTENTS

CHAPTER 1

1. INTRODUCTION

1.1 Background and rationale of the study

The National Department of Health (NDoH) remains committed to ensuring the availability and accessibility of good quality essential medicines that are effective, safe, and affordable as well as the rational use thereof (Standard Treatment Guidelines (STG) and Essential Medicines List (EML) for South Africa, Hospital Level Adults, 2019). The National Drug Policy (NDP) was developed in 1996 and adopted in part by the South African Government. One of the goals was to improve access to quality medicines for all South Africans and ensure rational drug use by prescribers, dispensers and consumers (National Drug Policy for South Africa, 1996).

Rational pain management is outlined in the STGs for South Africa. The goal of pain management, includes, in addition to pain reduction, the improvement of function, sleep and well-being (Schellack & Annor, 2016). The collaborative effort of the healthcare team managing the patient is required to achieve the best outcome in pain management which includes minimizing pain while managing the side effects of the pain medication (Schellack & Annor, 2016). The prevalence of pain was highlighted by a study in the Eastern Cape province of South Africa where it was found that pain was the common reason for almost three quarters of patient visits to primary health clinics (Igumbor, 2012). Pain is an important cause for the use of health care services and its high prevalence in the community reflects the social and economic impact it has on human populations (Igumbor, 2012).

The Hospital Level Adults (2019) STG and EML for South Africa, provide clear guidelines that should be followed by practitioners for the management of chronic mild to moderate pain. The medications paracetamol and ibuprofen are indicated for the management of chronic mild to moderate pain and ibuprofen can be used alone or in combination with paracetamol and opioids. The reason for this step-wise approach in pain management is because different analgesics are indicated for different conditions depending on the severity of pain (STG /EML for South Africa, Hospital Level Adults (2019). According to the Medicine and Related Substances Act No.65 of 1975 (as amended), tramadol is classified as a Schedule 5 medicine (Osman, 2003). It is indicated for moderate to moderately-severe pain with analgesic effects

occurring within one hour after oral administration (SAMF, 2014). It is considered a useful alternative to the typical opioids in situations of severe pain and its good bioavailability following oral administration reduces the need for parenteral administration (SAMF, 2014).

A drug utilization study to analyze opioid prescribing patterns in South African community pharmacies conducted in 2013 found that tramadol in combination with paracetamol, accounted for 71.90 % of products dispensed, followed by tramadol alone (22.74%) (Truter, 2016). This is consistent with global trends indicating an increase in the misuse of opioids which were noted in Africa and Asia (Chikezie & Ebuenyi, 2019). Tramadol use has been associated with higher health care costs as seen in the United States (US) where it was used for the treatment of osteoarthritis (Huizinga et al., 2022). The numerous side effects that can arise from the use of tramadol warrant that it be chosen carefully to treat patients, after assessing the risk to benefits ratio and that patients must be carefully monitored for any possible side effects (Subedi et al, 2018).

Guidelines are derived from synthesised evidence translated into practice-orientated recommendations and their goal is to guide decisions regarding the diagnosis and treatment in specific areas of health care (Govender *et al*, 2015). The overall role of guidelines is to standardise medical care and help clinicians make better decisions and poor adherence to these contribute to poor health outcomes and increased risks with resultant adverse events (Govender *et al*, 2015).

The STGs and EML serve as a guide for practitioners in the management of pain and other conditions, however, little is known with regards to compliance to these guidelines when prescribing analgesics at hospital level in Limpopo, South Africa. It is hoped that the findings of this study will address this gap.

1.2 Aims and objectives

The overall aim of the research was to review the use of analgesics in the management of chronic mild to moderate pain in terms of compliance with STGs by prescribers and to determine the cost implication of failure to follow STGs in pain management for the health care facility/department. Prescriber awareness of the cost implications of non-adherence to guidelines was also assessed.

The objectives of the study were:

1.2.1 To assess the utilization of analgesics in the management of chronic mild to moderate pain at a hospital level, in a general ward.

1.2.2 To determine whether the South African STGs were followed when treating patients for mild to moderate pain.

1.2.3 To determine prescriber awareness of STGs in the management of mild to moderate pain.

1.2.4 To ascertain prescriber experience on the misuse of tramadol when treating patients for pain.

1.2.5 To calculate the cost implication of non-compliance with the STGs by prescribing tramadol as first-line treatment in the management of mild to moderate pain instead of using paracetamol as prescribed in the guidelines.

1.3 Significance of the study

One of the aims of the NDP is "to promote rational prescribing, dispensing and use of drugs by medical, paramedical and pharmaceutical personnel and to support the informed and appropriate use of drugs by the community." (National Drug Policy for South Africa, 1996). The Hospital Level Adults (2019) STG and EML for South Africa, provides a guideline on optimal pain management which can be achieved by ascertaining the aetiology and perpetuating factors and managing the pain accordingly. The use of the Pain, Enjoyment and General Activity (PEG) scale is also recommended to measure care outcomes by evaluating the pain severity, quality of life and functionality (STG /EML for South Africa, Hospital Level Adults (2019).

Following a common concern expressed by all hospitals in the district regarding the prescribing patterns of tramadol (Department of Health, 2018); this study was undertaken to determine whether tramadol was prescribed in compliance with the recommendations in the STG.

The findings of the study provided information on compliance to STGs and recommendations to strengthen compliance with STGs. These might promote positive treatment outcomes for the patient population, thus reducing adverse reactions and the potential for dependence and abuse of tramadol. The cost implication for the increase in tramadol use were also highlighted.

1.4 Research methodology

1.4.1 Study design and setting

The hospital where the study was conducted was a district hospital in the Vhembe District of Limpopo. It is made up of four wards; general, paediatric, theatre and a maternity ward as well as a casualty and outpatient department.

This study was a prospective chart review which was conducted at the general ward of the district hospital for six months from the 1st of April 2021 to 30 September 2021 in Limpopo, South Africa. All the prescriptions of patients that were admitted and being treated for chronic mild to moderate pain in the general ward for the 6 months were recorded, resulting in 224 patients.

An Excel spreadsheet was used to record patient demographics; diagnosis; pain medication prescribed; dosage regimen; prescriber post and prescriber compliance with STGs. The treatment regimens for pain that were captured included paracetamol; ibuprofen; tramadol prescribed individually, as well as combinations of paracetamol and ibuprofen; paracetamol and tramadol; and a combination of all three, viz. paracetamol, ibuprofen and tramadol.

The STGs/EML Hospital level Adults (2019) guidelines for the management of chronic mild to moderate pain were used to assess the recorded prescriptions for compliance. According to these guidelines, paracetamol is indicated as first line treatment followed by a non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen which can be used alone or in combination with paracetamol and opioids, i.e. tramadol.

To determine the cost implication of failure to comply with STGs/EML Hospital level Adults (2019), the total cost of compliant and non-compliant prescriptions was calculated. The cost of each analgesic was obtained from the Limpopo Province Pharmaceutical Depot (LPPD).

Purposive sampling was used to identify prescribers. Upon completion of the six month prescription review, all the prescribers who were on duty in the general ward during the data collection period were presented with a questionnaire. For the purpose of obtaining informed consent, an information document was provided to the prescribers for review and their consent to participate in the study was obtained. Questionnaires were distributed to the prescribers who agreed to participate in the study. For this study, a community service doctor (CSD) is defined as a newly qualified medical practitioner working in the public sector to serve a year of community service as a primary requirement by the NDoH. A medical officer (MO) is a permanently appointed medical practitioner who has completed a year of community service.

1.4.2 Questionnaire design

A questionnaire was used to assess prescriber knowledge and compliance to STGs when prescribing treatment for chronic mild to moderate pain in the ward for which data was collected only. It was manually distributed to the prescribers. The questionnaire consisted of seven closed-ended questions relating to the prescribers' awareness and compliance to STGs when prescribing analgesics for pain. It also had questions on the awareness of the cost implications of failure to comply with STGs and their experience on the misuse of tramadol when treating patients for chronic mild to moderate pain. The questionnaire was administered in English and disseminated in the month of October 2021.

1.4.3 Data analysis

Descriptive statistics and Excel were used for data analysis. The diagnoses for the patients recorded were very broad and were therefore based on the classification used in the STGs/EML Hospital level Adults (2019). The number of compliant and non-compliant prescriptions was calculated to determine the ratio of non-compliance. The total cost of compliant and non-compliant prescriptions was also calculated. Cost calculations for different scenarios where the non-compliant prescriptions were assumed to be compliant by following the steps outlined in the STGs/EML and utilising the average costs of the different prescription regimens for pain were also done.

The responses of prescribers on compliance with the STGs were grouped for each question to determine the overall level of compliance to these guidelines when managing patients for pain and assessing the prescribing of and management of patients on tramadol by prescribers.

1.4.4 Ethical approval

Full ethical approval was obtained from the University of KwaZulu-Natal's Biomedical Research Ethics Committee (BREC) - reference number BREC/00001488/2020. In line with BREC recommendations, distributed questionnaires were accompanied by a letter of invitation outlining the purpose of the study to the potential participants, as well as an informed consent document (see Annexure 4) which was signed by the participants.

1.4.5 Permission from the Limpopo Department of Health

This study was granted gatekeeper approval by the Limpopo Department of Health (Ref: LP_2020_12_007) (see Annexure 2).

