The use of tramadol at the Groote Schuur Chronic Pain Management Clinic (CPMC): a Medicine Usage Evaluation

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Declaration

I, Dr Marie Astrid Muissa Mbombo, hereby declare that the work on which this dissertation is based on my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor part of it has been, is being, or is to be submitted for another degree at the University of Cape Town or any other university.

This dissertation has been submitted to the Turnitin module (or equivalent similarity and originality checking software) and I confirm that my supervisor has seen my report and any concerns revealed by such have been resolved with my supervisor.

This thesis is presented in fulfilment of the requirements for the degree of MMed (Anaesthesia)

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Date:
12/05/2023

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Acknowledgments, format and contributions

I would like to thank my supervisors for their guidance as well as the Groote Schuur Hospital Chronic Pain Management Clinic staff for their support throughout this project.

The paper has been prepared for submission to the Southern African Journal of Anaesthesia and Analgesia (SAJAA) with the following formatting requirements:

- Original articles on research relevant to anaesthesia and analgesia not exceeding 3200 words, 30 references, with up to 6 tables or figures
- A structured abstract under the headings, Background, Methods, Results, and Conclusions not exceeding 300 words

The formatting and referencing convention used throughout this dissertation include:

- UK English
- Times New Roman font type
- Vancouver format referencing style

Contents

List of Appendices

List of Tables

List of Figures

Abstract

Background: The use of tramadol in the management of chronic pain has recently become controversial. Amidst rising reports on potential for abuse and its exclusion from latest international guidelines, the conduct of a Medicine Usage Evaluation (MUE) of the drug is relevant to inform future training and practice.

Methods: A cross sectional retrospective descriptive chart review of the use of tramadol for the year 2021 was conducted at the Groote Schuur Chronic Pain Management Clinic (CPMC). A total of 104 folders were reviewed. Descriptive statistics summarise the data.

Results: The average person with chronic pain who was being prescribed tramadol included in this MUE was female, receiving a disability grant and in their late fifties (57.28y ±12.32). A median of three comorbidities (IQR 4) were recorded in the folders. The median duration of clinic attendance was 10,5 years (IQR 11,5). Chronic spinal pain (61%) was the most common diagnosis. Atypical tramadol dosages were recorded. Only 4% of patients attributed improvement of their pain to tramadol therapy. Good prescription practices were adhered to for the majority of criteria, the key domains with shortcomings were in documentation of the severity of pain, documentation of assessment for potential drug interactions, and documentation of referral for non-pharmacological treatments.

Conclusion: The MUE on the use of tramadol at the Groote Schuur CPMC was characterised by good prescription practices with regard to documentation on patient profile, pain diagnosis and management. We recommend the use of standardised protocols for follow up visits and moving to electronic records. The lack of improvement associated with tramadol therapy reported by patients was concerning. In such circumstances, we support the use of a patient-centred tapering strategy with atypical dosages not exceeding the maximum recommended daily dose and the integration of non-pharmacological treatments.

Publication-ready Manuscript

1. Introduction

Tramadol hydrochloride (tramadol) is a synthetic mixed centrally acting opioid used to relieve moderate to moderately severe pain in adults.[1, 2] Tramadol is a racemic mixture of two enantiomers, each contributing to its analgesic activity via different mechanisms. (+)-Tramadol and its metabolite M1 are agonists of the mu opioid receptor. (+)-Tramadol inhibits serotonin reuptake and (-)-Tramadol inhibits norepinephrine reuptake, enhancing inhibitory effects on transmission of nociception in the spinal cord. The complementary and synergistic actions of the two enantiomers improve the analgesic efficacy and tolerability profile of this racemate.[1-3]

In the low income regions of Africa, Asia and Latin America, tramadol remains essential for the provision of optimal pain management in the absence of access to strong opioids.[4-6] This is partly because tramadol, unlike other opioids, is not regulated by the International Narcotics Control Board (INCB); as it was previously perceived to have a lower side effect profile and a lower potential for abuse in comparison to other opioids and is therefore more accessible.[2, 7]

The use of tramadol in the management of chronic pain has become controversial. Previous systematic analyses advocated for the use of tramadol in the management of chronic pain of non-malignant origin.[2, 4] The drug was listed as a Step 2 analgesic in the 1986 WHO guidelines for the management of cancer pain.[8] Tramadol was frequently favoured in preference to morphine (greater nausea, constipation, tendency to tolerance development) and in preference to NSAIDs or selective COX-2 inhibitors (renal, gastrointestinal and cardiovascular side effects with long term use).[2]

However, in recent years, the drug has stopped being included in many international guidelines for the management of chronic pain. The latest 2017 Cochrane review on its usage in patients with neuropathic pain highlights the lack of convincing evidence for its effectiveness in relieving neuropathic pain.[9] Tramadol was not included in the 18th WHO Model List of Essential Medicines (April 2013) and is no longer listed as one of the weak opioids of choice in the revised WHO pharmacological management of cancer pain in adults and in adolescents.[10, 11] The latest NICE guidelines on the management of chronic primary pain state that the evidence of long-term harm, along with the lack of evidence on effectiveness of opioids, persuaded the committee to recommend against initiating opioid treatment for people with chronic primary pain.[12]

Recent data provide evidence that tramadol has a risk for abuse, although its risk is generally lower than most of the opioids to which it is compared. Abuse, dependence or intoxication occurs especially when given at supra-therapeutic doses.[10, 13] Epidemiological evidence of tramadol abuse appears to vary as a function of its regulatory status. Countries in which a wide variety of opioid products are available generally report low rates of tramadol abuse relative to other opioids; however, countries that impose greater restrictions on opioid products and rely more heavily on tramadol for primary pain management often report tramadol abuse.[13] This has become of particular concern in some African countries, which have also observed increases in the importation of illicit and adulterated tramadol.[7, 13]

