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Pregabalin and Gabapentin for the Management of Chronic Sciatica: Determining Utility, Effect on Functioning Capacity, Quality of Life and Clinical Outcome

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Specific Contributions

Approvals

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research, 2007. The research conducted within this thesis received human research ethics approval from the James Cook University Human Research Ethics Committee and the Townsville Hospital and Health Service Human Research Ethics Committee. Direction for approvals and preparation of the National Ethics Application Form applications where performed with the advice and guidance of all supervisors. The subsequent Australian and New Zealand Clinical Trial Registration was submitted by Kelvin Robertson with guidance from Associate Professor Laurence Marshman.

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Study

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Abstract

Background: Pain is a major clinical problem, the true prevalence of which is difficult to estimate as it encompasses a variety of disorders. Sciatica is considered a type of neuropathic pain (NP) characterised by severe low back pain radiating down the leg to below the knee. Chronic sciatica (CS) is sciatica lasting longer than three months. There are few clinical guidelines for treating of CS, reflecting a gap in quality evidence for effective therapies. Recently, two medications gabapentin (GBP) and pregabalin (PGB) have been used in the management of CS. Evidence for their usage is limited with no direct, high quality research to determine if one is superior to the other. This research answers that question and helps guide clinicians as to the best treatment option for CS.

Methods: The thesis includes a literature review to gauge current management of CS with PGB and GBP. The work uses a mixed-methods approach to gain evidence on efficacy, disability and personality traits which will guide clinician's choice of either GBP or PGB. A mix of methods was chosen, to capture patient's treatment experiences more broadly and not simply being restricted to symptom relief. Anecdotal evidence suggests a variable response to either drug, both in terms of efficacy and adverse events (AEs). However, we are unsure at what point the balance of benefits against AEs tips and patients make the decision to abandon treatment. To gather this information and draw conclusions regarding the optimal treatment for patients with CS, this project collects background information on patient's perceptions related to treatment, and conducts a novel randomised controlled trial to determine head to head which treatment is more efficacious. We set out to establish whether one drug has a superior profile to the other and if there are any other differences in treatment outcomes.

Hypothesis: We hypothesise that there are differences between the drugs, where (1) one drug (PGB) has a superior profile in pain and disability reduction, as well as (2) frequency and severity of adverse events.

Results: Retrospective data showed AEs to be a limiting factor for treatment outcomes and compliance when GBP was added to a first line agent. The clinical trial reported here showed that, while PGB and GBP were both significantly efficacious in reducing

pain intensity in patients with CS, GBP was superior when compared 'head-to-head'. Moreover, GBP was associated with fewer and less severe AEs. Neither drug was superior when compared 'head-to-head' for reducing disability in our study group. Our exploratory study on personality traits showed that patients with a predominantly external self-control had worse outcomes. Specifically, an external self-control resulted in lower pain severity reductions especially with PGB. Moreover, PGB alone demonstrated a high, and statistically significant, positive correlation with external self-control resulting in higher pain values for patients displaying this personality trait. There were no notable differences between drugs when personality and disability severity were compared.

Conclusion: This research makes a significant original contribution to the literature by addressing a key gap regarding the utilisation of pain medication for CS, namely with PGB and GBP. We found that GBP was superior to PGB for reducing pain severity and for being associated with fewer and less severe AEs. Moreover, our results show having a personality trait of external locus of self-control, negatively effects treatment outcomes with PGB. Our findings provide a body of evidence which can formally guide treatment decisions for patients with CS considering pain severity, disability severity, AEs and personality.

Statement of Access

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Statement on Sources

Declaration

I declare that this thesis is my own, original work carried out under the supervision of Associate Professor Laurence Marshman of the School of Medicine and Dentistry at James Cook University. No part of this work has been submitted in any form for another degree or diploma at any other university or institution of tertiary education. Any work that is not my own has been acknowledged in the text by appropriate references.

08.11.2018

_____   _____
Signature   Date

Kelvin Robertson

_____
Name

Dedication

To my colleagues in where "time" and "work" are diluted commodities with unnecessary deadlines and expectations, battling to achieve goals as individuals and who think that their work does not make a difference. This thesis is evidence that much can be achieved with communication, planning and teamwork. Thanks for the inspiration.

The work on pain treatment and in a broader sense the quality use of medications, I dedicate to the population of people who suffer every day. To think that going through a day pain free could mean so much and the reward of obtaining this achievement is what drives me to continue this line of work.