1.5 Chapter 1 summary

This chapter summarizes the study's background and rationale, aims and objectives, significance, and research methodology.

References:

Chikezie, U. E., & Ebuenyi, I. D. (2019). Tramadol misuse in the Niger Delta; A review of cases presenting within a year. *Journal of Substance use*, *24*(5), 487-491.

Department of Health (2018) PTC Meeting, Vhembe District , 25 June 2018.

Govender, I., Adedeji, A. R., & Tumbo, J. (2015). Adherence of doctors to a clinical guideline for hypertension in Bojanala district, North-West Province, South Africa. *African Journal of Primary Health Care and Family Medicine*, *7*(1), 1-6.

Igumbor, E. U., Puoane, T., Gansky, S. A., & Plesh, O. (2012). Pain as a reason for primary care visits: cross-sectional survey in a rural and periurban health clinic in the Eastern Cape, South Africa. *South African Family Practice*, *54*(3), 256-263.

National Department of Health, South Africa. (2019). Standard Treatment Guidelines and Essential Medicines List for South Africa: Hospital level (Adults). Availablefrom:http://www.health.gov.za/index.php/component/phocadownload/category/286-hospital-level-adults?download=2409:hospital-level-adult-2015-v5-0

National Drug Policy, South Africa. (1996). National Drug Policy for South Africa. *Department of Health*. Available from: http://apps.who.int/medicinedocs/documents/s17744en/s17744en.pdf

Osman, L. (2003). *PSSA Pharmacy Law Compendium* (Volume 1). Alexis Nexis, Butterworths.

Rossiter D. University of Cape Town & South African Medical Association (1998-). (2014). *South african medicines formulary* (11th ed.). Health and Medical Pub. Group of the South African Medical Association.

Schellack, N., & Annor, A. S. (2016). Optimising pain management-An update. *South African Family Practice*, *58*(2).

Subedi, M., Bajaj, S., Kumar, M. S., & Mayur, Y. C. (2019). An overview of tramadol and its usage in pain management and future perspective. *Biomedicine & Pharmacotherapy*, *111*, 443-451.

Truter, I. (2016). Prescribing patterns of opioids dispensed by pharmacies in South Africa. *Value in Health,* 19(7), A598.

CHAPTER 2

2. LITERATURE REVIEW

This chapter presents literature related to the management of chronic mild-to-moderate pain, the role of tramadol in pain management and the benefits of compliance to STGs. It presents research on the impact of tramadol use and misuse in different countries.

2.1 Background on pain and its management.

The goal of pain management, includes, in addition to pain reduction, the improvement of function, sleep and well-being. The collaborative effort of the healthcare team managing the patient is required to achieve the best outcome in pain management which includes minimizing pain while managing the side effects of the pain medication (Schellack & Annor, 2016). Pain can be classified as acute or chronic. Acute pain is defined as pain that is limited to a duration of fewer than 30 days and serves a protective purpose (Cole, 2002). Chronic pain on the other hand is pain that persists for more than 6 months despite normalization after injury and has little protective significance (Cole, 2002). Pain is not 'just' an indicator of an underlying disease or damage process but a problem in its own right and one that takes a great toll on individuals and society. To achieve the objective of improving the quality of life, the right approach based on the right communication between the caregiver and the patient should be followed. It is recommended that the alleviation of pain as a symptom should be seen as a therapeutic target (Kumar, 2007).

The Hospital Level Adults (2019) STG and EML for South Africa, provide clear guidelines on chronic mild to moderate pain management that should be followed by practitioners, as follows:

- **Mild/moderate pain:**

Paracetamol, oral, 1g 6 hourly when required.

- **Non-steroidal anti-inflammatory drug (NSAID)**

Example of NSAID – Ibuprofen 400mg 8 hourly with meals.

May be used in combination with paracetamol or opioids.

In high-risk patients i.e. patients older than 65 or with a history of peptic ulcer disease, or on concomitant warfarin, aspirin or corticosteroids:
Add a proton pump inhibitor such as lansoprazole, oral, 30 mg daily.

Opioids may be included in the pain management strategy for moderate-to-severe chronic pain with NSAIDs when optimal use of first-line therapy has failed (Raff et al., 2014). It is recommended by WHO (2014) that when the use of paracetamol and/or NSAIDs and COX-II inhibitors alone is inadequate and strong opioids are unavailable or their use is not yet warranted, tramadol can be used for the management of pain.

2.2 Tramadol use in the management of pain

Tramadol hydrochloride was synthesized by Drs Flick and Frankus at Grunenthal Research Laboratories in Aachen, Germany in 1962 (Zulkarnain, 2004). It has an agonist effect at the μ-opioid receptor and has noradrenergic and serotonergic effects (Raff et al.,2014).

Tramadol is extensively metabolized in the liver via CYP3A and CYP2D and thus other drugs acting on these and other enzymes may interact and affect the pharmacokinetics properties of tramadol. The serum concentrations of tramadol may be altered by inducers such (carbamazepine) or inhibitors (cimetidine, quinidine, fluoxetine and amitriptyline) of these two isoenzymes (Zulkarnain, 2004).

The numerous side effects that can arise from the use of tramadol indicate that it should be chosen carefully to treat patients outlining the risk to benefits ratio and patients must be carefully monitored for any possible side effects (Subedi et al, 2018).

The long-term use of tramadol can lead to physical dependence and addiction with the risk of an overdose which can lead to a coma and even death (Subedi et al., 2018). The withdrawal from tramadol could be one factor leading to abuse and therefore physicians are cautioned to be vigilant for any signs or symptoms of abuse in their patient population (Senay et al., 2003). To weigh the risk versus the benefits of tramadol in pain management, physicians must be

aware of its adverse effects, substantial abuse potential and drug interactions (Nakhaee et al., 2021).

Zin et al. (2018) mention in their study that the safe and appropriate use of analgesics is imperative as irrational use may have contributed to increased morbidity and mortality with a subsequent increase in the demand on health care resources and costs. The findings of the same study showed that the increase in tramadol use was reported to be linked with the increase of emergency department visits involving tramadol adverse reactions, misuse and abuse, and suicidal attempts.

Tramadol use in Australian hospitals was found to be on the rise since it was first marketed in 1998 and its widespread use in hospital settings would be associated with increased drug costs due to its significantly higher acquisition cost compared to alternative analgesics while yielding minimal benefit for the majority of patients (Zulkarnain, 2004).

A drug utilization study to analyze opioid prescribing patterns in South African community pharmacies conducted in 2013 found tramadol in combination with paracetamol to account for 71.90 % of products and it was followed by tramadol alone accounting for 22.74% (Truter, 2016). The use of the NSAIDs, diclofenac, was found to be a more cost-effective option than tramadol in patients with post cesarean pain emphasizing that the unwarranted use of tramadol can lead to an increase in medicine costs (Merrikhohaghi et al., 2015).

The prescribing of opioids for pain should be done with caution as although prescribed for legitimate pain, it can still lead to opioid use disorder (Patrick, 2017). Thiels et al. (2019) conducted a study to determine the risk of transition from acute to prolonged opioid use in opioid-naïve patients treated with tramadol for postoperative pain and the finding indicated that although the prescribing of tramadol was infrequent, it was the third most prescribed opioid and most discharge prescriptions were associated with a higher risk of prolonged opioid use.

Global trends indicating an increase in the misuse of opioids were noted in Africa and Asia (Chikezie & Ebuenyi, 2019). A drug utilization review of tramadol at a regional hospital in South Africa found the expenditure on tramadol to have doubled in recent years with the outpatient pharmacy department having the highest expenditure (Fynn et al., 2020). Of the 77 countries that responded to the International Narcotics Board survey on the issue of tramadol

abuse, it appeared to be problematic for 32 countries (Ahmed et al., 2018). Clinicians should consider various treatment options in the management of chronic pain and these include opioid and nonopioid pharmacotherapies (ibuprofen) and nonpharmacological treatments (physical therapy) that have been shown to be safer and more effective than opioids in some conditions (Saloner et al., 2018). Thus, globally guidelines have been introduced to assist prescribers in managing pain and minimizing tramadol use and abuse (Jayawardana et al., 2021).

2.3 Benefits of clinical guidelines

The Institute of Medicine (1990) as cited by Woolf et al. (1999) defines clinical guidelines as 'systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances' (p.527). It has also been identified by Woolf et al. (1999) that the increased interest in clinical guidelines arose from, among other issues, rising healthcare costs, fueled by increased demand for care, more expensive technologies and an aging population. Guidelines are seen by clinicians, policymakers and payers as a tool for closing the gap between what clinicians do and what sufficient evidence supports.

Practice guidelines have potential benefits for patients and these include improved health outcomes, promotion of interventions of proven outcome while discouraging ineffective ones, reducing morbidity and improving quality of life (Woolf et al., 1999). The potential benefits for health care professionals are the improvement in the quality of clinical services, improving the consistency of care and proving authoritative recommendations that reassure practitioners about the appropriateness of their treatment policies while alerting them to interventions unsupported by good science (Woolf et al., 1999). Health care systems have found that clinical guidelines may be effective in improving efficiency, often by standardizing care and optimizing value for money (Woolf et al., 1999).