In 2018, as a response to multiple international petitions, the WHO Expert Committee on Drug Dependence concluded that there is growing evidence of abuse of tramadol in many countries, in

some cases serious, accompanied by adverse reactions and tramadol-associated deaths. The Committee recommended that tramadol be subjected to a critical review at a subsequent meeting with the drug being kept under surveillance but not warranting any international scheduling.[13, 14]

In spite of these controversies, tramadol is still part of the national essential medicines list at primary healthcare as well as at hospital level in South Africa.[15, 16] This is partly because, in contrast to most other opioids, tramadol is only regulated at a national (versus international) level, and remains included on several national essential medicines lists.[10, 13] In the hospital setting, tramadol is recommended for the management of severe chronic pain of malignant and non-malignant origin at an oral dose of 50–100 mg 6 hourly. In patients with uncontrolled pain the dose can be increased to a maximum of 100 mg 6 hourly. However, the South African National Essential Medicines Guideline recommends warning patients of adverse effects and addiction potential, tapering and stopping tramadol if no reduction in pain occurs following four weeks of treatment, and cautions on its potential for fatality and respiratory depression in overdose.[15]

Regular MUEs are essential to promote appropriate and effective use of medications.[17] The Groote Schuur chronic pain management clinic (CPMC) is a specialist run clinic, directly focused on the management of patients with chronic pain and treating an average of 19 patients per consultation day, with regular prescribing of tramadol. Given all the recent controversies surrounding tramadol usage, efficacy and abuse, a Medicine Usage Evaluation (MUE) of tramadol at the Groote Schuur CPMC was indicated.

2. Methods

2.1 Study setting and design

A cross sectional retrospective chart review on the use of tramadol for the year 2021 was conducted at the Groote Schuur CPMC. The study population (n=104) included all patients treated with tramadol at the CPMC over the period January-December 2021 (Figure 1). This sample size is in keeping with WHO guidelines which recommend sampling a minimum population of 100 patients to obtain a representative sample of prescribing practices.[18]

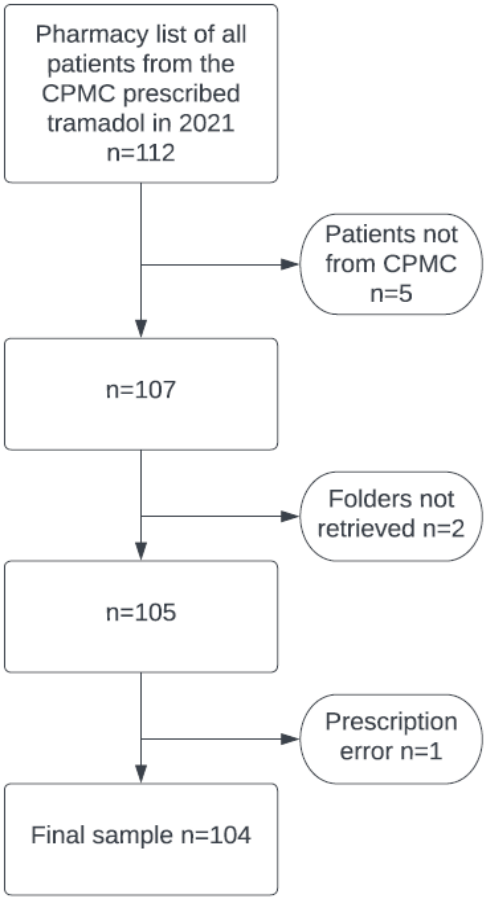

Figure 1: Flow chart of sample selection*
*Prescription error: tramadol was prescribed once without a clear indication; the patient was not on tramadol before or after that prescription

2.2 Data collection

From a pharmacy list of 112 patients receiving tramadol from the CPMC in 2021, 104 folders were retrieved (Figure 1). A MUE extraction tool was developed based on the literature with expert validation from the senior consultant at the CPMC and pharmacy manager.[17, 18] Data from the MUE were captured on an Excel spreadsheet populated with dropdown menus to reduce variability in responses.

2.3 Data Analysis

Descriptive statistics were used to summarise the data. Further analysis of prescribing practice was conducted using Chi-squared analysis of frequency distributions to explore association between prescribing and gender, diagnosis and sociodemographic profile. Data are presented as mean (SD), median (IQR), count or frequencies.

2.4 Ethical considerations

Ethical approvals were obtained from the Faculty of Health Sciences Human Research Ethics Committee (Ref 753/2021), GSH Department of Health (DoH) Ethics Committee and the GSH pharmacy manager.

3. Results

3.1 Sociodemographic and health profile

The ages of the patients on tramadol were normally distributed (K-S d=0.05, p>0.20) and are therefore presented as mean (SD). The average person included in this MUE was female, receiving a disability grant and in their late fifties (57.28y ±12.32) (Table 1). One patient was breastfeeding, and none were pregnant.

Table 1: Sociodemographic profile of patients (n=104)

Variable	**Mean (SD)**
Age	57.28 (12.32)
Sex	**Number (%)**
Female	71 (68%)
Male	34 (32%)
Receiving a Disability Grant	
Yes	59 (57%)
No	45 (43%)

The majority of patients on tramadol attending the CPMC had at least one other comorbidity (n=77, 75%). A median of three comorbidities (IQR 4) were recorded in the folders with a total of 37 different comorbidities recorded. The five most common comorbidities were hypertension (68%), gastro-oesophageal reflux disease (42%), type 2 diabetes mellitus (26%), dyslipidaemia (18%) and major depressive disorder (16%).

A range of medications were prescribed for the management of the above comorbidities and were recorded in the folders. Several patients (n=57) were being prescribed tricyclic antidepressants (n=46), SNRIs (n=21) or SSRIs (n=2). It was not possible to discern whether these were being prescribed for the management of psychiatric conditions or chronic pain.