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Abbreviations

Abbreviation	Name
AEs	Adverse Events
AMH	Australian Medicines Handbook
AMP	Amitriptyline
ANZCTR	Australian and New Zealand Clinical Trial Registry
ATG	Australian Therapeutic Guidelines (eTG)
ATSI	Aboriginal and Torres Strait Islander
BD	Twice per day
BNF	British National Formulary
CLBP	Chronic Low Back Pain
CNS	Central Nervous System
CS	Chronic Sciatica
CT	Computer Tomography
FDA	Food and Drug Association
GABA	Gamma-Aminobutyric Acid
GBP	Gabapentin
GCP	Good Clinical Practice
GMP	Good Manufacturing Principles
HREC	Human Research Ethics Committee
HLoC	Health Locus of Control
ITT	Intention to Treat
JCU	James Cook University
LOR	Loss of Response
MeSH	Medical Subject Headings

MRI	Magnetic Resonance Imaging
NHMRC	National Health and Medical Research Counsel
NICE	National Institute for Health and Clinical Excellence
NNT	Number Needed to Treat
NP	Neuropathic Pain
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
ODI	Oswestry Disability Index
PAGPROS	Pregabalin and Gabapentin Prospective Randomised Trial in the Treatment of Sciatica
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PGB	Pregabalin
QHMAC	Queensland Health Medicines Advisory Committee
SAE	Serious Adverse Event
SE	Side Effect
SPSS	Statistical Package for the Social Science
TCA	Tricyclic Anti-Depressant
TDS	Three times per day
VAS	Visual Analogue Scale

Chapter 1   Introduction

'The aim of the wise is not to secure pleasure, but to avoid pain.'

Aristotle

1.1   Context of this Research

Neuropathic pain (NP) is a major clinical and epidemiological problem, the prevalence of which is difficult to estimate as it encompasses a variety of disorders. Sciatica is considered a type of NP characterised by severe low back pain with radiating leg pain below the knee and considered a major clinical problem [3, 15]. Chronic sciatica (CS) is sciatica lasting longer than 3 months [14]. There are few clinical guidelines on the treatment of CS, reflecting the lack of quality evidence of effective therapies. Recently, two medications gabapentin (GBP) and pregabalin (PGB) have been used in the management of NP but there is limited, direct, high quality research to inform clinicians as to which of these to choose for the treatment of people with CS.

GBP and PGB both belong to the anti-convulsant class of medications. The exact mechanism of action is unknown; however, they are believed to bind to alpha-2 delta protein subunit of high threshold voltage-dependant calcium channels, reducing calcium influx and neurotransmitter release [5]. Consequently, a decrease in pain is observed in neuropathic aetiologies. Both GBP and PGB are titrated up to the maximum tolerated dose with GBP administered three times per day (tds) and PGB twice per day (bd) [5]. For NP, PGB is capped at 300mg bd while GBP is 1.2g tds [5]. Common adverse effects are similar between the medications and feature fatigue, sedation, dizziness, ataxia, tremor, diplopia, weight gain, dry mouth, hypertension and rash [5].

This thesis entails a mixed-methods approach to gain evidence on efficacy, disability and personality traits which will guide clinician's choice of either GBP or PGB. We have chosen a combined approach, designed to capture patient's treatment experience more broadly, not simply focussing on symptom relief. Anecdotal evidence suggests a variable response to either drug, both in terms of efficacy and adverse events (AE). However, we are unsure at what point the balance of benefits against AE tips and patients make the decision to abandon treatment. To gather this information and draw

conclusions regarding the optimal treatment for patients with CS, this project (1) will collect background information on patient's perceptions related to treatment, and (2) conduct a novel randomised controlled trial to determine head to head which treatment is more efficacious.

In terms of efficacy and AEs, we set out to establish whether one drug has a superior profile compared to the other. Conversely, we expect to encounter patients who abandon treatment after a short period with minor adverse events (AEs).

At the completion of this research, the aim is for a gap in the literature to be filled regarding the efficacy of PGB compared to GBP, and evidence made available to help guide treatment decisions based on disability severity and personality types for each patient.

1.2   Justification for the Research

Sciatic neuralgia (also known as sciatica), is a common form of lumbosacral radiculopathy. This condition is characterised by low back pain that radiates to the leg below the knee and can be accompanied by sensory loss, motor weakness and reflex abnormalities. Sciatica is a form of 'neuropathic' pain (NP) caused by compression or irritation of the roots of nerves that together comprise the sciatic nerve. CS is NP that has been present for more than three months. CS often complicates previous chronic low back pain (CLBP): however, it may present as an isolated phenomenon [4, 10].