A study by Siko & van De Venter (2017) indicated that the EML and STGs have enabled nurses to control clinical conditions of 68% of patients with hypertension (HPT), 82% with non-insulin dependent diabetes and 84% with asthma. Patient compliance, therefore, improved from 79% to 87% and the management of chronic diseases by nurses removed the burden of 79% of these patients from district hospitals (Siko & van De Venter, 2017).

Knowledge, guideline awareness and the period of working in private practice were one of the factors that influenced physician compliance with guidelines (Siko & van De Venter, 2017).

2.4 Factors that influence compliance to guidelines and the cost of non-compliance.

One of the factors that influence the compliance to guidelines was listed by Cabana et al. (1999) as the lack of awareness as a result of the expanding body of research which makes it difficult for any physician to be aware of every applicable guideline and critically apply it to practice. Physicians might not agree with specific guidelines or have a lack of expectancy that a recommendation will lead to an improved outcome and will therefore be less likely to adhere. Inertia to previous practice or the lack of motivation to change can also be a factor influencing compliance to guidelines.

A study by Szymanski, Badri and Mayosi (2018) found that the suboptimal adherence to evidence-based treatments as one of the reasons leading to high readmission rates of heart failure patients at Groote Schuur Hospital. A similar study in the North-West province of South Africa on the adherence of doctors to a clinical guideline had similar findings where doctors generally had poor adherence to clinical guidelines and adherence rates were related to the age and clinical experience of the practitioner (Govender *et al*, 2015). Irrational prescribing and poor compliance to hypertensive care was associated with comorbidities leading to a higher risk of polypharmacy, a high prevalence of adverse drug reactions and poor adherence (Mashoreza et al., 2021).

Menendez et. al (2006) conducted a study to assess the influence of guidelines on costs in the treatment of community-acquired pneumonia (CAP) and adherence to guidelines was found to be the cost-effective option with the ratio of 2,277 Euros per expected cure versus 2,567 Euros in those with nonadherent treatments. Orrick et al. (2004) as cited by Menendez et al. (2006) found that when comparing the cost of care in hospitalised patients with CAP, hospitalisation costs were higher; US$3,085, when treatment was not compliant with guideline recommendations compared with US$ 2,047 when compliant. Nonadherence to guidelines was also found to increase the risk of asthma-related hospitalization and health care costs as a result of an increase of exacerbations in patients (Piecoro et al.,2001).

Adherence to guidelines can be improved by training, increasing access to up-to-date STGs, regular availability of medicines listed in the STGs/EML and auditing of prescriber practices (Campbell et al., 2021). There is a gap in the literature concerning pain management and the assessment of prescriber compliance to guidelines in the setting of South African public hospitals and this study is necessary to identify and shed light on these factors.

References:

Ahmed, A. I., El-Dawy, K., Fawzy, M. M., Abdallah, H. A., & Elsaid, H. N. (2018). Retrospective review of tramadol abuse. *Slov Vet Res*, *55*(55), 471-483.

Cole, B. (2002). Pain Management: Classifying, understanding, and treating pain. *Hospital Physician, 38,* 23-30.

Fynn, A., Helberg, E., Godman, B., & Meyer, J. C. (2020). Drug utilization review of tramadol hydrochloride in a regional hospital in South Africa; findings and implications. *Hospital Practice*, *48*(2), 92-99.

Cabana, M. D., Rand, C. S., Powe, N. R., Wu, A. W., Wilson, M. H., Abboud, P. A. C., & Rubin, H. R. (1999). Why don't physicians follow clinical practice guidelines?: A framework for improvement. *Jama*, *282*(15), 1458-1465.

Campbell, S. M., Meyer, J. C., & Godman, B. (2021). Why compliance to national prescribing guidelines is important especially across sub-Saharan Africa and suggestions for the future. *Journal of Biomedical Pharmaceutical Sciences*, *4*(6),1-7.

Chikezie, U. E., & Ebuenyi, I. D. (2019). Tramadol misuse in the Niger Delta; A review of cases presenting within a year. *Journal of Substance use*, *24*(5), 487-491.

Govender, I., Adedeji, A. R., & Tumbo, J. (2015). Adherence of doctors to a clinical guideline for hypertension in Bojanala district, North-West Province, South Africa. *African Journal of Primary Health Care and Family Medicine*, *7*(1), 1-6.

Jayawardana, S., Forman, R., Johnston-Webber, C., Campbell, A., Berterame, S., de Joncheere, C., & Mossialos, E. (2021). Global consumption of prescription opioid

analgesics between 2009-2019: a country-level observational study. *EClinicalMedicine*, *42*, 101198.

Kumar, N. (2007). WHO normative guidelines on pain management. *Geneva: World Health Organization*, 3-4.

Mashozhera, S., Bamitale, S. K., Godman, B., & Kibuule, D. (2021). Compliance to hypertensive prescribing guidelines and blood pressure control in elderly patients in Namibia: findings and implications. *Journal of Pharmaceutical Health Services Research*, *12*(1), 53-60.

Menéndez, R., Reyes, S., Martínez, R., de la Cuadra, P., Vallés, J. M., & Vallterra, J. (2007). Economic evaluation of adherence to treatment guidelines in nonintensive care pneumonia. *European Respiratory Journal*, *29*(4), 751-756.

Merrikhihaghi, S., Farshchi, A., Farshchi, B., Farshchi, S., & Abedin-Dorkoosh, F. (2015). Tramadol versus diclofenac in pain management after cesarean section: A cost analysis study. *Journal of Pharmacoeconomics and Pharmaceutical Management*, *1*(1/2), 22-24.

Nakhaee, S., Hoyte, C., Dart, R. C., Askari, M., Lamarine, R. J., & Mehrpour, O. (2021). A review on tramadol toxicity: mechanism of action, clinical presentation, and treatment. *Forensic Toxicology*, 1-18.

National Department of Health, South Africa. (2019). Standard Treatment Guidelines and Essential Medicines List for South Africa: Hospital level (Adults). Availablefrom:http://www.health.gov.za/index.php/component/phocadownload/category/286-hospital-level-adults?download=2409:hospital-level-adult-2015-v5-0

Patrick S.W. (2017). A comprehensive approach to the opioid epidemic. Obstetrics and gynecology,103(1),7-9. https://doi.org/10.1079/AOG.0000000000002118

Piecoro, L. T., Potoski, M., Talbert, J. C., & Doherty, D. E. (2001). Asthma prevalence, cost, and adherence with expert guidelines on the utilization of health care services and costs in a state Medicaid population. *Health Services Research*, *36*(2), 357.

Raff, M., Crosier, J., Eppel, S., Sarembock, B., Meyer, H., & Webb, D. (2014). South African guideline for the use of chronic opioid therapy for chronic non-cancer pain: guideline. *South African Medical Journal*, *104*(1), 79-89.

Saloner, B., McGinty, E. E., Beletsky, L., Bluthenthal, R., Beyrer, C., Boticelli, M., & Sherman, S. G. (2018). A public health strategy for the opioid crisis. *Public Health Reports,* 133(1_suppl), 24S-34S.

Schellack, N., & Annor, A. S. (2016). Optimising pain management-An update. *South African Family Practice*, *58*(2).

Senay, E. C., Adams, E. H., Geller, A., Inciardi, J. A., Muñoz, A., Schnoll, S. H., ... & Cicero, T. J. (2003). Physical dependence on Ultram®(tramadol hydrochloride): both opioid-like and atypical withdrawal symptoms occur. *Drug and Alcohol Dependence*, *69*(3), 233-241.

Siko, P. R., & van Deventer, C. (2017). Compliance with standard treatment guidelines in the management of hypertension: a review of practice of healthcare workers in Potchefstroom, North West Province, South Africa. *South African Family Practice*, *59*(2), 72-77.

Subedi, M., Bajaj, S., Kumar, M. S., & Mayur, Y. C. (2019). An overview of tramadol and its usage in pain management and future perspective. *Biomedicine & Pharmacotherapy*, *111*, 443-451.

Szymanski, P. Z., Badri, M., & Mayosi, B. M. (2018). Clinical characteristics and causes of heart failure, adherence to treatment guidelines, and mortality of patients with acute heart failure: Experience at Groote Schuur Hospital, Cape Town, South Africa. *South African Medical Journal*, *108*(2), 94-98.

Thiels, C. A., Habermann, E.B., Hooten, W. M., & Jeffrey, M.M. (2019). Chronic use of tramadol after acute pain episode: cohort study. *British Medical Journal,* 365.

Woolf, S. H., Grol, R., Hutchinson, A., Eccles, M., & Grimshaw, J. (1999). Potential benefits, limitations, and harms of clinical guidelines. *British Medical Journal*, *318*(7182), 527-530.

World Health Organization, Expert Committee on Drug Dependence (2014) Tramadol Update Review Report. Available from: http://www.who.int/medicines/areas/quality_safety/TRAMADOL_IFPMA_Comments.pdf

Zin, C. S., Nazar, N. I., Rahman, N. S., Alias, N. E., Ahmad, W. R., Rani, N. S., ... & Ye, F. L. (2018). Trends and patterns of analgesic prescribing in Malaysian public hospitals from 2010 to 2016: tramadol predominately used. *Journal of Pain Research*, *11*, 1959.

Zulkarnain, B. S. (2004). The adherence to prescribing guidelines: a drug utilization evaluation of tramadol. *Folia Medica Indonesiana*, *40*(1).