3.2 Pain Profile

All patients had been referred to the CPMC suggesting that they had experienced pain on most days, for more than three months. The majority (n=84, 81%) had their pain assessed at the first consultation using the Brief Pain Inventory generating a pain severity and pain interference score.[19] Other pain assessment tools used included the Budapest diagnostic criteria for complex regional pain syndrome (n=1) and the new clinical fibromyalgia diagnostic criteria (n=2).[20, 21]

The patients presented with a range of chronic pain conditions, the most common being chronic spinal pain (Table 2). Of the 104 patients, eight had two pain diagnoses recorded, and one patient had three pain diagnoses recorded. The patients' duration of clinic attendance could be traced in 97 of the folders with a median duration of 10,5 years (IQR 11,5).

Table 2: Recorded pain diagnosis (n=104)

Diagnosis	**Count (%)**
Spinal pain	**58 (56%)**
Failed back syndrome	13 (13%)
Chronic lower back pain	12 (12%)
Degenerative spine	11 (11%)
Spinal stenosis	9 (9%)
Chronic back pain	4 (4%)
Scoliosis	3 (3%)
Radiculopathy	1 (1%)
Facet joint disease	1 (1%)
Annular tear L5/S1	1 (1%)
Cervical stenosis	1 (1%)
Cervical myelopathy	1 (1%)
Cervical stenosis and myelopathy	1 (1%)
Neuropathic pain	**19 (18%)**
Peripheral neuropathy	5 (5%)
Neuropathic pain post injury	5 (5%)
Neuropathic pain post-surgery	3 (3%)
Complex Regional Pain Syndrome (CRPS)	3 (3%)
Neuropathic pain post TB spine	1 (1%)
Neuropathic pain post syphilis myelitis	1 (1%)
Trigeminal neuralgia	1 (1%)
Others	**18 (17%)**
Fibromyalgia	6 (6%)
Chronic widespread pain	4 (4%)
Chronic abdominal pain	2 (2%)
Chronic left flank pain	2 (2%)
Chronic pelvic pain	1 (1%)
Chronic perineal pain	1 (1%)
Chronic right shoulder pain	1 (1%)
Chronic iliac fossa pain	1 (1%)
Two pain diagnoses	**8 (8%)**
CRPS & neuropathic pain	2 (2%)
Failed back syndrome & fibromyalgia	2 (2%)
Degenerative spine & Fibromyalgia	1 (1%)
Chronic lower back pain & diabetic neuropathy	1 (1%)
Chronic lower back pain & chronic right shoulder pain	1 (1%)
CRPS & central sensitisation	1 (1%)
Three pain diagnoses	**1 (1%)**
CRPS & Fibromyalgia & Chronic lower back pain	1 (1%)

3.3 Pain management

Medications other than tramadol used for the management of pain were clearly documented in 102 folders. These medications ranged from simple analgesics to centrally acting drugs (Table 3).

Table 3: Other medications documented for pain management (n=102)

Medication	Count (%)
Analgesics	
Paracetamol	93 (91%)
Morphine	7 (7%)
Ibuprofen	2 (2%)
Codeine phosphate	1 (1%)
TCA/SNRI/SSRI	
TCA	46 (45%)
SNRI	21 (21%)
SSRI	2 (2%)
Gabapentinoid	
Pregabalin	58 (57%)
Benzodiazepine	
Diazepam	2 (2%)
Clonazepam	1 (1%)
Other central acting medications	
Baclofen	7 (7%)
Carbamazepine	3 (3%)
Clonidine	3 (3%)
Chlorpheniramine	3 (3%)

Pain was also being treated with a range of other modalities (n=60) including steroid injections/local anaesthetic blocks (n=27), a behaviour change patient education empowerment program/Pain Education Empowerment Program (n=26), multidisciplinary referrals (n=6) and acupuncture (n=1).

3.4 Tramadol

Documentation on tramadol usage for the management of pain was traced in all 104 folders. These included documentation on its prescription dosage and interval (Table 4), its duration of use, the possibility of drug interaction and any record of pain improvement after therapy. Variations of prescription interval were noted, ranging from per required need (prn) dosing, to four times daily dosing.

Table 4: Tramadol dosage and interval (n=104)

Tramadol dosage and interval	Count (%)
Tramadol 50mg	**46 (44%)**
Once a day	**2 (2%)**
daily	1 (1%)
night	1 (1%)
Twice a day (bd)	**4 (4%)**
Thrice a day (tds)	**17 (16%)**
tds	16 (15%)
tds/prn	1 (1%)
Four times a day (qid)	**23 (22%)**
qid	22 (21%)
qid/prn	1 (1%)
Tramadol 100mg	**58 (56%)**
Twice a day (bd)	**1 (1%)**
Thrice a day (tds)	**13 (13%)**
Four times a day (qid)	**44 (42%)**

All the patients followed up at the CPMC had been on tramadol for a minimum of six months of treatment. The possibility of drug interactions was documented in 15 folders with an emphasis on supratherapeutic tramadol misuse in two of these folders. Out of 100 patients with documentation of pain improvement, only four based their improvement on tramadol treatment with two reporting improvement occurring mainly at initiation of therapy. The majority (n=64) reported no improvement, and a few (n=32) reported improvements following the addition of other interventions (injections/blocks were the main intervention associated with improvement).

During the year under review, two patients were down referred for management at their primary healthcare clinic, three were discharged and four were either reluctant to be discharged or were previously discharged and came back to re-attend the pain clinic.

3.5 Tramadol Medicine Usage Evaluation

The tramadol MUE evaluation is summarised in Table 5. The majority of the criteria for good practice in prescribing tramadol were being adhered to. The key domains with shortcomings were in documentation of the severity of pain, documentation of assessment for potential drug interactions, and documentation of referral for non-pharmacological treatments.