CS is considered to be a prognostic indicator of poor outcome among patients with low back pain with a substantial proportion continuing to have persistent pain for two years or more. The annual prevalence of CS is estimated to be between 1.6% and 43% [4, 14]. While guidelines provide clear and generally consistent recommendations for the prescription of drugs for non-specific low back pain, this is not the case for CS.

CLBP can often be managed with simple analgesic regime that includes paracetamol, non-steroidal anti-inflammatory agents (NSAIDs) (e.g. ibuprofen), or opioid analgesics (e.g. codeine or tramadol). CS, however, like most NP states, is often resistant to such conventional analgesics [4, 10]. NP is typically managed by add-on therapy of anti-convulsant drugs onto simple drug regimens: the drugs most commonly used are GBP or PGB. CS, an example of a NP state, is therefore increasingly being treated with

super-added GBP or PGB [4, 10]. Both are analogues of Gamma-Aminobutyric Acid (GABA) that modulate calcium-channel subunits, possibly decreasing neurotransmitter release associated with the central sensitisation that occurs in CS.

Background evidence suggests GBP is superior to placebo for patients experiencing pain from the NP state of radiculopathy. In a phase 2 trial, GBP (900-3600mg) showed significant overall pain relief in the short term (mean diff -26.6, -38.3 to -14.9; P<0.001) [10]. In a recent systematic review for the prevention of chronic postsurgical pain, of the 8 included trials, 4 reported GBP resulted in lower incidence of pain and/ or lower analgesic requirements. It was also found by extrapolation that GBP use would improve long-term functional status in the population studied [2]. A study of neuropathic cancer pain, showed a significant decrease in the pain visual analogue score (VAS) in the group administering GBP (7.5 to 3.0)[7]. The National Institute of Clinical Excellence (NICE) Neuropathic Pain Guidelines reports that GBP, when used as monotherapy in placebo-controlled trials, results in patients experiencing a 50% reduction in pain [9].

In previous clinical trials PGB provided significant pain relief and improved quality of life in both post herpetic neuralgia and painful diabetic neuropathy. Eight studies examined varying doses of PGB on post herpetic neuropathic pain which demonstrated an average relative benefit to placebo of 2.5 (1.9 to 3.4) and at least 50% pain relief number needed to treat (NNT) of 5.3 (3.9 to 8.5) [13]. For diabetic neuropathic pain, PGB has a dose-dependent clinical efficacy and appears not to be effective at 105mg per day dose and only slightly effective at higher doses (1.6 (1.4 to 1.9) and a NNT of 6.3 (4.6 to 10.3)) [13]. A meta-analysis of randomised placebo-controlled trials confirms PGB's efficacy to significantly reduce subjective pain for neuropathic conditions [8].

The precise role of PGB or GBP in CS has been surprisingly under-explored [1]. Most patients with chronic pain and neuropathic component, however, typically also take an antidepressant (such as Amitriptyline) in their drug regime [10]. Super-adding either GBP or PGB could produce or exacerbate AEs in such cases [10]. Nevertheless, despite some AEs, most patients typically continue to tolerate GBP or PGB because of the pain relief [12]. While ceasing concurrent medication would undoubtedly

ameliorate AEs with either PGB or GBP, most patients are understandably reluctant to stop drugs that reduce pain [12].

It is important to note that in current clinical practice, either PGB or GBP would be the next treatment offered after conventional analgesics: either as an alternative to surgery (with its greater risks), or as a penultimate step before committing to surgery. It is important to note that a position of equipoise exists in clinical practice regarding which drug (i.e. PGB or GBP) to prescribe in this situation. We believe that it is important and timely to establish the best choice in a scientific manner for the benefit of all CS patients.

1.3   Aim

The aim of this thesis is to investigate the pharmacological management of CS, including the utilisation, adverse events and efficacy of two key pain medications, PGB and GBP.

1.4   Hypotheses

H_1- There is a difference between PGB and GBP, in terms of reducing pain and disability severity when used for the treatment of CS.

H_2- There is a difference between PGB and GBP in terms of frequency and severity of adverse events when used for the treatment of CS.

H_3- Personality traits influence treatment outcomes with PGB and GBP when used for the treatment of CS.

H_0- There is no difference between PGB and GBP when used for the treatment of CS.

1.5   Objectives

- To confirm that PGB and GBP are efficacious in treating CS.

- To determine whether one medication (i.e. PGB or GBP) is superior over the other in terms of treatment efficacy for CS.