CHAPTER 3

MANUSCRIPT FOR SUBMISSION AND PUBLICATION

3.1 Introduction

This chapter describes the general findings and discussion of the results of the study and is presented in the form of a manuscript entitled "Drug utilization review of analgesics in the management of pain and the assessment of prescriber compliance with South African standard treatment guidelines at hospital level" submitted to Hospital Practice Journal (see Annexure 6) and formatted according to journal guidelines found at (https://www.tandfonline.com/action/authorSubmission?show=instructions&journalCode=ihop20).

3.2 Manuscript

Drug Utilization Review of Analgesics in the Management of Pain According to Guidelines at a Hospital Level in Limpopo, South Africa.

Muhluri Rikhotso[1], Fatima Suleman [2], Varsha Bangalee[3]

[1]School of Health Sciences, University of KwaZulu Natal, Westville Campus, Private Bag X54001, Durban 4000, South Africa. Contact number: 0769155214 email: muhlurialvn@gmail.com

[2]Professor Fatima Suleman, Research Professor, School of Health Sciences, Westville Campus, University of KwaZulu-Natal, South Africa. Postal Address: Private Bag X54001, Durban, 4000. Contact Details: Tel: +27 31 260 7941; Fax:+27 31 260 7906/7792; email: sulemanf@ukzn.ac.za

[3]Prof Varsha Bangalee (B.Pharm, M.Pharm, PhD) Institution: Discipline of Pharmaceutical Sciences, School of Health Sciences, Westville Campus, University of KwaZulu-Natal, South Africa. Postal Address: Private Bag X54001, Durban, 4000. Contact Details: Tel: +27 31 2607908; Fax: +27 31 260 7792; email: bangalee@ukzn.ac.za

*Corresponding author email: muhlurialvn@gmail.com

Contact number: +27 769155214

[1]School of Health Sciences, University of KwaZulu Natal, Westville Campus, Private Bag X54001, Durban 4000, South Africa.

ABSTRACT

Background

Standard Treatment Guidelines (STGs) offer guidance on rational medicine use for common conditions including pain. A perceived increase in tramadol use for chronic mild to moderate pain required that research be undertaken to confirm the use of tramadol outside prescribed guidelines.

Methods

A prospective quantitative study was conducted for 6 months at a district hospital in Limpopo. All records of patients admitted and treated for pain during this period, were reviewed for compliance to chronic mild to moderate pain management as per the 2019 Adult Hospital level STG for South Africa. The total cost of compliant and non-compliant prescriptions was calculated. A survey was disseminated among prescribers to determine awareness and compliance with STGs as well as cost implications of non-compliance to guidelines.

Results

In total, 224 prescriptions were recorded. Patients initiated on paracetamol for pain (57.5%), tramadol alone (8.5%); paracetamol and tramadol (24%); ibuprofen (1.3%); paracetamol and ibuprofen (5.4%); and 3% were switched between pain regimens. The prescription compliance rate in terms of the STGs stepwise process of pain management was 90.6% with 9.4% non-compliance.

The total cost of compliant and non-compliant prescriptions was R1128,10. It was found that STG/EML prescriber compliance would have resulted in a cost saving.

Prescribers' awareness of STGs was 100%, with a reported compliance rate of 33%, while 50% stated that they occasionally follow guidelines. Only 33% followed STGs when prescribing tramadol and 50% monitored patients although having encountered tramadol misuse. The study found that 67% of prescribers have poor knowledge of the cost implication of non-compliance to STG.

Conclusion

The study identified a prescription compliance rate of 90.6% for chronic mild to moderate pain prescriptions. This indicates an increased adherence to guidelines by prescribers, in contrast to previous studies.

Keywords: Drug utilization review, paracetamol, tramadol, standard treatment guidelines, pain management.

Background and introduction

The National Department of Health (NDoH) remains committed to ensuring the availability and accessibility of good quality essential medicines that are effective, safe, and affordable as well as the rational use thereof. Through the Standard Treatment Guidelines (STG) and Essential Medicines List (EML), practitioners are provided with a clear guideline on rational pain management [1]. It is recommended that the alleviation of pain as a symptom should be seen as a therapeutic target [2] and the goal of pain management, includes, in addition to pain reduction, the improvement of function, sleep and well-being [3].

The STG for South Africa, Hospital Level (Adults) [1] recommends paracetamol and ibuprofen for the management of chronic mild to moderate pain and tramadol can be added to NSAIDS for mild to moderate pain. It is recommended by the World Health Organization (WHO) [4] that when the use of paracetamol and/or NSAIDs and COX-II inhibitors alone is inadequate and strong opioids are unavailable or their use is not yet warranted, tramadol can be used for the management of pain. Tramadol hydrochloride was synthesized by Drs Flick and Frankus at Grunenthal Research Laboratories in Aachen, Germany in 1962 [5]. It has an agonist effect at the μ-opioid receptor and has noradrenergic and serotonergic effects [6]. The numerous side effects that can arise from the use of tramadol indicate that it should be chosen carefully to treat patients outlining the risk to benefits ratio and patients must be carefully monitored for any possible side effects [7].

The prescribing of opioids for pain should be done with caution as although prescribed for legitimate pain, it can still lead to opioid use disorder [8]. The long-term use of tramadol can lead to physical dependence and addiction with the risk of an overdose which can lead to a coma and even death [7]. To weigh the risk versus the benefits of tramadol in pain management,

physicians must be aware of its adverse effects, substantial abuse potential and drug interactions [9].

Global trends indicating an increase in the misuse of opioids were noted in Africa and Asia [10]. In South Africa, a drug utilization study to analyze opioid prescribing patterns in community pharmacies conducted in 2013 found tramadol in combination with paracetamol to account for 71.90 % of products and it was followed by tramadol alone accounting for 22.74 % [11]. These findings are similar to those of a drug utilization review by Fynn et al. [12] where the prescribing of tramadol in the surgical wards of a Regional Hospital in South Africa was found to be at 51.5%. The increase in tramadol use also has budget implications for institutions. In Australian hospitals, tramadol use was found to be on the rise since it was first marketed in 1998 and its widespread use in hospital settings was associated with increased drug costs due to its significantly higher acquisition cost compared to alternative analgesics while yielding minimal benefit for the majority of patients [5]. A recent drug utilization review in a Regional Hospital in South Africa found the expenditure on tramadol to have double with the highest expenditure in the outpatient department [12].

The overall aim of the research was to review the use of analgesics in the management of chronic mild to moderate pain in terms of compliance with STGs by prescribers and to determine the cost implication of failure to follow STGs. Prescriber awareness of the cost implications of non-compliance to guidelines was also assessed.

Methods

Study design and setting

The hospital where the study was conducted is a district hospital in the Vhembe District of Limpopo. It is made up of four wards; general, paediatric, theatre and a maternity ward as well as a casualty and outpatient department.

This study was a prospective chart review which was conducted at the general ward of the district hospital for six months from the 1st of April 2021 to 30 September 2021 in Limpopo South Africa. All the prescriptions of patients that were admitted and being treated for chronic mild to moderate pain in the general ward for the 6 months were recorded, resulting in a total of 224 patients.

An Excel spreadsheet was used to record patient demographics; diagnosis; pain medication prescribed; dosage regimen; prescriber post and prescriber compliance with STGs. The treatment regimens for pain that were captured included paracetamol; ibuprofen; tramadol as prescribed individually, as well as combinations of paracetamol and ibuprofen; paracetamol and tramadol; and a combination of all three, viz. paracetamol, ibuprofen and tramadol.

The STGs Hospital level Adults (2019) guidelines for the management of chronic mild to moderate pain were used to assess the recorded prescriptions for compliance. According to these guidelines, paracetamol is indicated as first line treatment followed by a non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen which can be used alone or in combination with paracetamol and opioids, i.e. tramadol.

To determine the cost implication of failure to comply with STG/EML Hospital level Adults (2019) [1], the total cost of compliant and non-compliant prescriptions was calculated. The

cost of each analgesic was obtained from the Limpopo Province Pharmaceutical Depot (LPPD) [13].

Purposive sampling was used to identify prescribers. After the six months of data collection was completed, a roster for that period was used to identify the prescribers who were on duty. For the purpose of obtaining informed consent, an information document was provided to the prescribers for review and their consent to participate in the study or not was obtained. Questionnaires were distributed to the prescribers who agreed to participate in the study.

Questionnaire design

A questionnaire was used to assess prescriber knowledge and adherence to STGs when prescribing treatment for chronic mild to moderate pain in the ward. It was manually distributed to the prescribers. The questionnaire had seven close-ended questions relating to the prescribers' awareness and compliance to STGs when prescribing analgesics for pain. It also had questions on the awareness of the cost implication of failure to comply with STGs and their experience on the misuse of tramadol when treating patients for pain. The questionnaire was administered in English and this was done in the month of October 2021.

Data analysis

Descriptive statistics and Excel were used for data analysis. The diagnoses for the patients recorded were very broad and therefore classification of conditions used in the STG/EML Hospital level Adults (2019) was followed [1]. The number of compliant and non-compliant prescriptions was calculated to determine the ratio of non-compliance. The total cost of compliant and non-compliant prescriptions was also calculated. Cost calculations were modelled for different scenarios where the non-compliant prescriptions were assumed to be

compliant by following the guidelines for mild to moderate chronic pain management as outlined in the STGs/EML and utilising the average costs of the different prescription regimens for pain.