Table 5: Summary of the Medicine Usage Evaluation

Criteria		**Data recorded**
CHRONIC PAIN CONDITION	Has the clinician documented chronic pain as the diagnosis?	100% of patients had a diagnosis for their chronic pain condition (n=104) The BPI was used in 80 % of cases as a pain assessment tool (n=84)
TYPE	Has the clinician classified the chronic pain?	100% All patients had their chronic pain classified (n=104)
SEVERITY	Has the clinician documented the severity of the pain?	80% of patients had the severity of their pain assessed and documented using the BPI
DURATION	Has the duration of the pain been documented?	100% of cases had the duration of pain documented. The year of initiating attendance at the chronic pain clinic was documented in 93% of cases (n=97)
PATIENT DETAILS	Has the patient age, gender, current co-morbidities, pregnancy, breastfeeding, allergies been documented?	100% of cases had age and gender documented. 99% of cases had presence of comorbidities, pregnancy, breastfeeding, and allergies documented.
PATIENT DETAILS	Is the patient on a disability grant?	99% of cases had documentation of whether or not the patient was receiving a disability grant.
OTHER MEDICATIONS AND INTERACTIONS	Has the clinician mentioned and taken note of other medications the patient is on and possible interactions?	98% of cases had documentation of other medications being prescribed. 14% of cases had some documentation of possible drug interactions
TRAMADOL DOSE, INTERVAL AND DURATION	Has the dosage, interval and duration for which tramadol must be used been documented?	100% of cases had the dosage, interval and duration of treatment for tramadol recorded.
FOLLOW UP PLAN	1.Has the clinician set a date for reassessment? During reassessment was the pain reassessed in terms of improved function and severity? 2.Did the clinician plan or refer for non-pharmacological treatment?	1. 100% of cases had a follow up plan and date documented (n=104) 99% of cases a pain reassessment was performed (n=103) 2. 26% of cases had documented referral for non-pharmacological treatment (n=27)
PATIENT EDUCATION	Did the clinician mention a discussion with the patient in terms of possible side effects of the medication and goals of treatment?	97% of cases had documentation of patient education recorded

4. Discussion

The review of 104 folders at the Groote Schuur CPMC for the year 2021 showed that a large proportion of the population being prescribed tramadol for the management of their chronic pain were female (n=71), on a disability grant (n=59) with a mean age of 57.28 years (SD 12.32) and a median of three comorbidities per patient (IQR 4).

Nationwide cross-sectional studies of tramadol prescribed for chronic non-cancer pain in the three countries of South Korea, Denmark and Norway reported similar findings with regard to age and gender distribution: the majority of patients on tramadol for chronic pain were female in their late fifties.[22-24] A nationwide review of tramadol prescription in US Emergency Departments from 2007 to 2018 showed the largest increase in tramadol use was seen among patients aged 55-64 years, a relative increase of 285.1%.[25] The South Korean review of over six million patients prescribed tramadol for the management of their chronic lower back pain found hypertension, diabetes mellitus and peptic ulcer disease to be the three most common comorbidities. A finding similar to our review, although with a lower proportion of patients presenting with these comorbidities (14.2%, 7.5% and 5.3% respectively).[22]

We found that tramadol was mainly prescribed for the treatment of chronic spinal pain (61%). Neuropathic pain (23%) including CPRS (7%) and fibromyalgia (10%), were among the other conditions for which the drug was being used. Similar to our findings, chronic back pain often features as a prescribing diagnosis in various global reviews of tramadol prescription.[4, 22, 23] In a Southeast Asian study, tramadol was used for the treatment of osteoarthritis and chronic lower back pain extending to being used as a second line treatment for neuropathic pain and fibromyalgia.[4]

Good prescription practices were adhered to for the majority of the MUE criteria. From the first consultation at the chronic pain clinic, the diagnosis, type and duration of the pain were clearly documented, all socioeconomic demographic and health profiles of patients were noted, and a follow up plan and date were specified. A BPI assessment was performed and a standardised first consultation form used. The standardised form includes a detailed assessment of the pain history, medical and surgical history including allergies, a detailed social history, a detailed psychological/psychiatric history, and a general clinical examination, including an examination of the affected region. The form extends to include a CRPS checklist, a lower back pain assessment and a full neuromuscular examination. Tests and investigations performed, diagnosis and assessments formulated and multidisciplinary plans and follow ups were clearly documented in the appropriate sections of the form. These documents align with the Health Professional Council of South Africa (HPCSA) guidelines on patient record keeping; promoting good clinical practice and allowing for a biopsychosocial assessment and treatment of the chronic pain condition.[26]
Their use contributes to continuity of care and simplified pain reassessment and management on follow up visit(s). The documentation of a clearly formulated multidisciplinary plan allowed for reassessment of pain on every follow up visit with emphasis on patient education. The folder review showed that the documentation in the first consultation formed the basis of the tramadol prescription review.

South Africa, as a lower middle-income country, suffers from high patient load and scarcity of resources in its public health sector. Resources are mainly allocated on actual patient care and minimally on upgrading facilities, including filing systems. The Groote Schuur CPMC still uses a manual record keeping system. Except for the first visit standardised consultation forms, subsequent prescriptions are entirely hand-written and subject to individual variability. With a median duration of attendance of 10,5 years (IQR 11,5), tracing all documentation for the MUE

became challenging. Many initial patient records were lost, including the assessment of the severity of the pain done using the BPI questionnaire on the first visit. This is one of the recognised weaknesses of handwritten, paper-based records in large institutions.[27] Moving to electronic records is proposed as one method to overcome this weakness.[27]

Chronic pain assessment and management can be time consuming and requires a multidisciplinary approach. With every interview, the physicians must be prepared to deal with the psychological and social manifestations, as well as negative emotions such as depression, anxiety and anger associated with chronic pain.[28] In the absence of clear protocols; high patient loads, the need for multidisciplinary input, time constraints, the emotional load associated with every interview; and inevitable practitioner fatigue, the use of paper based records may contribute to the omission of important information in record keeping.[27] Items such as reassessment of pain severity, discussions on drug interactions and advice on non-pharmacological treatments might have occurred but might not have been clearly documented in the patient file. Furthermore, some important documentation might have been lost with multiple file duplicates and long duration of clinic attendance by patients.

