Gabapentinoids for treatment of neuropathic pain: a medicines usage evaluation at the Groote Schuur hospital chronic pain management clinic

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Thesis Presented for the Degree of
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In the Department of Anaesthesia and Perioperative Medicine
Faculty of Health Sciences
UNIVERSITY OF CAPE TOWN

Supervisors:
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Declaration

I, Dr Machuene Agnes Moabelo, hereby declare that the work on which this thesis is based is 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 in University of Cape Town or any other university.

This thesis is presented in fulfilment of the requirements for the degree of MMed in Anaesthetics

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Signed by candidate

Date:
20/06/2017

Acknowledgments

Thank you to the Groote schuur hospital chronic pain management clinic staff

Abstract

Title: Gabapentinoids for treatment of neuropathic pain: a medicines usage evaluation at the Groote Schuur hospital chronic pain management clinic

Background

Neuropathic pain (NP), defined as pain caused by a lesion or disease of the somatosensory system, affects 6.9 – 10 % of people worldwide. Pregabalin is currently recommended as a first line drug for NP in South Africa.

Methods

A cross-sectional retrospective descriptive medicines usage evaluation (MUE) of Pregabalin at Groote Schuur Chronic Pain clinic for the year 2017 was conducted. A MUE using a standardized data collection form was performed on 100 randomly selected folders. Data are summarized using descriptive statistics.

Results

The majority of cases were women (76) with a mean age of 55.9y (SD12.49). A diagnosis of NP was recorded in 58 folders and a "possible" diagnosis recorded in 7 folders. In 79 cases there was no mention of a tool/method used to diagnose NP. The most common condition diagnosed was chronic post-surgical pain with a neuropathic component (n=16), followed by NP (n=15). The most common initiating and current dose of Pregabalin was 75mg twice daily. In 56 patients, Pregabalin was prescribed in conjunction with a tricyclic antidepressant (TCA) or selective noradrenaline reuptake inhibitor (SNRI). Patient education was documented as having taken place in 76 of cases.

Conclusions

Based on this MUE we recommend the use of screening tools for the diagnosis of neuropathic pain, and a focus on the initiating dose of Pregabalin. The use of a standardized assessment document and the interdisciplinary team input at this clinic appears to optimize prescribing of Pregabalin in line with practice guidelines.

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Section A: Introduction

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory system. Neuropathic pain is not a single disease, but a syndrome, which may be caused by a range of different diseases and lesions in the somatosensory nervous system, manifesting as an array of symptoms and signs.[1] Neuropathic pain can further be classified on the basis of etiology; thus, lesions can be central or peripheral, focal or generalized. There are multiple screening tools to aid in the diagnosis of neuropathic pain, including the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique 4 (DN4), Pain detect, ID Pain, and the neuropathic pain questionnaire.[2, 3] A recent systematic review reported an estimated population prevalence of pain with neuropathic characteristics of between 6.9% and 10%.[4, 5]

For South Africa, no published studies of the prevalence of neuropathic pain could be found. However, it is possible that there is a higher prevalence than elsewhere due to the burden of HIV/AIDS and diabetes, both of which are often associated with painful peripheral neuropathies.[6] The prevalence of neuropathic pain was reported as 23% among South African AIDS patients who had not received prior antiretroviral treatment, increasing to 40% in HIV-positive black South Africans exposed to stavudine.[7]

The pathology of neuropathic pain is complex and it is therefore not surprising that all treatment guidelines recommend multimodal treatment strategies and a biopsychosocial approach.[8] To select the most effective multimodal approach, the pathological mechanisms that contribute to neuropathic pain need to be considered to inform the selection of treatments that target those mechanisms.

The consequences of lesions in the somatosensory system include peripheral and central sensitization.[9] Lesions in the peripheral nerves result in peripheral sensitization via an increased expression of Na^+ channels and voltage gated Ca^{2+} channels in the C- and Aδ-nociceptive fibres.[9] This sensitization results in spontaneous ectopic-like discharges, decreased threshold of activation, and enhanced responsiveness to stimuli. Input from sensitized C-fibres can initiate and maintain activity dependant central sensitization in the dorsal horn of the spinal cord with enhanced neural excitability due to enhanced neurotransmitter release (glutamate) and

upregulation of glutamate (N-Methyl D-Aspartate) NMDA receptors.[10] The enhanced excitability and upregulation results in expansion of the receptive field and abnormal neural sprouting within the dorsal horn of the spinal cord.[9,10] All these changes alter nociceptive transmission manifesting clinically as hyperalgesia and allodynia.
Another mechanism that contributes to central sensitization is the dysfunction of the descending inhibitory serotonergic and noradrenergic pathways.[10] Originating from the anterior cingulate gyrus, amygdala and hypothalamus, and traveling via the brain stem nuclei in the periaqueductal grey and rostroventral medial medulla, the descending inhibitory pathways modulate the spinal transmission of nociceptive input at the spinal cord.[10] The neurotransmitters involved include noradrenaline, serotonin, and endogenous opioids. After a nerve injury, these pathways begin to dysfunction resulting in the effect of noradrenaline on α_2 noradrenergic receptors being suspended, with a net effect of the serotonergic input changing from inhibition to facilitation.[11] Therefore, the use of tricyclic antidepressants and serotonin noradrenaline reuptake inhibitors (SNRI) in the treatment of NP aims to facilitate endogenous inhibition and inhibit central sensitization.
As is evident from the above discussion of neuropathic mechanisms, the Ca^{2+} channels in the spinal cord are potential targets for the treatment of neuropathic pain. [10] Ca^{2+} is required for exocytosis of vesicles containing neurotransmitters from the presynaptic neuron into the synapse. By blocking or decreasing activity of the Ca^{2+} channels, a reduction in the synaptic release of excitatory neurotransmitters such as glutamate, substance P, noradrenaline, serotonin and calcitonin gene-related peptide results. By reducing the release of excitatory neurotransmitters, the effect of peripheral sensitization can be reduced, and central sensitization mechanisms diminished. The gabapentinoids, derivatives of the inhibitory neurotransmitter g-aminobutyric acid (GABA), bind to the $\alpha_2\delta$ auxiliary subunit of voltage-gated calcium channels, decreasing the influx of Ca^{2+} into the presynaptic neuron.[12]

The gabapentinoids include Pregabalin and gabapentin. Pregabalin is more potent and has a higher binding affinity for the $\alpha_2\delta$ subunit of voltage gated calcium channels than gabapentin [12]. In South Africa, Pregabalini s currently recommended as a first line drug for treatment of neuropathic pain. [13-15]

Pregabalin has been used at the Groote Schuur Hospital (GSH)Chronic Pain Clinic for eight years. The license on the drug has recently expired, and, with a potential shift in

availability, it is appropriate to conduct a Medicines Usage Evaluation (MUE) to optimize future practice. The GSH Chronic Pain Clinic is a specialist run clinic, treating an average of 100 patients monthly. At GSH, in line with WC DoH guidelines, Pregabalin and gabapentin must be consultant initiated i.e. prescriptions cannot be filled without the approval of a consultant aneasthetist listed as working in the Chronic Pain Clinic. On average, patients seen at the clinic are 52.8 y; predominantly female (68.7%) and unemployed (51%). We conducted a MUE of Pregabalin in the chronic pain management clinic (CPMC) of Groote Schuur Hospital to describe the prescription pattern and clinical use.

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Publication requirements

The paper was accepted for publication by the South African Journal of Anaesthesia and Analgesia on (insert date and link to the Appendix).