The responses of prescribers on compliance with the STGs were grouped for each question to determine the overall level of compliance to these guidelines when managing patients for pain and assessing the prescribing of and management of patients on tramadol by prescribers. For this study, a community service doctor (CSD) is defined as a newly qualified medical practitioner working in the public sector to serve a year of community service as a primary requirement by the NDoH. A medical officer (MO) is a permanently appointed medical practitioner who has completed a year of community service.

Ethical approval

Full ethical approval was obtained from the University of KwaZulu-Natal's Biomedical Research Ethics Committee (BREC)- reference number BREC/00001488/2020. In line with BREC recommendations, distributed questionnaires were accompanied by a letter of invitation outlining the purpose of the study to the potential participants, as well as an informed consent document which was signed by the participants. Gatekeeper permission was granted by the Limpopo Department of Health (Ref: LP_2020_12_007).

Results

The total number of inpatient prescriptions recorded for 6 months was 224; 103 (46%) females and 121 (54%) males. The ages of these patients ranged between 14 and 106 years. Table 1 provides data on the prescription of analgesics as per patient demographics.

Table 1: Descriptive data on analgesics prescriptions.

Medicine Regimen	Number of Prescriptions per Gender		Age Range	Mean Duration of Treatment	Number of Prescriptions by Post of Prescriber
	Male	Female			
Paracetamol	62	67	14 - 100	4 days	39 (CS); 90 (MO)
Ibuprofen	2	1	26 - 62	3 days	1 (CS); 2 (MO)
Paracetamol and ibuprofen	6	6	18 - 106	3 days	3 (CS); 9 (MO)
Tramadol	12	7	20 – 89	3 days	2 (CS); 17 (MO)
Paracetamol and tramadol	35	19	18 - 92	4 days	20 (CS); 34 (MO)
Started on paracetamol and switched to tramadol	2	1	20 - 80	5 days	2 (CS); 1 (MO)
Started on ibuprofen and switched to paracetamol and tramadol	1	0	37	4 days	MO
Started on tramadol and switched to paracetamol	0	1	28	4 days	CS
Started on paracetamol and ibuprofen then switched to tramadol	0	1	53	4 days	MO
Started on paracetamol and tramadol then switched to paracetamol	1	0	80	3 days	MO
Total	**121**	**103**			

As presented in Table 1, the highest number of patients were on paracetamol with 129 prescriptions, 90 prescriptions prescribed by medical officers. The paracetamol and tramadol regimen had the second highest number of prescriptions, (54), and 34 of these prescriptions were prescribed by medical officers. Both the tramadol, and paracetamol and tramadol regimen patients were predominantly issued to male patients. The duration of treatment for all medicine regimens ranged between three and five days.

The prescriptions were categorized into the diagnosis of patients as recorded on the prescriptions (see Table 2).

Table 2: Number of patients (%) per medicine regimen according to diagnosis categories

Diagnosis Category	Paracetamol Total n (%)	Ibuprofen Total n (%)	Paracetamol and ibuprofen Total n (%)	Tramadol Total n (%)	Paracetamol and tramadol Total n (%)	Patients with regimen switch Total n (%)
Blood and blood forming organs (Anemia) n= 8	7 (5.4)				1 (1.8)	
Cancer n=5					5 (9.3)	
Conditions of the alimentary canal (GI disorders, hepatic disorders, diarrhea) n=12	10 (7.8)			1 (5.2)	1 (1.8)	
Conditions of the cardiovascular system n=15	12 (9.3)	1 (33.3)			2 (3.7)	
Conditions of the endocrine system (Diabetes Mellitus) n=15	12 (9.3)			1 (5.2)	2 (3.7)	
Conditions of the respiratory system n=29	27 (21)		1 (8.3)		1 (1.8)	
Dermatology /wounds n=23	11 (8.5)	1 (33.3)	3 (25)		5 (9.3)	3 (42.8)
Fractures n=45	9 (6.9)		2 (16.6)	8 (42)	24 (44)	2 (28.5)
Gynecological conditions (miscarriage, termination of pregnancy) n=20	14 (10.9)		2 (16.6)	3 (15.8)	1 (1.8)	
Musculoskeletal system (arthritis) n=1					1 (1.8)	
Neurological disorders n=13	10 (7.8)			1 (5.2)	2 (3.7)	

Trauma n=20	3 (2.3)		2 (16.6)	4 (21)	9 (17)	2 (28.5)
Urological disorders n=6	5 (3.8)		1 (8.3)			
Other n=12	9 (6.9)	1 (33.3)	1 (8.3)	1 (5.2)		
Total = n=224	**129**	**3**	**12**	**19**	**54**	**7**

Diagnosis categories were according to the Standard Treatment Guidelines (STG) and Essential Medicines List (EML) for South Africa, Hospital Level Adults, (2019).

Patients initiated on paracetamol (Table 2)

From the 224 prescriptions reviewed, the number of patients that received paracetamol as first-line treatment was 129 (58%) with 67 being females and 62 being males (Table 2). The age range of these patients was between 14 and 100 years. The mean duration of treatment was 4 days. The doses prescribed for these patients were within the maximum recommended dose of 4g daily although some patients received a dose of 1g 8 hourly while others received a dose of 1g 6 hourly. Patients with conditions of the respiratory tract and those with gynecological conditions formed the majority of patients in this group i.e. 21% and 10.9% respectively. Seventy percent of these prescriptions were written by medical officers and 30% were prescribed by community service doctors.

The STG for Hospital level for Adults in South Africa (2019) [1] recommends paracetamol for the management of mild to moderate pain and therefore these 129 prescriptions were compliant with these guidelines.

Patients initiated on ibuprofen (Table 2)

Three patients (1.3%) were started on ibuprofen as first-line treatment for pain. Two were males and one was female, and the age range was between 26 and 62 years (Table 2). The dosage prescribed was similar for all three patients, that being 400 mg 8 hourly with the mean duration of treatment being 3 days. Two prescriptions were written by medical officers and one was written by a community service doctor.

According to the STG for Hospital level Adults (2019) [1] and guidelines outlined for the management of pain, these prescriptions were compliant. The diagnosis for this group of patients was conditions of the cardiovascular system and wounds.

Patients initiated on paracetamol and ibuprofen (Table 2)

There were 12 patients (5.3%) that were started on paracetamol in combination with ibuprofen. This group, comprised of six male and six female patients (Table 2). The age range for this group of patients was between 18 and 106 years. The majority of patients in this group presented with the diagnoses for the treatment of wounds, trauma, fractures and gynecological conditions. The average number of days on treatment was 3 days.

Nine prescriptions were written by medical officers and three were written by community service doctors. According to the treatment for mild to moderate pain as outlined in the STG for Hospital level Adults (2019) [1], these prescriptions were compliant.

Patients initiated on tramadol (Table 2)

A total of 19 patients (8.5%) were initiated on tramadol as first-line treatment for pain. Twelve of these patients were male and 7 were female. The age range for this group of patients was between 20 and 89 years. The mean duration of days on treatment was 3 days. The doses of tramadol were 50mg daily for 1 patient; 50 mg 12 hourly for 7 patients; 50 mg 8 hourly for 9 patients and 100 mg 12 hourly for 2 patients. The diagnosis for the majority of these patients was fractures for eight patients, trauma for four patients and three patients with gynaecological conditions. The prescriptions written by medical officers were 17 (89%) and 2 (11%) were by community service doctors.

According to the STG for Hospital level Adults (2019) [1] and the guidelines outlined for the management of pain, these prescriptions were not compliant as tramadol is indicated in

combination with NSAIDS for mild to moderate pain if a patient did not experience pain relief from paracetamol and ibuprofen.

Patients initiated on paracetamol and tramadol (Table 2)

A total of 54 (42%) patients, were initiated on a combination of paracetamol and tramadol. Of this group of patients, 35 were males and 19 were females. The age range was between 18 and 92 years. The mean duration of treatment was 4 days. The number of prescriptions written by medical officers was 34 (63%) and 20 (37%) were by written community service doctors.

The group that formed the largest percentage to receive this combination of analgesics was found to be those presenting with fractures and trauma patients. According to the STG for Hospital level Adults (2019) [1] tramadol has an improved effect when given with paracetamol for severe pain and the combination of these analgesic agents was found to enhance efficacy in complex pain states as they demonstrate a synergistic effect [14]. Tramadol has also been recommended for patients with musculoskeletal pain due to its safety and efficacy in this type of pain [14]. Paracetamol has a rapid onset and tramadol has a prolonged analgesic effect and therefore this combination delivers rapid and sustained pain relief greater than either agent alone [14]. This combination of analgesics is therefore rational treatment for this group of patients and is compliant according to the STG for Hospital level Adults (2019) [1].

Patients switched between treatment regimens (Table 2)

A total of 7 (3%) patients recorded were switched between the different analgesic agents. Of these patients, 3 were males and 4 were females.

Three patients were started on paracetamol 8 hourly for the average duration of 5 days and then switched to tramadol 50mg 8 hourly. The diagnoses for this group of patients were wounds, burns and trauma. These prescriptions were compliant according to the STGs Hospital level Adults (2019) [1]. The severity of pain and contraindications to ibuprofen could be the reasons ibuprofen was not prescribed. For selected patients in whom NSAIDs are contraindicated or who have not responded to simple analgesics such as paracetamol or aspirin, tramadol can be used for the management of pain [15].