Based on the South African National Essential Medicines Guidelines, tramadol is recommended for the management of moderate to severe pain at an oral dose of 50 to 100 mg, 4 to 6 hourly, with a maximum dose not exceeding 100 mg 6 hourly.[15] However, a heterogenicity of prescription practice was noted in this MUE. Tramadol prescription ranged from 50 mg daily (2%), twice daily (4%), thrice daily (16%), four times daily (22%) to 100mg twice daily (1%), thrice daily (13%) and four times daily (42%). Although, no prescription dosage exceeded the maximum recommended daily dose, prescription variability not in keeping with national guidelines were recorded. The cause could be multifactorial. Firstly, by virtue of being a specialist run clinic, the CPMC only manages referred chronic pain patients. All patients seen at the clinic are on some form of chronic pain medications before their first consultation: all tramadol treatments were already initiated at referral hospitals or at other Groote Schuur outpatient clinics. Secondly, a patient-centred opioid tapering strategy is used in the clinic (Rowan Duys, personal communication, November 23, 2022). Patients are empowered to decide on the minimum effective dose of tramadol necessary for the management of their chronic pain as typical biomedical interventions are often inadequate. Pain is a complex phenomenon with inputs from biological as well as psychosocial and socioeconomic factors.[29] In addition, analgesic effects of opioids often attenuate over time due to physiological tolerance, physical dependence or opioid-induced hyperalgesia.[30]

In our study, only 4% of patients attributed improvement of their pain to tramadol therapy. This is in keeping with a recent Cochrane review, WHO and NICE guidelines which no longer recommend tramadol for the management of chronic pain.[9, 11, 12] Furthermore, recent African studies have highlighted the potential for abuse of tramadol especially in circumstances where the lack of resources or greater restrictions on other opioid therapy drive heavy dependence on tramadol as primary pain management.[7, 13] Paradoxically, circumstances that generate potential tramadol abuse are the same circumstances that perpetuate the drug being an essential medicine for the management of chronic pain in many countries. In such situations, where tramadol will continue to be initiated before referral to an appropriate chronic pain clinic; a patient-centred tapering strategy seems an appropriate compromise with atypical dosage in situations where abrupt discontinuation would be difficult.

5. Conclusion

The MUE on the use of tramadol at the Groote Schuur CPMC was characterised by good prescription practices with regard to documentation on patient profile, pain diagnosis and management. Record keeping adhered to HPCSA guidelines and was facilitated by a standardised first consultation approach to patients with multidisciplinary team involvement. Based on the complexity of chronic pain management and the long clinic attendance of patients in this high throughput clinic, we recommend the use of standardised protocols for follow up visits and the move to electronic records.

The lack of improvement associated with tramadol therapy reported by patients was concerning and highlighted the need for further research in this area. In such circumstances, we support the use of a patient-centred tapering strategy with atypical dosages not exceeding the maximum recommended daily dose for patients already on tramadol treatment. In addition, in line with international guidelines, the use of non-pharmacological treatments should be encouraged.

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Appendices

Appendix A: Letter of Ethical Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45, E-52- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

16 November 2021

HREC REF: 753/2021

Prof R Parker
Division of Anaesthesia & Perioperative Medicine
D-23 NGSH
Email: Romy.parker@uct.ac.za
Student: mmamuissa@yahoo.com

Dear Prof Parker

PROJECT TITLE: THE USE OF TRAMADOL AT THE GROOTE SCHUUR CHRONIC PAIN MANAGEMENT CLINIC (CPMC): A MEDICINE USAGE EVALUATION-MMED CANDIDATE-DR MARIE MBOMBO

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020; 06 July 2020 & 01 July 2021.

Approval is granted for one year until the 30 November 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Marie Mbombo will also be involved in this study.

Please quote the HREC REF 753/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/REF 753/2021sa

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/11/2024
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	19/4/2023

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC
Thank you for your Study Deviation HREC Chair Signature Date: 19/4/2023

Principal Investigator to complete the following.

1. Protocol information

Date (when submitting this form)	18/04/2023		
HREC REF Number	753/2021	Current Ethics Approval was granted until	30/11/2022
Protocol title	The use of tramadol at the Groote schuur Chronic Pain Management Clinic (CPMC): a Medicine Usage Evaluation		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		☐ Yes	√ No
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Dr Marie Astrid Muissa Mbombo		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

HUMAN RESEARCH ETHICS COMMITTEE
19 APR 2023
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Appendix B: Tramadol Medicine Usage evaluation

CRITERIA		DATA RECORDED
CHRONIC PAIN CONDITION	Has the clinician documented chronic pain as the diagnosis?	Y/N Diagnostic tool used
TYPE	Has the clinician classified the chronic pain?	Y/N
SEVERITY	Has the clinician documented the severity of the pain?	Y/N Documented data
DURATION	Has the duration of the pain been documented?	Y/N Documented data
PATIENT DETAILS	Has the patient age, gender, current co-morbidities, pregnancy, breastfeeding, allergies been documented?	Documented data
PATIENT DETAILS	Is the patient on a disability grant?	Y/N
OTHER MEDICATIONS AND INTERACTIONS	Has the clinician mentioned and taken note of other medications the patient is on and possible interactions?	Y/N Documented data
TRAMADOL DOSE, INTERVAL AND DURATION	Has the dosage, interval and duration for which tramadol must be used been documented?	Y/N Documented data
FOLLOW UP PLAN	1.Has the clinician set a date for reassessment? During reassessment was the pain reassessed in terms of improved function and severity? 2.Did the clinician plan or refer for non-pharmacological treatment?	Y/N Document data – treatment goals and referral plan
PATIENT EDUCATION	Did the clinician mention a discussion with the patient in terms of possible side effects of the medication and goals of treatment?	Y/N

Appendix C: Standardised assessment form

Groote Schuur Hospital

PAIN MANAGEMENT CLINIC

PATIENT STICKER:

REFERRING DOCTOR:

SPECIALITY:

TODAY'S DATE:

CLERKING DOCTOR:

HISTORY OF PAIN:

SITE:

PRECIPITATING EVENT:

DATE OF ONSET:

RADIATION:

EXACERBATING FACTORS:

ANALGESICS (CURRENT):

ANALGESICS (PREVIOUSLY):

OTHER SPECIALITIES INVOLVED AND TREATMENTS GIVEN:

MEDICAL HISTORY:

CNS:

CVS:

RESP:

GIT:

GUT:

GYNAE:

RENAL:

ENDOCRINE:

OTHER MEDICAL HISTORY:

SURGICAL HISTORY:

ALLERGIES:

SOCIAL HISTORY:

Occupation/Level of Education:

Marital Status/Children:

Social support/Disability Grant:

Exercise/Physical
Activity: Alcohol Abuse:
Smoking:
Other Agent Abuse:
Litigation/Compensation
Pending:

PSYCHOLOGICAL/PSYCHIATRIC HISTORY:

Previous history of psychiatric disorders:

How have you been sleeping?