Formatting and referencing requirements for the journal are:

- Original research: 2800 -3200 words/4-5 pages
- UK English, typed in Microsoft Word with no double spaces after the full stops. 1,5 double spacing, font size 12 and font type of Times New Roman
- Must include:
    - Title page of article with surnames, initials, qualifications and affiliation of each author; the name, postal address, e-mail address and telephonic contact details. At least 5 keywords.
    - Abstract with 200 -230 words. Four paragraphs labelled background, methods, results and conclusion
    - Acknowledgements
    - References: Cited in numerical order in the text, in superscript format. References typed in single–spaced and numbered in numerical order, to follow Vancouver format.
    - Tables and figures: Each table and figure should include a clear descriptive title on top for table and bottom for figures. Numbered in Roman letters for tables and Arabic for figures.
    - All numbers below ten, without percentages or units, must be written in words

Gabapentinoids for treatment of neuropathic pain: a medicines usage evaluation at the Groote Schuur hospital chronic pain management clinic

1.INTRODUCTION

The prevalence of chronic musculoskeletal pain in South Africa has been reported to be higher than that in developed countries by multiple authors.[1, 2] A Western Cape community clinic based study reported the prevalence of chronic musculoskeletal pain to be 36%, higher than the 24% reported in the USA. [2] Chronic musculoskeletal pain is costly to manage due to its recurrence and potentially debilitating nature. When the chronic pain has a neuropathic component, management may increase in complexity.[3]

Neuropathic pain is defined as pain which occurs due to a lesion or disease affecting the sensory nervous system. [4] In South Africa, it is estimated that up to 30% of people with diabetes suffer from neuropathic pain[5], similarly up to 30% of people living with HIV develop painful peripheral neuropathy. [6] The prevalence of chronic pain musculoskeletal pain with a neuropathic component in South Africa is unknown, however it is estimated that up to 50% of people with chronic lower back pain will have a neuropathic component. [3]Other chronic pain conditions which present with a neuropathic component include: post-traumatic neuralgia (peripheral neuropathic); phantom limb pain (central neuropathic); stroke and other brain injuries (central neuropathic); and complex regional pain syndrome (Type I: central neuropathic; Type II: peripheral neuropathic). [3]

Chronic pain has an impact on multiple spheres of an individual's life such as psychological state, mood and activities of daily living.[7] When there is a neuropathic component, the impact on mood, function and participation is increased. [8]

The South African guidelines for the management of neuropathic pain recommend that if neuropathic pain is suspected, clinicians should screen for it using an appropriate tool such as the DN4[9] or the LANSS [10]. There appears to be consensus that on confirmation that the pain has a neuropathic component, treatment should be initiated with pregabalin or gabapentin as a first line drug with tricyclic antidepressants and topical lidocaine suggested as first line alternatives. [11-14] Pregabalin and gabapentin are $\alpha_2\delta$-ligands with similar targets but with differing

pharmacokinetics. Gabapentin, the older of the two drugs, has nonlinear pharmacokinetics and dosing requires careful titration. Pregabalin has linear pharmacokinetics and can thus be titrated more rapidly to effective dosages. [13]

The drawback of Pregabalin as a first-line treatment for neuropathic pain in South Africa is that it is a relatively new drug, still under license to its developers with cost implications for the user. At Groote Schuur Hospital, the prescribing of pregabalin is restricted to specialist neurologist, neurosurgeon, oncologist, chronic pain clinic practitioner and rehabilitation centers. The license on the drug has recently expired which means that generic forms of the drug may shortly become available. It is possible that this will result in greater availability and consequent changes in prescribing practices.

Guidelines recommend interdisciplinary treatment strategies which integrate pharmacological and non-pharmacological treatments rather than one-dimensional pharmacological management alone. [3, 15] This means that prescribing of the drug should take place in conjunction with non-pharmacological treatments. Chronic pain management is complex and expensive. The direct and indirect costs (i.e. cost associated with consequent disability, lost time from work, reduced productivity) of medical care are substantial. The most effective treatment strategies target a variety of factors simultaneously, using the biopsychosocial multidisciplinary approach. In 2014, the International Association for the Study of Pain (IASP) released guidelines that defined a multidisciplinary pain center as being a facility staffed by a variety of health care professionals with expertise in pain management, including physicians, nurses, mental health professionals, and physical therapists. Chronic pain requires a biopsychosocial approach using pharmacological and non-pharmacological approaches in tandem.

Given that pregabalin has been used at the GSH Chronic Pain Clinic for 5 years (personal communication, Dr van Nugteren) and that the license on the drug has recently expired with a potential shift in availability, it is appropriate to conduct a MUE to determine to who and how pregabalin has been used in the clinic to inform training and practice in the future.

2.AIMS and OBJECTIVES

The aim of this study is to conduct a Medicines Use Evaluation (MUE) for pregabalin in the chronic pain management clinic (CPMC) of Groote Schuur Hospital.

Using a cross-sectional chart review design, in patients who have been prescribed pregabalin at the CPMC , the objectives are to:

1. Describe the medical conditions for which pregabalin is being prescribed using the WHO ICD codes
2. Describe the prescribing practices of clinicians including:
    a. Full description of pain including type, severity and duration
    b. Patient details including age, gender, pregnancy, breastfeeding, allergies, comorbidities and whether they are receiving a disability grant
    c. Consideration of other medications and interaction with pregabalin
    d. Pregabalin dose, interval and duration documentation
    e. Follow up plan mentioned: including assessment of response to treatment or referral for non-pharmacological treatment
    h. Patient education about pregabalin, possible side effects and interactions

3.METHODOLOGY

3.1:RESEARCH DESIGN

A cross sectional descriptive study will be conducted. This type of study design will allow for the study of the characteristics of a population at one point in time, help in identifying the common medical conditions that pregabalin is being prescribed for and describe the prescribing practices of clinicians.

3.2:SAMPLE SIZE

To obtain a representative sample of prescribing practices in this population, the WHO recommends sampling a population of 100 patients. [16] As this study aims to describe prescribing practice of clinicians in Groote Schuur chronic pain clinic, the sample has been calculated based on a total number of patients seen in the chronic pain clinic on a monthly base.

3.3:PROCEDURE

Following ethical approval from the Faculty of Health Sciences Human Research Ethics Committee and the Groote Schuur Hospital Department of Health (DoH) Ethics Committee,

3.4:MEASUREMENT INSTRUMENTS

A data collection sheet based on the literature has been developed (Appendix A). Each question in the data collection sheet has been peer reviewed and referenced with supporting literature to ensure validity. The excel data collection tool will be populated with dropdown menus to reduce variability in responses.

3.5:DATA ANALYSIS

Data from the MUE will be entered into an excel spreadsheet. Descriptive statistics will be used to summarize the data. Further analysis of prescribing practice will be conducted using Chi-squared analysis of frequency distributions to explore association between prescribing and gender, diagnosis and sociodemographic profile.

4.ETHICAL APPROVAL

Ethical approval will be applied from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee and the Groote Schuur Hospital Ethics committee. Approval for the chart review process will also be obtained from senior consultant responsible for the CPMC and pharmacy manager.

The principles of the Declaration of Helsinki will be adhered to throughout. [17] The principles of autonomy, beneficence, non-maleficence and justice will be applied. [18] Autonomy will be maintained by keeping all patient details anonymous. As this is a chart review, patients will not be approached directly. Data collection will be conducted using two laptops. Information will be combined and saved to an external hard drive daily. The information gathered on the personal laptops will then be deleted to ensure that no information is available. The data will be stored on a password protected external hard drive kept in a locked office in the Department of Anaesthesia and Perioperative Medicine.

Beneficence will be observed by reviewing the patient's prescription charts individually, allowing the researchers to identify pharmacological errors that might cause patient harm. This study will also benefit patients' chronic pain management by addressing the role and importance of referral to multidisciplinary teams. Identifying and addressing the incorrect prescribing practice of clinicians and thus improving clinician's pregabalin prescribing practice in the future will ensure non-maleficence. In terms of justice this study will help in saving the DoH money by documenting the use of pregabalin and in the long run assist with resource allocation.

5.BUDGET

Copies of MUE: 100 copies. R1.50 per copy. Estimated cost R150.

6.PROJECT TIMELINES

Data collection: June – July 2018

Data analysis: July - August 2018

Write up: August -September 2018

Hand in: September 2018

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Section C: Paper accepted for Publication in South African Journal of Anaesthesia and Analgesia

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Gabapentinoids for treatment of neuropathic pain: a medicines usage evaluation at the Groote Schuur hospital chronic pain management clinic

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Keywords: Neuropathic pain, Pregabalin, Chronic pain clinic, Prescribing practices

ABSTRACT

Background: Neuropathic pain (NP), defined as pain caused by a lesion or disease of the somatosensory system, affects 6.9 – 10 % of people worldwide. Pregabalin is currently recommended as a first line drug for NP in South Africa.