A female patient with multiple abscesses was initiated on paracetamol and ibuprofen for five days and later switched to tramadol. According to the STGs for Hospital level Adults (2019), [1] the guidelines outlined for the management of pain were followed and therefore compliant.

Two patients, one male and one female, had the diagnosis of fractures. One patient was initiated on tramadol 50mg daily when necessary then switched to paracetamol 1g 8 hourly. This prescription was non-compliant according to the STGs for Hospital level Adults (2019) [1]. The other patient was initiated on paracetamol 1g 8 hourly then switched to tramadol 50mg 8 hourly and was compliant according to the STGs for Hospital level Adults (2019) [1].

This group only had one patient that was started on ibuprofen 400mg 8 hourly and then switched to tramadol and paracetamol. According to the STGs for Hospital level Adults (2019) [1], the steps followed for this patient were compliant with the guidelines.

Table 3: Total number of compliant versus non-compliant pain management prescriptions

Compliance with STGs/EML	**Number (%) of prescriptions (n=224)**
Compliant	203 (90.6%)
Non-compliant	21 (9.4%)

As can be seen in Table 3, the total number of compliant prescriptions was 203 (90.6%) and the total number non-compliant prescriptions was 21 (9.4%).

Table 4: The total and the average cost of compliant and non-compliant prescriptions

The total and the average cost of compliant and non-compliant prescriptions		
Compliance with STGs/EML	**Total cost of prescriptions (ZAR)**	**Average cost of prescriptions (ZAR)**
Compliant	R 1041.37	R 5.13
Non-compliant	R 86.73	R 4.13
Total cost of compliant and non-compliant prescriptions	**R1128,10**	

The total cost of both compliant and non-compliant prescriptions was calculated and found to be R 1128,10 (see Table 4). The total cost of compliant prescriptions was R 1041.37 with the average cost per prescription being R 5,13 and the total cost of non-compliant prescriptions was R 86.73 with the average cost being R 4.13.

Comparative expenditure on prescriptions that were compliant to the steps on pain management outlined in the STGs/EML Hospital level Adults (2019) to those that were not.

Scenario 1

The total cost of prescriptions if the non-compliant prescriptions were initiated on paracetamol was calculated. This was achieved by using the average cost of paracetamol per prescription regardless of the duration of treatment and the average cost was R3,11.

Table 5

Total expenditure of compliant and non-compliant prescriptions if the non-compliant prescriptions were initiated on paracetamol	
Total cost of compliant prescriptions (ZAR)	R 1041.37
Total cost of non-compliant prescriptions if initiated on paracetamol (ZAR)	R 65.31
Total cost	**R 1106.68**

The total cost of prescriptions when the non-compliant prescriptions were initiated on paracetamol was R 1106.68 (see Table 5).

Scenario 2

The total cost of prescriptions if the non-compliant prescriptions were initiated on paracetamol and ibuprofen according to the steps outlined in the STGs/EML Hospital level Adults (2019) was calculated. The average cost of compliant prescriptions initiated on paracetamol and ibuprofen regardless of the duration of treatment was utilised. This average cost was calculated and found to be R8.02.

Table 6

Total expenditure of compliant and non-compliant prescriptions if the non-compliant prescriptions were initiated on paracetamol and ibuprofen

Total cost of compliant prescriptions (ZAR)	R 1041.31
Total cost of non-compliant prescriptions if the non-compliant prescriptions were initiated on paracetamol and ibuprofen (ZAR)	R 168.42
Total cost	**R 1209.73**

The total expenditure of prescriptions if the non-compliant prescriptions were initiated on paracetamol and ibuprofen was found to be R 1209.73 (see Table 6).

Scenario 3

The total cost of prescriptions if the non-compliant prescriptions initiated on tramadol were instead initiated on paracetamol first, then ibuprofen and lastly tramadol was calculated. The cost of initiating patients as per the latter, as recorded in the data collected was used regardless of the duration of treatment and the cost was R 23,81.

Table 7

Total expenditure of compliant and non-compliant prescriptions if the non-compliant prescriptions on tramadol were initiated on paracetamol, ibuprofen and tramadol	
Total cost of compliant prescriptions (ZAR)	R 1041.31
Total cost of non-compliant prescriptions if the non-compliant prescriptions on tramadol were initiated on paracetamol firstly, then ibuprofen and finally on tramadol (ZAR)	R 500.09
Total cost	**R 1541.46**

The total cost of compliant and non-compliant prescriptions in this scenario was R1541.46 (see Table 7).

Prescriber responses in terms of compliance to Standard Treatment Guidelines (STGs) when prescribing medication for mild to moderate pain.

The questionnaire was distributed to ten prescribers who were working in the general ward during the data collection period, of which six gave consent to participate in the study and completed the questionnaire. Awareness of STGs by prescribers was at 100% while compliance reported by prescribers was at 33%. Fifty percent stated that they only follow guidelines occasionally. Although 83% stated that they do prescribe paracetamol for mild to moderate pain, only 33% agreed that they comply with STGs when prescribing tramadol. All prescribers had encountered patients who misuse tramadol but only 50% monitored patients after the medicine was prescribed. Knowledge on the cost implication of non-compliance with the STG was low as 67% of prescribers were not aware of these cost implications.

Table 8 summarizes the responses provided by prescribers on the questionnaires.

Table 8 – Prescribers' responses to questionnaires (n=6)

Questions	**Yes**	**No**	**Sometimes**
Are you aware of the STGs for the management of mild to moderate pain?	6	0	0
Do you follow these guidelines when prescribing treatment for the management of mild to moderate pain?	2	1	3
Do you prescribe paracetamol in the management of mild to moderate pain?	5	1	0

Do you follow the steps stated in the STGs when prescribing tramadol for pain?	2	2	2
Do you monitor patients on tramadol for adverse effects following prescribing the drug?	3	3	0
Have you encountered any patients who misuse tramadol?	6	0	0
Are you aware of the cost implication of not following Standard Treatment Guidelines (STG)?	2	4	0

Discussion

One of the aims of the NDP is "to promote rational prescribing, dispensing and use of medicines by medical, paramedical and pharmaceutical personnel and to support the informed and appropriate use of drugs by the community" [16].

The STGs serves to provide guidelines on the prescribing of analgesics along with other medicines. It was therefore important to assess the compliance by medical practitioners when prescribing treatment for the management of chronic mild to moderate pain, to identify possible reasons for non-compliance and to determine the cost implication of failure to follow these guidelines.

The STG for South Africa, Hospital Level Adults (2019) [1] provides guidelines on the management of chronic mild to moderate pain and paracetamol is the recommended first-line medicine. The number of patients that were treated for pain in compliance with these guidelines was 90.6% of the total number of patients.

It is recommended by the WHO [4] that when the use paracetamol and/or NSAIDs and COX-II inhibitors alone is inadequate and strong opioids are unavailable or their use is not yet warranted, tramadol can be used for the management of pain. Tramadol is indicated for severe pain, however, it should be considered when no response to pain management was achieved after the use of paracetamol or NSAIDs for patients in whom these medicines are not contraindicated.

In our study, 8.5% of prescriptions were for tramadol and 42% were for a combination of paracetamol and tramadol. These findings are similar to those of a drug utilization review by Fynn et al. [12] where the prescribing of tramadol in the surgical wards of a Regional Hospital in South Africa was found to be at 51.5%. It was further recommended that to prevent dependence on tramadol by patients, hospital management of different institutions should introduce, through the Pharmacy and Therapeutics Committee (PTC), drug monitoring and evaluation tools to assess the prescribing and dispensing patterns of tramadol on a monthly basis [12].

Ibuprofen is indicated for the management of chronic mild to moderate pain and it can be given alone or in combination with paracetamol. In our study, only 3 (1.3%) patients received ibuprofen and 12 (5.3%) were initiated on paracetamol and ibuprofen. The side effects of NSAIDs require that the prescriber should assess the patient for possible contraindications and in high-risk patients, over the age of 65, a history of peptic ulcer disease or if the patient is on warfarin, aspirin or corticosteroids, a proton pump inhibitor (lansoprazole 30mg daily) should be added [1]. It is also recommended that NSAIDs should be prescribed for a short duration and in the lowest effective dose to minimize the possible side effects. This indicates that by following these precautionary measures, NSAIDs can still be effectively and safely utilized for

the management of pain and can be combined with paracetamol without having to initiate patients on tramadol. The low number of NSAID prescriptions could however be attributed to the side effects that can be experienced with their use.

It is recommended in the STGs that the treatment regimen for the management of pain can be switched or another analgesic can be added in cases where there is no response or pain relief is not achieved. Only 3% of the patients recorded were switched between treatment regimens. One of these patients had a diagnosis of multiple abscesses and was started on paracetamol and ibuprofen then switched to tramadol after five days. For this patient, the steps of prescribing in pain management were followed and following no response, tramadol was prescribed to achieve the desired control of pain. The numerous side effects that can arise from the use of tramadol indicate that it should be chosen carefully to treat patients outlining the risk to benefits ratio and patients must be carefully monitored for any possible side effects [7].