Appetite?

Lost interest in things you usually enjoy?

What has your mood been like?

What are your expectations of this clinic?

What do you think is wrong with you?

CLINICAL EXAMINATION:

GENERAL:

CVS: BP: HR:

RESP:

GIT:

CNS:

AFFECTED REGION:

Inspection:

Palpation:

Gross sensory changes:

Masses:

Trigger Points:

CRPS CHECKLIST: (See Budapest criteria below)

Oedema/Muscular atrophy/hypertrophy:

Surgical/Traumatic Scars:

Sudomotor changes:

Hyperalgesia/Allodynia:

Skin Changes:

Abnormal Hair Growth:

Cutaneous Temperature:

Table 1 Diagnostic criteria for CRPS ('Budapest criteria')[21] (A–D must apply)*

A) The patient has continuing pain which is disproportionate to any inciting event			☐
B) The patient has at least one sign in two or more of the categories			☐
C) The patient reports at least one symptom in three or more of the categories			☐
D) No other diagnosis can better explain the signs and symptoms			☐
Category		**Sign (you can see or feel a problem)**	**Symptom (the patient reports a problem)**
1 'Sensory'	*Allodynia* (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) and/or *hyperalgesia* (to pinprick)	☐	*Hyperesthesia* does also qualify as a symptom ☐
2 'Vasomotor'	Temperature asymmetry and/or skin colour changes and/or skin colour asymmetry	If you notice temperature asymmetry: must be >1°C ☐	☐
3 'Sudomotor/oedema'	Oedema and/or sweating changes and/or sweating asymmetry	☐	☐
4 'Motor/trophic'	Decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair/nail/skin)	☐	☐

CRPS CHECKLIST: (See Budapest criteria below)

Oedema/Muscular atrophy/hypertrophy:

Surgical/Traumatic Scars:

Sudomotor changes:

Hyperalgesia/Allodynia:

Skin Changes:

Abnormal Hair Growth:

Cutaneous Temperature:

When doing a lower back pain evaluation think the following:

Is this axial? (Muscular/ myofascial/ Facets)

Or axial back pain with **radiculopathy?** (Referred leg pain)?

Or previous surgery- **failed back syndrome** – which often has both features?

BACK:

General (appearance, palpation, mobility):

MOVEMENTS:

Flexion:	Extension:	Lateral (L):	Lateral:
SLR(R):	SLR (L):		

POWER:

HIP	**Right**	**Left:**
Flexion		
Extension		
Abduction		
Adduction		

KNEE

Flexion

Extension

ANKLE

Flexion

Extension

Inversion

Eversion

SENSATION

Touch

Pinprick

REFLEXES

L3/L4 Patellar Reflex

S1/S2 Achilles Reflex

Peripheral Pulses

Femoral:

Popliteal:

Anterior Tibial:

Dorsalis Tibial:

NECK

General:

Movements:

Flexion (degrees):	Extension:	Lateral (L)
Rotation (L):	Rotation(R)	Lateral (R)

Power:	*Right*	*Left*
Shoulder abduction		
Elbow Flexion/Extension		
Wrist flexion/Extension		
Hand Grip		

Sensation:

Touch:

Pinprick:

Reflexes	Right	Left
C5/C6 Biceps		

C6/C8 Triceps

Peripheral Pulses

Radial

Ulnar

TESTS AND INVESTIGATIONS

Bloods:

ESR: Hb: Other:

X Rays:

MRI:

CT:

Other:

DIAGNOSIS AND ASSESSMENT:

1.

2.

3.

4.

Plan:

Medication:

Interventional/Procedure Blockade Referral

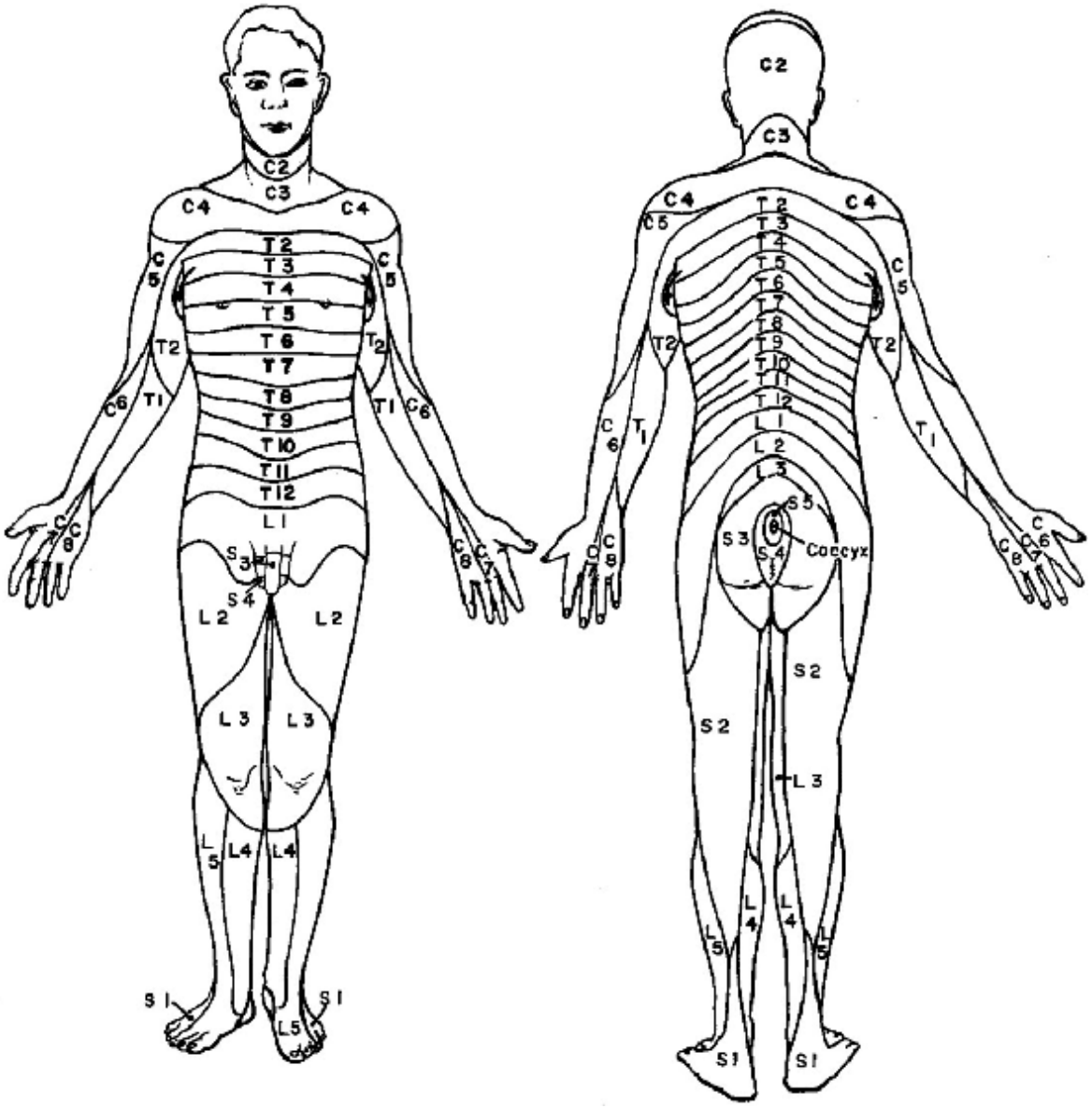
Team Members: Physiotherapy (1:1):

Chronic Pain Management Programme: Social Worker:

Psychiatry:

Psychology:

Other Speciality: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Appendix D: SAJAA Instructions for Authors

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

- This manuscript has currently only been submitted to SAJAA and has not been published previously.
- This work is original and all third party contributions (images, ideas and results) have been duly attributed to the originator(s).
- Permission to publish licensed material (tables, figures, graphs) has been obtained and the letter of approval and proof of payment for royalties have been submitted as supplementary files.
- The submitting/corresponding author is duly authorised to herewith assign copyright to the South African Society of Anaesthesiologists (SASA).
- All co-authors have made significant contributions to the manuscript to qualify as co-authors.
- Ethics committee approval has been obtained for original studies and is clearly stated in the methodology as well as provided as a supplementary file.
- A conflict of interest statement has been included where appropriate.
- The submission adheres to the instructions to authors in terms of all technical aspects of the manuscript.
- Plagiarism: The submitting author acknowledges that the Editorial Board reserves the right to use plagiarism detection software on any submitted material.

Author Guidelines

Submitted manuscripts that are not in the correct format and without the required supporting documentation specified in these guidelines will be returned to the author(s) for correction and will delay publication.

AUTHORSHIP

Named authors must consent to publication **by signing a covering letter** which should be submitted as a supplementary file. Authorship should be based on substantial contribution to:
(i) conception, design, analysis and interpretation of data;
(ii) drafting or critical revision for important intellectual content; and
(iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**); and
(iv) exact contribution of each author must be stated.

DECLARATION OF CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute a conflict of interest. If there is no conflict of interest to declare please include the following statement: The authors declare no conflict of interest.

FUNDING SOURCE

All sources of funding should be declared. Also define the involvement of study sponsors in the study design, collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication. If the study sponsors had no such involvement, this should be stated as follows: No funding source to be declared.

RESEARCH ETHICS COMMITTEE APPROVAL

The submitting author must provide written confirmation of Research Ethics Committee approval for all studies including case reports. The ethics committee as well as the approval number should be included.

STATISTICAL ANALYSIS

Authors are advised to involve medical statisticians at the protocol stage of their research project: to plan sample size, and the selection of appropriate statistical tests for analysis and presentation.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION

The rationale for analysis based on racio-ethnic-cultural categorisation should be indicated.

CATEGORIES OF SUBMISSIONS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles

Original articles on research relevant to anaesthesia and analgesia should not exceed 3 200 words, no more than 30 references, with up to 6 tables or figures. A structured abstract under the following headings, Background, Methods, Results, and Conclusions is a requirement and should not exceed 300 words.

Clinical Review articles

Review articles relevant to anaesthesia and analgesia should not exceed 2 400 words, with a maximum of 20 references and no more than 6 tables or figures. A summary of 300 words or less is required.

Case reports

Case reports should not exceed 1 800 words with no more than 10 references. Figures are limited to 2 figures and may include images or photographs. The case report should have three headings: Summary (not exceeding 100 words), Case report (with no introduction) and Discussion. Case reports will be published online only. The summary and the URL will appear in the printed version.

Scientific Letters

Scientific Letters should not exceed 2 400 words with a maximum of 10 references. Only one table or illustration is permissible. A structured abstract under the following headings, Background, Methods, Results, and Conclusions, is a requirement and should not exceed 250 words.

Letters to the editor

Letters to the editor should be 800 words or less with only one image or table.

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details

This information must be provided for ALL authors and must be submitted as a supplementary file.

Email addresses of all author must be provided.