Methods: A cross-sectional, retrospective, descriptive medicines usage evaluation (MUE) of Pregabalin at Groote Schuur Hospital (GSH) Chronic Pain Management clinic for the year 2017 was conducted. A MUE using a standardized data collection form was performed on 100 randomly selected patient folders. Data was summarized using descriptive statistics.

Results: The majority of cases were women (76) with a mean age of 55.9y (SD12.49). A diagnosis of NP was recorded in 58 folders and a "possible" diagnosis recorded in 7 folders. In 79 cases there was no mention of a tool/method used to diagnose NP. The most common condition diagnosed was chronic post-surgical pain with a neuropathic component (n=16), followed by NP (n=15). The most common initiating and current dose of Pregabalin was 75mg twice daily. In 56 patients, Pregabalin was prescribed in conjunction with a tricyclic antidepressant (TCA) or selective noradrenaline reuptake inhibitor (SNRI). Patient education was documented as having taken place in 76 of cases.

Conclusions: Based on this MUE we recommend the use of screening tools for the diagnosis of neuropathic pain, and a focus on the initiating dose of Pregabalin. The use of a standardized assessment document and the interdisciplinary team input at this clinic appears to optimize prescribing of Pregabalin in line with practice guidelines.

INTRODUCTION

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory system.[1] Neuropathic pain is not a single disease, but a syndrome, which may be caused by a range of different diseases and lesions, manifesting as an array of symptoms and signs. Neuropathic pain can further be classified on the basis of etiology; thus, lesions can be central or peripheral, focal or generalized. There are multiple screening tools to aid in the diagnosis of neuropathic pain, including the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique 4 (DN4), Pain detect, ID Pain, and neuropathic pain questionnaire.[2, 3] A recent systematic review reported an estimated population prevalence of pain with neuropathic characteristics of between 6.9% and 10%.[4, 5]

For South Africa, no published prevalence studies of neuropathic pain could be found. However, it is possible that there is a higher prevalence than elsewhere due to the burden of HIV/AIDS and diabetes, both of which are often associated with painful peripheral neuropathies. The prevalence of neuropathic pain was reported as 23% among South African AIDS patients who had not received prior antiretroviral treatment, increasing to 40% in HIV-positive black South Africans exposed to stavudine. [7] Stavudine, a nucleoside reverse transcriptase antiretroviral is neurotoxic, causing peripheral neuropathy in a dose dependent manner. The wide spectrum of diseases with a neuropathic component, combined with the different tools used to diagnose neuropathic pain, makes evaluation of epidemiological studies difficult.

The pathology of neuropathic pain is complex and it is therefore not surprising that all treatment guidelines recommend multimodal treatment strategies and a biopsychosocial approach.[8] To select the most effective multimodal approach, the pathological mechanisms that contribute to neuropathic pain need to be considered to inform the selection of treatments that target those mechanisms.

The consequences of lesions in the somatosensory system include peripheral and central sensitization.[9] Lesions in the peripheral nerves result in peripheral sensitization via an increased expression of Na^+ channels and voltage gated Ca^{2+} channels in the C- and Aδ-nociceptive fibres. This sensitization results in spontaneous ectopic-like discharges, decreased threshold of activation, and enhanced responsiveness to stimuli.[9] Input from sensitized C-fibres can initiate and maintain activity dependant central sensitization in the dorsal horn of the spinal cord with

enhanced neural excitability due to enhanced neurotransmitter release (glutamate) and upregulation of glutamate (N-Methyl D-Aspartate) NMDA receptors.[10] The enhanced excitability and upregulation results in expansion of the receptive field and abnormal neural sprouting within the dorsal horn of the spinal cord.[9, 10] All these changes alter nociceptive transmission manifesting clinically as hyperalgesia and allodynia.
Another mechanism that contributes to central sensitization is the dysfunction of the descending inhibitory serotonergic and noradrenergic pathways. Originating from the anterior cingulate gyrus, amygdala and hypothalamus, and traveling via the brain stem nuclei in the periaqueductal grey and rostroventral medial medulla, the descending inhibitory pathways modulate the spinal transmission of nociceptive input at the spinal cord.[10] The neurotransmitters involved include noradrenaline, serotonin, and endogenous opioids. After a nerve injury, these pathways begin to dysfunction resulting in the effect of noradrenaline on α_2 noradrenergic receptors being suspended, with a net effect of the serotonergic input changing from inhibition to facilitation. [11] Therefore, the use of tricyclic antidepressants and serotonin noradrenaline reuptake inhibitors (SNRI) in the treatment of NP aims to facilitate endogenous inhibition and inhibit central sensitization.
As is evident from the above discussion of neuropathic mechanisms, the Ca^{2+} channels in the spinal cord are potential targets for the treatment of neuropathic pain. Ca^{2+} is required for exocytosis of vesicles containing neurotransmitters from the presynaptic neuron into the synapse. By blocking or decreasing activity of the Ca^{2+} channels, a reduction in the synaptic release of excitatory neurotransmitters such as glutamate, substance P, noradrenaline, serotonin and calcitonin gene-related peptide results. By reducing the release of excitatory neurotransmitters, the effect of peripheral sensitization can be reduced, and central sensitization mechanisms diminished. The gabapentinoids, derivatives of the inhibitory neurotransmitter g-aminobutyric acid (GABA), bind to the $\alpha_2\delta$ auxiliary subunit of voltage-gated calcium channels, decreasing the influx of Ca^{2+} into the presynaptic neuron.[12]

The gabapentinoids include Pregabalin and gabapentin. Pregabalin is more potent and has a higher binding affinity for the $\alpha_2\delta$ subunit of voltage gated calcium channels than gabapentin.[12] In South Africa, Pregabalin is currently recommended as a first line drug for treatment of neuropathic pain. The recommenations comes from an expert panel. [13] Pregabalin is hydrophilic and double stranded at neutral pH, and so it crosses

membrane barriers via a specialised transport system (system L). [12, 31] Pregabalin has an oral bioavailability of up to 90% and time to peak plasma concentration in healthy volunteers is one hour. Absorption of Pregabalin is not saturable, resulting in a linear pharmacokinetic profile. It undergoes less than 1% metabolism and 95% is excreted unchanged by the kidneys. As Pregabalin clearance decreases with increasing age and decreased creatine clearance, dose reduction is recommended in elderly patients (>65 years) and patients with compromised renal function.

Pregabalin has been used at the GSH Chronic Pain Clinic for eight years. The license on the drug has recently expired, and, with a potential shift in availability, it is appropriate to conduct a Medicines Usage Evaluation (MUE) to optimize future practice. GSH Chronic Pain Clinic is a specialist run clinic, treating an average of 100 patients monthly. At GSH, in line with WC DoH guidelines, Pregabalin and gabapentin must be consultant initiated i.e. prescriptions cannot be filled without the approval of a consultant aneasthetist listed as working in the Chronic Pain Clinic. On average, patients seen at the clinic are 52.8 y; predominantly female (68.7%) and unemployed (51%), (personal communication from Dr Van Vrede). We conducted a MUE of Pregabalin in the chronic pain management clinic (CPMC) of Groote Schuur Hospital to describe the prescription pattern and clinical use.

METHODS

A cross-sectional retrospective descriptive chart review of the use of Pregabalin in Groote Schuur chronic pain clinic for the year 2017 was conducted. This type of study design allows the researchers to investigate the characteristics of this specific population at one point in time and helps to identify the indications for Pregabalin prescription.

To obtain a representative sample of prescribing practices in this population, the WHO recommends sampling a population of 100 patients. [28] As this study aimed to describe prescribing practice of clinicians in the Groote Schuur chronic pain management clinic, the population was patients being treated with Pregabalin at the CPMC of GSH in one year.

Ethical approval was obtained from the Faculty of Health Sciences Human Research Ethics Committee (Ref: 278/2018), Groote Schuur Hospital Department of Health (DoH) Ethics Committee and the Groote Schuur hospital pharmacy manager.