Comparative expenditure on prescriptions that were compliant to the steps on pain management as outlined in the STGs/EML Hospital level Adults (2019) to those that were not.

The rate of compliance to STGs in the management of pain was satisfactory at 90.6%. While this is higher than in other reported studies, it is important that all prescribers be made aware of not only the cost implications of non-compliance but also the impact it can have on the therapeutic outcomes of patients. Failure to prescribe analgesics as outlined in the STGs can negatively impact patients as seen in a study in the emergency department of some clinics in Columbia where in comparison to patients treated with NSAIDs, those treated with tramadol were found to be at a higher risk of continued opioid use 12 months following their care [17].

Zin et al. [18] mention in their study that the safe and appropriate use of analgesics is imperative as irrational use may have contributed to increased morbidity and mortality with a subsequent increase in the demand on health care resources and costs. The budget impact of failure to comply with STGs is something the prescribers should be aware of when initiating patients on pain medication.

The responses given by doctors indicated that prescribers are well aware of the STGs however, the prescriptions recorded indicate the need for reminder reinforcements on compliance to these guidelines. Guidelines have a purpose to assist prescribers in making appropriate health care decisions for patients and only 33% reported that they comply with these guidelines while the remainder of the prescribers stated that they do not follow or do so partially despite the awareness of the available STGs. The benefits of adhering to clinical guidelines have proven to improve treatment outcomes and compliance in the management of chronic conditions [19]. Compliance to guidelines is also cost saving. Compliance to Clinical Practice Guidelines (CPGs) in the management of patients with sarcoma was found to increase the rate of relapse-free survival meaning that it was less costly and more effective [20].

All prescribers that took part in the survey had encountered patients that misused tramadol and it was, therefore, a clear indication of the need for improved control in the prescribing and use of tramadol in public institutions. Caution should be exercised by physicians when prescribing tramadol and it should be prescribed when it is strictly necessary and at the lowest effective dose [17]. The lack of knowledge on the cost implication by prescribers highlights the need for more information on the budget impact of failure to comply with STGs in pain management and this role should be undertaken by the PTC.

Non-compliance to STGs has a negative impact on treatment outcomes as seen in tuberculosis (TB) patients who received directly observed therapy only in the continuation phase of treatment and had a threefold increased risk of poor treatment outcomes as compared to those that received DOT throughout the period of treatment as recommended by the STGs [21]. Siko and van De Venter [19] identified the relationship between the number of years in service by prescribers with their compliance to treatment guidelines. It was found that compliance was higher among GPs who were in practice for less than 2 years as compared to those who were in practice for more than 20 years [19].

Limitations

The study was only conducted in the general ward of a district hospital and therefore the results cannot be generalized to other departments of the hospital although the prescribing patterns of tramadol in the outpatient department were the reason for interest in this topic. The data was collected while the patients were in the ward and the prescribing pattern of these analgesics for the remainder of the patient's stay in the ward, in the case of those admitted for longer than the recorded average duration of days on treatment, is therefore unknown.

Another limitation to the study is that we did not consider those patients who had contraindications to NSAIDs, as it was not captured on the charts. The underlying reasons for patients not being initiated on the appropriated analgesic regimen as outlined in the STGs were also not recorded during the data collection. Pain is also a relative concept and some patients could have developed severe pain after receiving paracetamol and were switched to other treatment regimens but this could however not be measured in our study.

The questionnaire that was used to assess prescriber compliance with STGs was not piloted and this was also a limitation of the study.

Conclusion

This study has identified that there is a compliance rate of 90.6% and a non-compliance rate of 9.4% in prescribing analgesics for pain management as outlined in STGs for Hospital level Adults (2019) [1]. The cost implications were considered for a sample of prescriptions, and therefore these can possibly be multiplied across the public health system which caters for 84% of the population.

References:

1. National Department of Health, South Africa. (2019). Standard Treatment Guidelines and Essential Medicines List for South Africa: Hospital level (Adults). Availablefrom:http://www.health.gov.za/index.php/component/phocadownload/category/286-hospital-level-adults?download=2409:hospital-level-adult-2015-v5-0

2. Kumar, N. (2007). WHO normative guidelines on pain management. *Geneva: World Health Organization*, 3-4.

3. Schellack, N., & Annor, A. S. (2016). Optimizing pain management-An update. *South African Family Practice*, *58*(2).

4. World Health Organization, Expert Committee on Drug Dependence (2014) Tramadol Update Review Report. Available from: http://www.who.int/medicines/areas/quality_safety/TRAMADOL_IFPMA_Comments.pdf

5. Zulkarnain, B. S. (2004). The adherence to prescribing guidelines: a drug utilization evaluation of tramadol. *Folia Medica Indonesiana*, *40*(1).

6. Raff, M., Crosier, J., Eppel, S., Sarembock, B., Meyer, H., & Webb, D. (2014). South African guideline for the use of chronic opioid therapy for chronic non-cancer pain: guideline. *South African Medical Journal*, *104*(1), 79-89.

7. Subedi, M., Bajaj, S., Kumar, M. S., & Mayur, Y. C. (2019). An overview of tramadol and its usage in pain management and future perspective. *Biomedicine & Pharmacotherapy*, *111*, 443-451.

8. Patrick S.W. (2017). A Comprehensive approach to the opioid epidemic. Obstetrics and gynecology,103(1),7-9. https://doi.org/10.1079/AOG.0000000000002118

9. Nakhaee, S., Hoyte, C., Dart, R. C., Askari, M., Lamarine, R. J., & Mehrpour, O. (2021). A review on tramadol toxicity: mechanism of action, clinical presentation, and treatment. *Forensic Toxicology*, 1-18.

10. Chikezie, U.E., & Ebuenyi, I.D. (2019). Tramadol misuse in the Niger Delta; A review of cases presenting within a year. *Journal of Substance Use*, 24(5), 487-491.

11. Truter,I. (2016). Prescribing patterns of opioids dispensed by pharmacies in South Africa. *Value in Health,* 19(7), A598.

12. Fynn, A., Helberg, E., Godman, B., & Meyer, J. C. (2020). Drug utilization review of tramadol hydrochloride in a regional hospital in South Africa; findings and implications. *Hospital Practice*, *48*(2), 92-99.

13. Limpopo Province Pharmaceutical Depot (LPPD). Master Procurement Catalogue (MPC) and Master Health Product List (MHPL), 1 December 2020 supplied by Mr Solly Rasekele.

14. Schug, S. A. (2007). The role of tramadol in current treatment strategies for musculoskeletal pain. *Therapeutics and Clinical Risk Management*, *3*(5), 717.

15. Kaye K. Trouble with tramadol. Australian prescriber 2004;27:26-7. http://doi.org/10.18773/austprescr.2004.023

16. National Drug Policy, South Africa. (1996). National Drug Policy for South Africa. *Department of Health*. Available from: http://apps.who.int/medicinedocs/documents/s17744en/s17744en.pdf

17. Machado-Alba, J. E., Serna-Echeverri, L. S., Valladales-Restrepo, L. F., Machado-Duque, M. E., & Gaviria-Mendoza, A. (2020). Use of tramadol or other analgesics in patients treated in the emergency department as a risk factor for opioid use. *Pain Research and Management*, *2020*.

18. Zin, C. S., Nazar, N. I., Rahman, N. S., Alias, N. E., Ahmad, W. R., Rani, N. S., ... & Ye, F. L. (2018). Trends and patterns of analgesic prescribing in Malaysian public hospitals from 2010 to 2016: tramadol predominately used. *Journal of Pain Research*, *11*, 1959.

19. Siko, P. R., & van Deventer, C. (2017). Compliance with standard treatment guidelines in the management of hypertension: a review of practice of healthcare workers in Potchefstroom, North West Province, South Africa. *South African Family Practice*, *59*(2), 72-77.

20. Perrier, L., Buja, A., Mastrangelo, G., Vecchiato, A., Sandonà, P., Ducimetière, F., ... & Ray-Coquard, I. (2012). Clinicians' adherence versus non adherence to practice guidelines in the management of patients with sarcoma: a cost-effectiveness assessment in two European regions. *BMC Health Services Research*, *12*(1), 1-8.

21. Ershova, J. V., Podewils, L. J., Bronner, L. E., Stockwell, H. G., Dlamini, S., & Mametja, L. D. (2014). Evaluation of adherence to national treatment guidelines among tuberculosis patients in three provinces of South Africa. *South African Medical Journal*, *104*(5).

CHAPTER 4
CONCLUSIONS

4.1 Introduction

The purpose of this study was to conduct a review on the use of analgesics in the management of pain and assess compliance with Standard Treatment Guidelines (STGs) by prescribers when managing pain. It was also to further determine the cost implication of failure to follow these STGs. The increase in the use of tramadol in the hospital was the factor leading to the need to conduct this review.

4.1.1 Strengths of the methodology and design

This study was a prospective chart review conducted at the general ward of a district hospital and no costs were incurred in conducting the study. New data was recorded weekly as new patient records became available at the ward.

4.1.2 Limitations of the study

The study was only conducted in the general ward of the hospital and therefore the results cannot be generalized to other departments of the hospital although the prescribing patterns of tramadol in the outpatient department were the reason for interest in this topic.