ORCID number of **ALL** authors must be provided - if authors do not have ORCID, please register at https://orcid.org/

Abbreviations

All abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements

Scientific measurements must be expressed in SI units except blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age) should also be preceded by a space e.g. > 20 years. No spaces should precede ± and °, i.e. '35±6' and '19°C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting

The manuscript must be in Microsoft Word or RTF document format. Text must be 1,5-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, except for Tables). *The manuscript must be free of track changes.*

Disclaimers should follow the Conclusion and it should be in the following order: Acknowledgements, Declaration conflict of interest, Funding source, Ethics declaration and ORCID.

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file **and** provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes, tabs or enters) and

accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Figure 1)'. Figure legends: Figure 1: 'Title...'. All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft PowerPoint or Excel must be accompanied by the original workbook.

REFERENCES

Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists may be generated with the use of reference manager software, but the final document must be delinked from the reference database or otherwise generated manually. Citations should be inserted in the text as superscript, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] The superscript reference number should come after the punctuation mark and should not be in brackets.

All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first four names should be given followed by et al. First and last page, volume and issue numbers should be given. **Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID).** Authors are encouraged to use the DOI lookup service offered by **CrossRef**. Crossref DOIs should always be displayed as a full URL link in the form https://doi.org/10.xxxx/xxxxx

Journal references:

1. Jun BC, Song SW, Park CS, Lee DH. The analysis of maxillary sinus aeration according to aging process: volume assessment by 3-dimensional reconstruction by high-resolutional CT scanning. Otolaryngol Head Neck Surg. 2005 Mar;132(3):429-34.
2. Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 Jan [cited 2007 Jan 5];27(1):34-7. Available from: http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf.

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

COVERING LETTER

A covering letter to the editor is mandatory and must include statements that the manuscript has not been published previously and is not under review elsewhere. It should state details of any prior publication of the research in abstract form or in Congress proceedings. The letter must declare if any of the authors have a conflict of interest and that the requirements for submission, including ethics approval and patient permission for case reports have been fulfilled. All authors must sign the covering letter.

REVIEW PROCESS

Manuscripts, after vetting by the editorial team, are assigned for peer-review to 2 reviewers, conversant with the particular field of research. The reviewers and the authors are blinded to each other's identity. The turn-around time for review and initial editorial decision notification aims to be within 6 weeks of submission.

PROOFS

A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, **only** typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled.

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CHARGES

There is no charge for the publication of manuscripts.

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(400-800 words) (1 page)

Original Research

(2800-3200 words) (4-5 pages)

Scientific Letters

(2400 words) (3-4 pages)

Case Studies

(1 800 words) (3 pages)

Clinical reviews

(2 400 words) (3-4 pages)

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Appendix E: Examiners Comments and Responses

Comments	Responses
Examiner 1	
Introduction	
The second last paragraph may be reworded and simplified to avoid ambiguity. The candidate mentions that it is recommended that 50-100mg 4-6hrly be prescribed. She then says the dose can be increased to 100mg 6hrly – this would be less than the suggested 100mg 4hrly that she mentioned.	We rephrased the statement to 50-100mg 6 hourly to avoid ambiguity. Although it is stated as 50-100mg 4-6hourly in the South African National Essential Medicines Guideline.
Her last sentence. Regular MUE are essential etc should have come earlier in her introduction as this according to me, it is the 'punch-line' for this story.	The sentence is indeed the 'punch-line' for the story. We corrected by introducing it earlier in the paragraph.
Results	
The candidate mentions that it was not possible to discern whether/why antidepressants were prescribed for psychiatric or chronic pain condition. This must be clear form the patient file – either form history or the person who prescribed. This however I agree that it was not the objective of this study and may be left out.	Chronic pain and depression often coexist and are difficult to separate from each other. The long duration of clinic attendance and manual record keeping system used at the CPMC made it difficult to trace whether the antidepressants were prescribed for psychiatric or chronic pain condition as many initial patient records were lost.
Under pain profile – the majority of patients had had…."wouldn't have had read better?". She can decide this with supervisors.	We agree that your suggestion reads better and corrected the sentence.
Examiner 2	
This document could have included a description of the makeup of the pain clinic,	The median duration of clinic attendance was 10,5 years (IQR11,5). The makeup of

the number of specialists working there, and whether the patients are mostly followed up by the same doctors, their training in pain, other trainees and allied health personnel who are involved in the clinic and see patients.	the pain clinic and workflow might have changed over the years. The descriptions of the pain clinic was not part of the objectives of the study and every patients exposure to the clinic might have been different owing to the long duration of attendance.
It was very interesting to see that woman in there 50's on grants with co-morbidities made up the largest group of users and that most of them received a grant. Would the writer be willing to write their opinion on why this might be the case.	The study was a Medicine Usage Evaluation of tramadol and the discussion addressed the possible reasons for the deviation to standard prescription practice. Although interesting, writing our opinion on why women in their 50's on grants with comorbidities made up the largest group of users was not part of the objectives of the study.
It might be useful to see which side effects these patients experience and to understand what drugs are available for this specific pain clinic to use as an alternative to tramadol. Also, a mention about the opioid crisis and the alternative options in a pain clinic. It would have been useful to know if patients, from whom Tramadol has not improved their pain, would be willing to stop its use and to try alternative pain therapy (non-pharmacological and pharmacological).	All this information might be useful and might be part of further research in this area. However, this study only looked at the prescription practices and documentations based on WHO guidelines.
I may disagree that the side effect profile of tramadol is more favorable than that of morphine. I think this might vary with different cultures and genders.	We agree that the side effect profile of tramadol might not be more favourable than morphine and might vary with different cultures and genders. We stated that tramadol was previously favoured over

	morphine and recent studies have highlighted the fact that the drug might not be a better alternative (controversies surrounding usage, efficacy and abuse). These controversies were the main drive to conduct the study.
I also think the conclusion should include the need for future research in this area, especially because of the concerns that was raised.	We agree and included the statement as part of our conclusion.