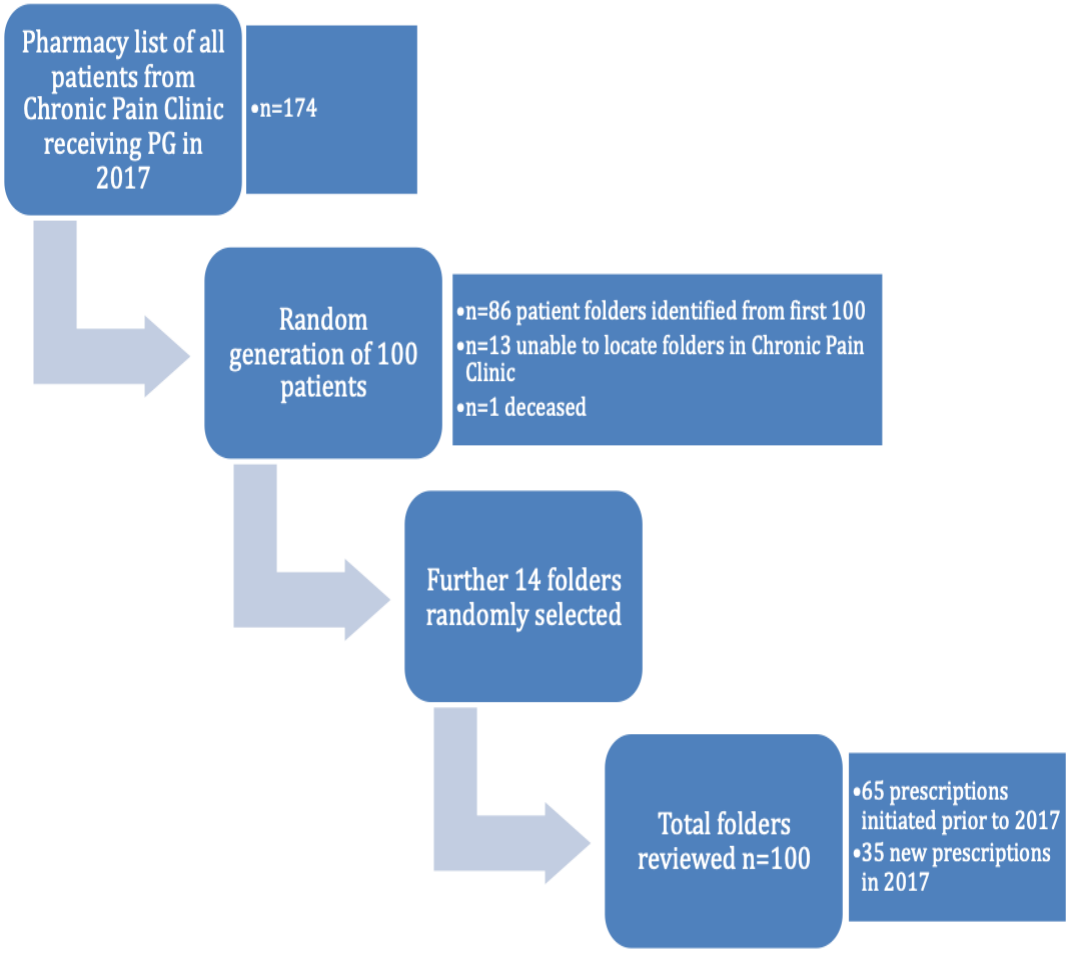

Figure 1: Flow chart illustrating data collection process.

From a list of 174 patients receiving Pregabalin in 2017, 100 folders were retrieved. (Figure 1). A medicine use evaluation (MUE) chart for Pregabalin based on the literature was developed (Appendix A). Each question in the data collection chart was peer reviewed by a chronic pain specialist. Items on the data collection sheet included: a documented diagnosis of neuropathic pain, the diagnostic tool used for the diagnosis, and documentation of the severity and duration of the condition. Charts were also examined to determine the presence of patient associated factors including age, gender, and presence of co-morbidities, allergies, pregnancy and breastfeeding. Data were collected on the prescribing practice of the clinician with respect to documentation of dosage, interval and duration of pregabalin, consideration of other

medications used by the patient and the possible interactions. Data from the MUE were entered into an excel spreadsheet. Descriptive statistics were used to summarize the data that are presented as mean (SD) or frequencies.

RESULTS

The mean patient age was 55.9y (SD12.49), ranging from 27y to 88y, and the majority (76 out of 100) were women (Table I). In all of the 100 folders reviewed, patient details including age, gender, presence of co-morbidities and allergies were documented. In one folder, note was made that screening for pregnancy was performed. In terms of socioeconomic profile, all 100 folders had documentation of whether the patient was receiving some form of social grant (disability grant or pension) with 36 documented as receiving a grant (Table I).

Table I: Demographic characteristics (n=100)

Descriptor	Mean (SD)
Age	55.9 (12.49)
Gender	**Frequency (%)**
Female	76
Male	24
Receiving a social grant	36
Applying for a disability grant	6
Temporary disability grant	7
Permanent disability grant	22
Workmen's compensation application	1

Diagnosis of Neuropathic Pain

The first criteria explored in the MUE was whether a diagnosis of NP was documented and whether a diagnostic tool was used to assist in making the diagnosis. A "diagnosis of NP" was classified as being made if the notes specified neuropathic

pain, neuropathy, radiculopathy, complex regional pain syndrome (CRPS) or post-herpetic neuralgia. A “possible diagnosis of NP” was classified as being made if the terms “possible” or “query” were used in the documentation in conjunction with any of the above terms. If no documentation was found using the above terms, a diagnosis of NP was recorded as not being documented. A clear diagnosis of NP was documented in 58 of the folders with a “possible” diagnosis recorded in a further seven folders (Table II).

Table II: Recording of Neuropathic pain diagnosis and method used (n=100)

Diagnosis of Neuropathic Pain Recorded	**Frequency (%)**
Yes	58
Possible diagnosis	7
No	35
Diagnostic tool/method recorded	
None recorded	79
Yes (EMG method recorded)	2
Yes (used a diagnostic tool)	19

The DN4 was used as a diagnostic tool for NP in one of the folders reviewed. The Budapest Criteria for the diagnosis of CRPS were completed in 18 folders. The criteria confirmed the diagnosis of CRPS in 9 cases (four CRPS Type 1; five CRPS Type II), with nine cases not meeting the criteria for CRPS. In two folders, EMG studies were documented as being performed, one of these was normal and one confirmed a diagnosis of NP.

The most common diagnoses were the neuropathic pain syndromes, which were recorded in 35 of the folders (Table III). The most common single condition

diagnosed was chronic post-surgical pain with a neuropathic component (n=16). This was followed by a diagnosis of neuropathic pain (n=15) and radiculopathy (n=12).

Table III: Diagnoses recorded in the patient folders

Diagnosis	Frequency (%)
Neuropathic diagnoses	**35**
Neuropathic pain	15
Complex regional pain syndrome Type 2	5
Complex regional pain syndrome Type I	4
Trigeminal neuralgia	3
Post herpetic neuralgia	3
Phantom limb pain	2
Peripheral neuropathy	1
Retroviral disease peripheral neuropathy	1
Motor axonal neuropathy	1
Spinal pain	**26**
Radiculopathy	12
Spinal stenosis	7
Chronic lower back pain	4
Tuberculosis of the spine	1
Spondylosis	1
Chronic lower back pain with neuropathic pain	1
Chronic post-surgical pain	**25**
Chronic post-surgical pain with a neuropathic component	16
Failed back syndrome	5
Chronic post-surgical pain	2
Failed back syndrome with fibromyalgia	1
Chronic post-surgical pain & fibromyalgia	1
Other	**14**
Fibromyalgia	7
Chronic pelvic pain	3
Chronic epigastric pain	1
Carpal tunnel syndrome & fibromyalgia	1
Loin pain haematuria	1
Chronic pancreatitis	1

Documentation of condition (pain severity, duration)

Pain severity was documented in 96 of the folders reviewed. The Brief Pain Inventory [32] was used to record pain severity and pain interference with function in 87 of the folders. Other methods used to record pain severity were the verbal rating scale (mild/moderate/severe) (n=8), and the visual analogue scale (n=1). The length of time the symptoms had been present was documented in all 100 folders with either the date of injury or surgery recorded or the number of months/years since the onset of pain.

Documentation of medical management

In 99 of the folders, there was clear documentation regarding medication other than Pregabalin being prescribed. In 11 of these folders, potential interactions with Pregabalin were noted.

In terms of Pregabalin dosages, clear prescribing was documented in all 100 folders including dosage, interval and duration. The most common initiating dose was 75mg twice daily (Table IV). There was a wide variety of current doses recorded with the most common being 75mg twice daily (Table V). One patient had stopped using the drug.