4.2 Conclusions drawn from the study findings

It can be concluded from the study findings that there is a generally good compliance (90.6%) among prescribers in prescribing analgesics for pain management as outlined in STGs/EML Hospital level Adults (2019). However, there is a need for prescribers to make careful consideration before prescribing opioids for the management of pain, and following up on abuse thereafter. This will benefit the patient population by minimizing the risk of dependence and side effects that can be experienced with the use of tramadol as all prescribers that completed the questionnaire had encountered a patient that misuses tramadol.

4.3 Significance of the study

The STGs serve to provide guidelines on the prescribing of analgesics along with other medicines and it was seen as necessary to assess the compliance by medical practitioners when prescribing treatment for the management of mild to moderate pain, to identify possible reasons for non-compliance and to determine the cost implication of failure to follow these guidelines.

The findings of the study provide information on compliance to STGs and recommend interventions to strengthen compliance with STGs while promoting positive treatment outcomes for the patient population, thus reducing adverse reactions and the potential for dependence and abuse of tramadol.

4.4 Recommendations

The PTC together with prescribers should create institution-specific guidelines for pain management based on the STGs to ensure uniform prescribing in terms of pain management in the hospital and continue to monitor use. The scarcity of health care resources is also one factor to be considered and choosing the best treatment for patients to achieve the desired therapeutic outcome should go hand in hand with the desire to save costs and ensure the efficient use of health care resources.

Future studies can assess the impact that the shortage of first-line analgesics has on the initiation of patients on tramadol. Another area for future studies to investigate is the extent of dependence on tramadol following the initial prescription for mild to moderate pain. A wider national study would help to shed light on the extent of tramadol use and misuse in South Africa while also providing ways to improve control in this regard.

4.5 Chapter summary

This chapter highlighted the conclusions drawn from the findings of the study, described the significance, strengths and limitations of the study, as well as provided the recommendations for improving compliance to STGs in the management of pain.

References:

National Drug Policy, South Africa. (1996). National Drug Policy for South Africa. *Department of Health*. Available from: http://apps.who.int/medicinedocs/documents/s17744en/s17744en.pdf

Annexure 1:

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

06 December 2020

Ms Muhluri Alvinah Rikhotso
(218044999)School of
Health Sciences
Westville

Dear Ms Rikhotso,

Protocol reference number: BREC/00001488/2020
Project title: Drug utilisation review of paracetamol and tramadol in the management of pain in the general wardof Louis Trichardt Hospital and the assessment of prescriber compliance with South African Standard Treatment Guidelines.
Degree: Masters

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 06 December 2020. Please ensure that outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is subject to national and UKZN lockdown regulations dated 10th November 2020, see (http://research.ukzn.ac.za/Libraries/BREC/BREC_Lockdown_Level_1_Guidelines.sflb.ashx). Based on feedback from some sites, we urge PIs to show sensitivity and exercise appropriate consideration at sites where personnel and service users appear stressed or overloaded.

This approval is valid for one year from 06 December 2020. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before theexpiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 09 February

2021.Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Biomedical Research
Ethics Committee
Chair: Professor
D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan
Mbeki BuildingPostal Address: Private Bag
X54001, Durban 4000
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

Annexure 2

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

Department of Health

Ref : LP_2020_12_007
Enquires : Ms PN Motimele
Tel : 015-293 6028
Email : Phoebe.Mahlokwane@dhsd.limpopo.gov.za

Muhluri Rikhotso

PERMISSION TO CONDUCT RESEARCH IN DEPARTMENTAL FACILITIES

Your Study Topic as indicated below**;**

Drug utilisation review of paracetamol and tramadol in the management of pain in the general ward of Louis Trichardt Hospital and the assessment of prescriber compliance with South African Standard Treatment Guidelines.

1. Permission to conduct research study as per your research proposal is hereby Granted.
2. Kindly note the following:
    a. Present this letter of permission to the institution supervisor/s a week before the study is conducted.
    b. In the course of your study, there should be no action that disrupts the routine services, or incur any cost on the Department.
    c. After completion of study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
    d. The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
    e. The approval is only valid for a 1-year period.
    f. If the proposal has been amended, a new approval should be sought from the Department of Health
    g. Kindly note that, the Department can withdraw the approval at any time.

Your cooperation will be highly appreciated

[redacted]

08/02/2021

A/**Director Research**
Dr. Ramalivhana NJ

Date

Annexure 3

Questionnaire for prescribers:

1. Are you aware of the STGs for the management of chronic non-cancer pain?
2. Do you follow these guidelines when prescribing treatment for the management of chronic non-cancer pain?
3. Do you prescribe paracetamol for the management of chronic non-cancer pain?
4. Do you follow the steps stated in the STGs when prescribing tramadol for pain?
5. Do you monitor patients on tramadol for adverse effects following prescribing the drug?
6. Have you encountered any patients who misuse tramadol ?
7. Are you aware of the cost implications of not following standard treatment guidelines?

Annexure 4

INFORMATION DOCUMENT AND CONSENT FORM (DOCTORS)

STUDY TITLE:
Drug utilisation review of paracetamol and tramadol in the management of pain in the general ward of Louis Trichardt Hospital and the assessment of prescriber compliance with South African Standard Treatment Guidelines.
Date:

Dear colleague (Doctor). My name is Muhluri Rikhotso and I am employed at Louis Trichardt Memorial Hospital in the Vhembe District of Limpopo. You are being invited to consider participating in a study that I am conducting at your facility.

INTRODUCTION TO AND PURPOSE OF MY STUDY

In the South African public health care system, the Standard Treatment Guidelines and Essential Medicines List serve as a foundation in the management of patients with different conditions and offer guidance on the drugs and treatment methods that should be followed with the goal of ensuring positive treatment outcomes and the efficient use of resources. The overall aim of the research is to assess the use of tramadol in the facility.
STUDY PROCEDURES

If you agree to participate you will be asked to complete a questionnaire and this will take place at the hospital upon a time and date which will be agreed upon.

RISKS
There are no known risks to you or the people you work with for taking part in the study.

BENEFITS

There are no direct benefits for participants.

VOLUNTARY PARTICIPATION

Participation in the study is completely voluntary. You may refuse to participate or may withdraw from the study at any time.

CONFIDENTIALITY

The information collected in the study will be used for research purposes only. The study will be completely confidential and your name will not appear anywhere in the study. A pseudonym will be used instead of your name and efforts will be made not to disclose your identity. Your participation and input will be strictly confidential.
This study has been ethically reviewed and approved by the UKZN Biomedical Research Ethics Committee (approval number_____).

In the event of any problems or concerns/questions you may contact the researcher on 015 516 0148 or muhlurialvn@gmail.com or the UKZN Biomedical Research Ethics Committee, contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

CONSENT

I (Name) _____have been informed about the study entitled _____by_____.

I understand the purpose and procedures of the study.

I have been given an opportunity to answer questions about the study and have had answers to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any treatment or care that I would usually be entitled to.

If I have any further questions/concerns or queries related to the study I understand that I may contact the researcher at 015-516 0148 or muhlurialvn@gmail.com

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

I consent to take part in the survey yes no

_____ _____
Signature of Participant Date

_____	_____
Signature of Witness (Where applicable)	Date
_____	_____
Signature of Translator (Where applicable)	Date

Annexure 5

Supplementary data

Detailed classification of conditions

Classification of conditions										
Conditions of the respiratory system	**Conditions of the cardiovascular system**	**Conditions of the endocrine system**	**Conditions of the alimentary canal**	**Gynaecological conditions**	**Conditions blood and blood forming organs**	**Neurological conditions**	**Urological conditions**	**Trauma**	**Fractures**	**Other**
Lower respiratory tract infection (LRTI)	Congestive Cardiac failure (CCF)	Diabetes Mellitus	Dehydration secondary to diarrhoea	Threatening miscarriage	Anaemia	Cerebrovascular accident (CVA)	Urinary Tract Infection (UTI)	Assault	Fracture of tibia / fibula	Covid-19 vaccine effects
Asthma	Hypertension	Diabetic ketoacidosis (DKA)	Gastritis	Post evacuation	Septicaemia	Uncontrolled epilepsy	Obstructive uropathy	Stab on chest	Ankle dislocation	Acute confusion
Pneumonia	Hypotension	Uncontrolled hyperglycaemia	Gastroenteritis	Ectopic pregnancy		Cryptococcal Meningitis	Right testicular torsion	Gunshot wound	Femur fracture	Backache and headache
Covid-19 pneumonia	Peripheral vascular disease		Upper gastrointestinal bleeding	Blighted ovum		Status epilepticus		Motor vehicle accident	Right acetabular fracture	Cervical lymphadenitis
Pulmonary tuberculosis (PTB)			Liver disease	Incomplete abortion					Mandibular fracture	Painful right leg
Miliary TB				Inevitable abortion					Supra condylar fracture	Parasuicide
				Septic miscarriage					Commuted fracture of radius	RVD/general body weakness

Annexure 6

Submission Confirmation

Print

Thank you for your submission

Submitted to	Hospital Practice
Manuscript ID	HP-ST-2022-0126
Title	Drug Utilization Review of Paracetamol and Tramadol in the Management of Pain According to Guidelines at a Hospital Level in Limpopo, South Africa.
Authors	Rikhotso, Muhluri Suleman, Fatima Bangalee, Varsha
Date Submitted	30-Nov-2022