Table IV: Frequency of initiating doses of Pregabalin (n=100)

Initiating Dose	Frequency (%)
Night only	
25 mg	14
50mg	2
75mg	15
Total night only	31
Twice daily	
25mg	19
25mg morning/50mg night	2
25mg morning/75mg night	19
75mg	20
100mg	1
150mg	5
300mg	3
Total twice daily	69

Table V: Frequency of current doses of Pregabalin (n=100)

Current dose	Frequency (%)
Night only	
25mg	5
50mg	4
75mg	14
150mg	1
Twice daily	
Uneven dosing	
25mg morning/75mg night	9
50mg morning/75mg night	2
50mg morning/100mg night	1
25mg morning/150mg night	1
50mg morning150mg night	1
75mg morning/150mg night	7
100mg morning/150mg night	2
75mg morning/225mg night	1
150mg morning/225mg night	2
150mg morning/300mg night	1
150mg morning/300mg night	2
275 mg morning/300mg night	1
Even dosing	
25mg	1
75mg	21
150mg	17
225mg	2
300mg	4
Stopped	1

⁎Patient stopped due to significant side effects and switched to venlafaxine

Patients were receiving a wide variety of other medications indicated for pain including analgesics and centrally acting drugs (Table VI). The majority, (95 patients) were receiving analgesics in addition to pregabalin. Only five patients were receiving no medication other than pregabalin.

There were 56 cases where Pregabalin was prescribed in conjunction with an antidepressant (TCA or SNRI). Notably, in seven folders, patients were prescribed Pregabalin with both a TCA and a SNRI. More than half of the patients were on weak opioids, (tramadol, n=50) with a further 14 on morphine.

A follow up plan in terms of a reassessment date to evaluate the effect of the treatment was documented in all 100 folders. In 96 of the folders, patients were documented as being referred for non-pharmacological treatment (physiotherapy or psychology).

Patient Education

Patient education was documented as having taken place in 76 of the folders. The education conducted varied in topic. In 28 folders it was recorded that patients were educated about pregabalin, its effects and potential side effects. In 30 folders it was recorded that patients received pain neuroscience education. In 48 folders it was recorded that patients were referred to the Physiotherapy led Chronic Pain Management Program which includes education on both pharmacological and non-pharmacological management of pain, pain neuroscience education, self-management training, exercise and relaxation training. Seven of the 48 referred to this program were documented as not having attended.

Table VI: Other medications documented for pain management (n=100)

Medication: Analgesics	**Frequency (%)**	**Medication: TCA/SSRI/SNRI**	**Frequency (%)**	**Medication: Central acting**	**Frequency (%)**	**Medication: Other**	**Frequency (%)**
Paracetamol		***Amitriptyline* (nocte)**	37	***Carbamazepine***	7	***Prednisone***	
1g QID	78	10mg	7	100mg	4	7.5mg	1
1g TDS	6	25mg	12	200mg	3	60mg	1
		50mg	10				
Tramadol		75mg	5	***Clonidine (25-150mcg)***	8		
100mg QID	36	100mg	2				
50mg TDS	10	200mg	1	***Baclofen***			
100mg TDS	2			10mg TDS	1		
50mg BD	1	***Venlafaxine***	19	20mg TDS	1		
25mg	1	150mg	3				
		175mg	11				
Morphine		225mg	4				
10mg QID	6	300mg	1				
20mg QID	8						
		***Mianserin* 30mg**	2				
		***Fluoxetine* 20mg**	1				
		***Citalopram* 20mg**	1				

DISCUSSION

A cross-sectional retrospective MUE of the use of Pregabalin at Groote Schuur Chronic Pain management Clinic in 2017 was conducted. The mean age of the patients reviewed was 55.9 years (SD12.49); a large proportion were females (n=76) and more than a quarter (n=36) were receiving or applying for social grants. Although it is possible that our population was biased, as Groote Schuur Hospital is an academic tertiary hospital that predominantly services those who do not have access to private health insurance or private healthcare, this profile is similar to that reported in the literature on chronic neuropathic pain with the condition being more prevalent in older individuals, females, and in those of low socioeconomic status. [5]

Comparison of our patient population with medicines usage evaluations in countries as varied as the United Kingdom, Sweden and Japan shows a similar pattern with regard to age and gender distribution. The UK cohort, had a median age of 59y and the majority were female (60.1%) [33], while in Sweden the median age was 55 years, of which 63% were female[34]. The Japanese cohort was slightly older (66.8y) with 51% females.[35]

In this study, the most common condition diagnosed was chronic post-surgical pain with a neuropathic component (n=16). Post-traumatic and post-surgical nerve injuries are common causes of NP with post-herpetic neuralgia and distal polyneuropathy the next most common causes. [36, 37] In a tertiary care hospital in Saudi Arabia, the majority of patients were receiving Pregabalin for painful diabetic neuropathy[38] whereas a UK primary care setting reported that only 17.8% of the Pregabalin prescriptions were for neuropathic pain with the majority being for epilepsy.[33] The GSH cohort appeared to be different, with spinal related neuropathic pain being more common than the post-herpetic neuralgias and distal polyneuropathies reported as the most common conditions in other settings. This might be due to the presence of a specialist diabetic clinic at the hospital where patients with diabetic related distal polyneuropathy may be managed without referral to the pain clinic. Alternatively, these patients may be receiving treatment at a primary health care level. It is likely that these patients are being treated elsewhere as the incidence of both painful diabetic neuropathy and post herpetic neuralgia in South Africa are reported to be higher than elsewhere in the world as a consequence of the prevalence of diabetes and HIV. [7, 39, 40]

According to the South African guidelines, Pregabalin is indicated for use in the presence of neuropathic pain only, specifically for post-herpetic neuralgia and painful diabetic neuropathy. [13-15] It is encouraging that in the majority of folders reviewed, Pregabalin was being prescribed according to evidence-based guidelines unlike the 35.5 % diagnostic rate of neuropathic pain reported in a Swedish setting.[34] However, this diagnostic rate still falls short of expectations.

The diagnosis of NP is made on history and clinical examination, which can be facilitated by a variety of screening tools. There are five validated screening tools recommended for use in the diagnosis of neuropathic pain: the DN4, LANSS, PainDETECT, ID pain and Neuropathic pain questionnaire.[3] Most of these tools have a sensitivity and specificity of about 80% [3] indicating that the screening tools fail to clearly identify neuropathic pain in 20% of cases. In an ideal practice setting, a MUE of Pregabalin where screening tools are routinely used would report 80% of the patients as having a clear diagnosis of neuropathic pain and the remainder being diagnosed with "possible" neuropathic pain. In this study, a neuropathic pain screening tool was only used in 21 cases. The routine use of neuropathic screening tools may optimize the diagnosis and management of neuropathic pain.

Current guidelines recommend initiating Pregabalin at a dosage of 25mg at night to minimize initial side effects; with a maximum dose of 300-400mg daily in divided doses, to minimize dose dependent side effects. [8, 13, 41] The South African Medicines Formulary (SAMF), Monthly Index of Medical Specialities (MIMS) and the Pregabalin package insert recommend different initiating doses from those in the guidelines.[14, 15] In the SAMF and MIMS this is 75mg twice daily, while 150mg in two or three divided doses is specified in the package insert. This difference in recommendations, might contribute to variations in the prescribed initiating dose for pregabalin. Several factors have been identified which directly and indirectly affect prescribing patterns. [42] These include the clinical and behavioral characteristics of the patient, scientific evidence, drug efficacy, habitual or non-habitual choice, peer influence (community of physicians), education and pharmaceutical advertising, and the high cost of drugs. The patients seen at chronic pain clinic are usually patients that have experienced incomplete or failed management from another hospital or specialist clinic, and so they often present with complex pathology and anxiety. Pregabalin's high symptom amelioration and effectiveness makes it a common first line drug for the treatment of neuropathic pain. Peer influence may play a role as the clinic is staffed by one consultant with registrars rotating every two months. It is likely that the consultant influences the

registrar prescribing pattern more than the current literature as a consequence of the conflicting recommendations.[13, 14] However, to make a definitive statement regarding the influence of these factors on prescriber practice, a study of clinical reasoning processes is needed.

The efficacy of simple analgesics for neuropathic pain has not been established. However, 84 patients were on paracetamol, a simple analgesic agent. As mentioned above, physician prescribing practice is influenced by multiple factors. The high usage of paracetamol might be due to the concomitant presence of complex pain with a nociceptive component (the clinical characteristics of the patient) or to prescribing practices related to habit and peer influence. [42] In addition, 56 patients were on combination treatment with an SNRI or TCA. These antidepressants are recommended for the management of neuropathic pain as first line (monotherapy) or second line (combination) therapy with pregabalin. [8, 13, 41] The concomitant use of these drugs in neuropathic pain target the mechanisms of dysfunction in the descending inhibitory pathway and address the mood and sleep disorders associated with chronic pain states. As mentioned in the introduction, the neurotransmitters involved in this pathway include serotonin and noradrenaline. The use of these drugs in addition to Pregabalin potentiates the descending inhibitory pathways and thus inhibits central sensitization.

In all 100 folders reviewed, documentation of medical conditions, allergies, and medication doses were correctly recorded. In addition, pain severity was fully documented using the Brief Pain Inventory (BPI) in 96 of the folders reviewed. There was a 100% follow up of patients, where treatment effectiveness and development of side effects was reviewed. The excellent documentation and follow up is most likely achieved due to the use of a standardised assessment document used in the initial assessment of the patient. This standardised assessment document incorporates the BPI in addition to sections for past medical history (including history of mental health disorders), social history, level of education and employment, current mood and evaluation of the patient's ideas, concerns and expectations. Therefore, this document thoroughly covers a biopsychosocial patient history and allows for the documentation of the management plan by the interdisciplinary team. The use of this document means every patient assessment is standardized, reminds clinicians of important factors to document, and reduces the risk of clinician bias or fatigue, habitual choices and peer influence, and facilitates patient follow up.[43]

All current guidelines on the management of neuropathic pain and any chronic pain state emphasize the importance of a multidisciplinary team approach to the treatment of

neuropathic pain, as well as the role of patient education. [13, 27, 37] In this MUE, 96 patients were referred for non-pharmacological management of pain, documented as referral for physiotherapy, psychiatry, psychology, mirror therapy, graded motor imagery therapy, breathing and relaxation techniques. Patient education was specifically recorded in 76 of the folders; including education about pregabalin, its effects and side effects, pain neuroscience and the chronic pain management program. Documentation included decisions made at regular interdisciplinary meetings (medical doctors, physiotherapists, psychologists, consultation liaison psychiatrists) where each new patient is discussed, and appropriate management plans developed according to guidelines recommending holistic, pharmacological and non-pharmacological approaches for better efficacy. [37]

This study was a retrospective descriptive chart review of one hundred randomly selected folders reducing selection bias. Misclassification bias was minimized by the investigators performing all the data collection. The 100 folders represent 57.47% of the prescriptions written for Pregabalin by the chronic pain clinic in one year, limiting generalizability. Our study was conducted in an academic, public hospital where the patient population may be of lower socioeconomic status and have a higher burden of co-morbidities than elsewhere

CONCLUSION

Based on this study we recommend the routine use of screening tools in the diagnosis of neuropathic pain, in particular the use of the DN4 screening tool as per the South African guidelines.[13] This recommendation was made because the DN4 is short, quick and easy to follow in regular clinical practice.We also recommend initiating Pregabalin at a dose of 25mg at night and titrating subsequent doses over one to two weeks based on efficacy and side effects to a maximum of 400mg daily in divided doses. Finally, we recommend that the risks of polypharmacy be raised with prescribers with emphasis on ceasing drugs that are not effective for the treatment of any given condition. The use of Pregabalin in this Chronic Pain Management clinic is characterized by appropriate prescribing for neuropathic pain, good clinical documentation and appropriate management with follow up. This clinical practice may have been facilitated by the use of a standardized assessment document, the involvement of an interdisciplinary team with every new patient and active engagement with patients regarding treatment options. It would be beneficial to specifically explore the effects of these practices on patient care.

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Section D: Conclusion

The use of Pregabalin in this Chronic Pain Management clinic appears to be characterized by appropriate prescribing for neuropathic pain, good clinical documentation and appropriate management with follow up. This clinical practice may have been facilitated by the use of a standardized assessment document, the involvement of an interdisciplinary team with every new patient and active engagement with patients regarding treatment options.

Based on this MUE, we recommend the routine use of screening tools in the diagnosis of neuropathic pain, in particular the use of the DN4 screening tool as per the South African guidelines.[13] We also recommend initiating Pregabalin at a dose of 25mg at night and titrating subsequent doses over one to two weeks based on efficacy and side effects to a maximum of 400mg daily in divided doses. Finally, we recommend that the risks of polypharmacy be raised with prescribers with emphasis on ceasing drugs that are not effective for the treatment of any given condition.

This study was a retrospective descriptive chart review of one hundred randomly selected folders. This type of study is associated with recall and classification bias. To reduce selection bias, random selection of 100 folders was performed and misclassification bias was minimized by the investigators performing all the data collection. The 100 folders represent 57.47% of the prescriptions written for Pregabalin by the chronic pain clinic in one year, limiting generalizability. Our study was conducted in an academic, public hospital where the patient population may be of lower socioeconomic status and have a higher burden of co-morbidities than elsewhere. Another limitation of chart reviews is the reliance on documentation alone. There is a risk that patients may have been screened for pregnancy and negative responses were not documented with no room elaboration of what was discussed during patient education of pain and medication side effects in the notes.

Future research needs to be focussed on the translation and validation of neuropathic pain screening tools for use in South African populations. This study provides a basis of comparison of Pregabalin use and neuropathic pain treatment amongs clinician in private and state institutes. A detailed investigation of the prescribing practice of clinicians in Groote Schuur Hospital chronic pain management clinic can assist in identify specific factors that will describe the pattern of prescribing that was observed in our study.

Appendices

Appendix A:

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

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
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30 May 2018

HREC REF: 278/2018

A/Prof R Parker
Anaesthesia and Perioperative Medicine
D23
NGSH

Dear A/Prof Parker

PROJECT TITLE: THE USE OF PREGABALIN IN THE GROOTE SCHUUR HOSPITAL CHRONIC PAIN MANAGEMENT CLINIC: A CROSS-SECTIONAL DESCRIPTIVE STUDY (MMED Candidate - Dr M Moabelo

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

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

Approval is granted for one year until the 30 May 2019.

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)

Please quote the HREC REF 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.

The HREC acknowledge that the student, Dr Machene A Moabelo will also be involved in this study.

Yours sincerely

Signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938
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 Convention on Harmonisation 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 278/2018

Appendix B: Data Collection Documents (Medicines usage evaluation)

CRITERIA		DATA RECORDED	REFERENCES
DIAGNOSIS: NEUROPATHIC PAIN	Has the clinician documented neuropathic pain as the diagnosis?	Y/N	Chetty, S., et al., 2012
DIAGNOSTIC TOOL	Was a diagnostic tool such as the DN4/LANSS or Budapest criteria used?	Y/N Document data	Chetty, S., et al., 2012
SEVERITY	Has the clinician documented severity of the pain? Either mild/moderate/severe or NRS (out of 10)	Y/N Document data	Organization WH. Promoting rational use of medicines: core component. 2002-3 ed2002. [28]
DURATION	Has the duration of the pain been documented? Days or months	Y/N Document data	Organization WH. Promoting rational use of medicines: core component. 2002-3 ed2002. [28]
PATIENT DETAILS	Patient age, gender, any current co-morbidities(all medical, psychiatric conditions including epilepsy), pregnant, breastfeeding, allergies been documented?	Document data	[44444343]Practical Approach to Care Kit (PACK); Global Adult 2017. [44] Finch, E., E.L. Geddes, and H. Larin 2005. [30]

PATIENT DETAILS	Is the patient on a disability grant?	Y/N	[28]
OTHER MEDICATIONS AND INTERACTIONS	Has the clinician mentioned and taken note of other medication the patient is on and possible interactions?	Y/N Document data	[28]
PREGABALIN DOSE, INTERVAL AND DURATION	Has the dosage, interval and duration for which Pregabalin must be used been documented?	Y/N Document data	[28]

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	[28]
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	[28]
TOTAL SCORE OF Y/N (x/11)			

Appendix C: Standardized assessment dcument

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)	☐	☐

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)	Lateral (R)
Rotation (L):	Rotation(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):

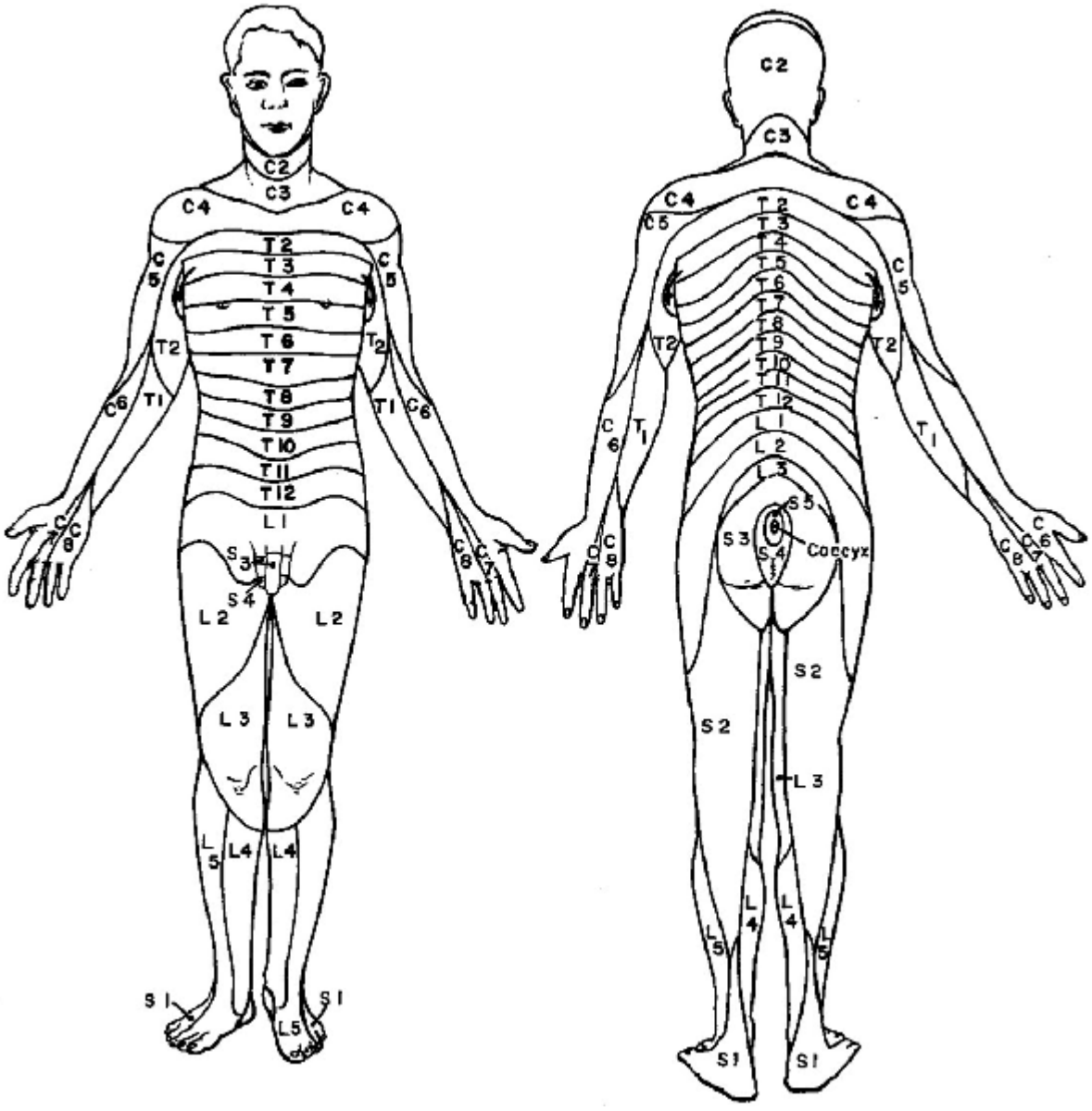
Chronic Pain Management Programme:

Social Worker:

Psychiatry:

Psychology:

Other Speciality: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Appendix D: Reviewer comments and responses

First Round of Review:

COMMENTS	RESPONSES
Comment 1: Both reviewers feel that this title does not quite match the scope of your article. You have presented quite a detailed review of neuropathic pain and the role of the gabapentinoids in the management thereof.	Thank you, we have tried to expand the title slightly to include the scope of the review and the MUE: "Gabapentinoids for treatment of neuropathic pain: a medicines usage evaluation at the Groote Schuur hospital chronic pain management clinic"
Comment 2: 76 or 79? Differs in Table 1 and the discussion	Our apologies, the correct number is 76. This typing error has been corrected throughout.
Comment 3: 76 female patients and 76 cases with no mention of tool. This is unusual. Please confirm these figures	79 cases with no mention of tool Typing error
Comment 4: Please write out in full (predefine) before using abbreviations	The full names have now been included: The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique 4 (DN4)
Comment 5: "Soft reference (not a systematic review relevant to current practice as main deductions are from studies pre-dating NP diagnosis) #4 is not firm on prevalence and specifically mentions broad variations and challenges in diagnosis, specifically in Brazil. While of interest, this is not a NP article and broad statements and unqualified % unhelpful. " Perhaps you could include a second reference here?	Thank you for highlighting the need to provide more robust evidence. We have now included reference to a more recent systematic review of epidemiological studies "A recent systematic review reported an estimated population prevalence of pain with neuropathic characteristics of between 6.9% and 10%."

Comment 6: Reviewer 1: Selection process is shown in the chart therefore this paragraph is unnecessary Reviewer 2: Were these new patients and new Pregabalin prescriptions in the 2017 time frame specified? Editor: perhaps you can answer reviewer 2 question and eliminate part of this paragraph, referring to the flow chart.	We have streamlined the presentation of the procedure followed: "A total of 100 patient folders were reviewed; 35 prescriptions were made in 2017 and 65 were from previous years. Figure 1"
Comment 7: If 76 out of 100 were women, then this makes 76% unless you had some "non male non female" patients in the study, which should be indicated in the table	Apologies and thanks for identifying this error. Corrected
Comment 8 and 9: 76 or 79?	Corrected throughout. Correct number 76
Comment 10: I don't think there is a reason to reiterate the results in the discussion section, only if the authors are drawing a comparison to other data or population. It is easier to say that such a % from our study shows this kind of NP and put this in perspective to published data. Ie is there any data on how Pregabalin is being prescribed in other pain units either in SA, or worldwide? This can then be compared with your data.	We have reduced the repetition of results and drawn a comparison to other literature: "Comparison of our patient population with medicines usage evaluations in countries as varied as the United Kingdom, Sweden and Japan shows a similar pattern with regard to age and gender distribution. The UK cohort, had a median age of 59y and the majority were female (60.1%) [33], while in Sweden the median age was 55 years, of which 63% were female[34]. While the Japanese cohort was slightly older (66.8y) with 51% females."

	"In a tertiary care hospital in Saudi Arabia, the majority of patients were receiving Pregabalin for painful diabetic neuropathy[38] whereas a UK primary care setting reported that only 17,8% of the Pregabalin prescriptions were for neuropathic pain with the majority being for epilepsy. " "It is encouraging that in the majority of folders reviewed, Pregabalin was being prescribed according to evidence-based guidelines unlike the 35.5 % diagnostic rate of neuropathic pain reported in a Swedish setting."
Comment 11:I do not understand this term. Do you mean a high curative effect or rate of cure?	Thank you for highlighting the need to clarify the term – we have corrected throughout to "Curative effect"
Comment 12: Curative effect	See above
Comment 13: Curative effect	See above
Comment 14: Many other effects on pain, peripheral nerves, NP, mood and sleep.	We have included the following to clarify: "The concomitant use of these drugs in neuropathic pain target the mechanisms of dysfunction in the descending inhibitory pathway and address the mood and sleep disorders associated with chronic pain states.."
Comment 15:A very ambitious statement regarding BPI" Consider rephrasing	We have rephrased the statement to clarify the scope of the Brief Pain Inventory and the scope of the entire pain assessment form used in the clinic: "This

	standardised assessment document incorporates the BPI in addition to sections for past medical history (including history of mental health disorders), social history, level of education and employment, current mood and evaluation of the patient's ideas, concerns and expectations."
Comment 16: Each patient discussed? 100 per month?	We realise the way this was presented was ambiguous, we have clarified as follows: "Each new patient is discussed"
Comment 17: I believe this discussion is lacking a reference to published data, rate of use of Pregabalin in the Middle East (might be a comparable population and closer demographics), and perhaps an international reference study. Other pain centres (stand alone, or part of tertiary hospitals) have their own long term records and the authors must show such a comparison." I agree that a comparison with other pain units would strengthen this discussion	Thank you for highlighting the need to provide more comparison data with similar populations and international studies: We have now included comparison from different countries in the discussion
Comment 18: How often titrated?	Details have been included: "We also recommend initiating Pregabalin at a dose of 25mg at night and titrating subsequent doses over one to two weeks based on efficacy and side effects to a maximum of 400mg daily in divided doses"
Comment 19:Should some prescriptions not be ceased if ineffective as per NNT in	We have clarified the language in this sentence by replacing the word

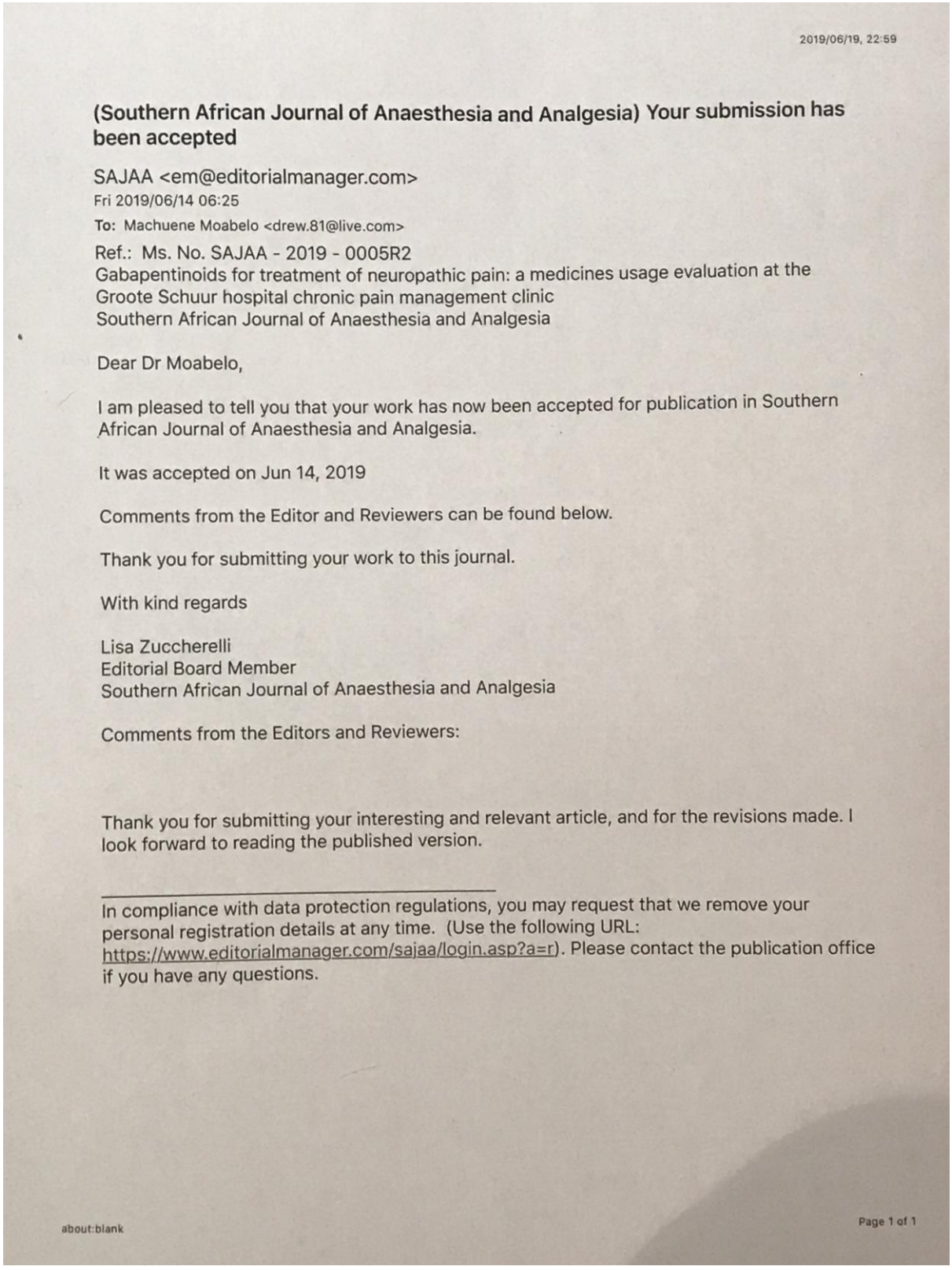
NP for Pregabalinand to avoid misuse?	"removing" with "ceasing"
Comment 20: How did you involve each patient. Do you mean "patient engagement"	The concluding sentences have been adjusted as per the next comment. Please see below.
Comment 21: Myself and reviewer 2 think that this statement is quite presumptive based on the data presented in this MUE. The MUE was not intended to assess the efficacy of a standardized assessment document. Consider rewriting please.	Indeed, the objective of this study was not to evaluate the assessment approach. We have adjusted the conclusion as follows: "The use of Pregabalin in this Chronic Pain Management clinic is characterized by appropriate prescribing for neuropathic pain, good clinical documentation and appropriate follow up. This clinical practice may have been facilitated by the use of a standardized assessment document, the involvement of an interdisciplinary team with every new patient and active engagement with patients regarding treatment options. It would be beneficial to specifically explore the effects of these systems on patient care."

Second Round of Review:

COMMENTS	RESPONSE
Comment 1: Formatting of flow chart needs attention as writing is partially obscured in the last box	Thank you for highlighting the need to edit the table format.
Comment 2: Is this correct? In Australia, Pregabalin is indicated for epilepsy and fibromyalgia. Not sure what it is registered for in SA. Please check this.	Clarity has been provided as follows: According to the South African guidelines, Pregabalin is indicated for use in the presence of neuropathic pain only, specifically for post-herpetic neuralgia and painful diabetic neuropathy.
Comment 3: It may be worthwhile adding a comment that use of a valid diagnostic tool was only recorded in 21 cases in your cohort, which is a low number. One might assume that all the other cases were diagnosed based on history and physical examination only? This would also reinforce your conclusion where you have recommended the use and documentation of DN4	Thank you for highlighting the need to support the discussion: In this study, a neuropathic pain screening tool was only used in 21 cases. The routine use of neuropathic screening tools may optimize the diagnosis and management of neuropathic pain.
Comment 4: I read the reference article for this term and did not see the term used directly. I think you should change this to “drug efficacy” or “potential curative effect”	Thank you for highlighting the need to clarify the term: Drug efficacy
Comment 5: This sentence is redundant, as you have detailed the factors above – could it be deleted? Or perhaps rephrase	Deleted

what you are trying to say	

Letter Indicating Paper Accepted for Publication:



2019/06/19, 22:59

(Southern African Journal of Anaesthesia and Analgesia) Your submission has been accepted

SAJAA <em@editorialmanager.com>
Fri 2019/06/14 06:25
To: Machuene Moabelo <drew.81@live.com>

Ref.: Ms. No. SAJAA - 2019 - 0005R2
Gabapentinoids for treatment of neuropathic pain: a medicines usage evaluation at the Groote Schuur hospital chronic pain management clinic
Southern African Journal of Anaesthesia and Analgesia

Dear Dr Moabelo,

I am pleased to tell you that your work has now been accepted for publication in Southern African Journal of Anaesthesia and Analgesia.

It was accepted on Jun 14, 2019

Comments from the Editor and Reviewers can be found below.

Thank you for submitting your work to this journal.

With kind regards

Lisa Zuccherelli
Editorial Board Member
Southern African Journal of Anaesthesia and Analgesia

Comments from the Editors and Reviewers:

Thank you for submitting your interesting and relevant article, and for the revisions made. I look forward to reading the published version.

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/sajaa/login.asp?a=r). Please contact the publication office if you have any questions.

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