- To determine whether one medication is superior over the other (PGB or GBP) in terms of frequency and severity of AEs.

- To determine whether personality traits influence treatment outcomes with PGB and GBP.

1.6   Methodology

The study consists of three parts:

Part one

A review of the literature to compile up-to-date evidence concerning the use of PGB and GBP for CS;

- Literature review

Part two

Compile evidence on the efficacy and AE profile of PGB and GBP when used to treat CS, using retrospective clinical data collection;

- Retrospective study with existing data

- Questions of AEs, medication experience and perceptions

- Develop methodology for a randomised clinical trial

Part three

Determine the efficacy of PGB and GBP when used to treat CS and whether one is superior to the other. Determine the frequency and severity of AEs when patients are treated with PGB and GBP for CS. Explore if personality traits have any effect on treatment outcomes.

- A double-blind, randomised, cross over clinical trial

- Sub analysis to examine Health Locus of Control (HLoC) in patients being treated with PGB and GBP for CS.

This study has received ethical approval from the Townsville Hospital and Health Service District Human Research Ethics Committee and the James Cook University Human Research Ethics Committee (appendices)

Further information on methodology can be found within chapters, however a synopsis is given below.

Part One: A review of the literature regarding current evidence on the use of PGB and GBP for CS.

This comprehensive background search forms the foundations of this research and provides information on effect measures and expected outcomes.

Studies included in this review were identified using electronic searching of the PubMed/Medline, CINAHL and Cochrane databases**.** Key search and MeSH terms were used. Search terms were not used individually, but in combination in order to achieve focused results. Combinations include "Pregabalin AND Sciatica", Gabapentin AND Sciatica" and "Pregabalin AND Gabapentin AND Sciatica".

The focus is on publications in English and studies carried out in humans. Further refinement includes studies limited to describing safety, efficacy and/or tolerability of PGB and/or GBP in CS. Studies analysing other NP conditions in combination with sciatica were considered. Articles exploring PGB and GBP as combination treatments with non-opioid analgesics were excluded as well as trial protocols and post-surgical populations.

A reviewer screened all relevant titles and abstracts and excluded papers not relevant to this research. Another reviewer independently evaluated the full reports for eligibility. Discussion and consensus were used to resolve differences in assessment. To identify potential articles missed by the electronic search, the bibliographies of the identified articles were analysed, and any appropriate article based on title and abstract was also retrieved.

Part Two: Compile evidence based on retrospective data collection on the efficacy and AE profile of PGB and GBP when used to treat CS.

The method for this section includes accessing retrospective data for a cohort of patients with unilateral CS attending a specialist spine clinic. Data were collected as part of routine care. Eligible patients have experienced partial benefit to a pre-existent regime containing a first line drug: none had significant AE. Addition or discontinuation of drugs during the study were limited to only GBP. VAS, Oswestry Disability Index (ODI) and AE were recorded as markers for efficacy.

Part Three: Determine the efficacy of PGB and GBP when used to treat CS. Sub analysis to examine HLoC in patients being treated with PGB and GBP for CS.

This prospective, randomised, double-blind, double-dummy cross-over study recruited patients over 18 years, with unilateral CS and radiological confirmation of corresponding neural compression/irritation. Pregnant women, those with major organ disease, creatinine clearance <60ml/min or another neuropathy were excluded. Patients continued their pain medication used at study onset and the prior 30 days. No drug changes or other pain interventions were permitted throughout the period of study. Each drug was titrated to a target dose (GBP: 400-800mg tds, PGB: 150-300mg bd) and taken for 8 weeks. The first drug was then ceased. Cross-over was deferred for a 1-week washout period. Drug efficacy was assessed by the VAS, ODI Index and HLoC. AEs and psychological functioning were also assessed. Assuming the hypothesis that one drug was superior (or both drugs were different), the sample size required is n=38 with 80% power and 5% type 1 error rate. Results were analysed via intention-to-treat methodology.

The HLoC sub-study was carried out as part of a randomised controlled trial. The adapted HLoC questionnaire was used to assess the participant's sense of self control over his/her own health. The score for each subsection (internal, chance, external) relates to the patient's belief in the importance of being able to influence their own treatment decisions. Pain intensity was measured by VAS and disability level by ODI and used as markers for efficacy of medications.

1.7　　Study Management

The supervisory team met regularly (every 2-4 weeks) to review the progress, outcomes, and conduct of the research project. A progress report was sent to any of the supervisors unable to attend the meeting in person. Regular informal communication was also conducted to ensure consistency and robustness of the project.

1.8　　Expected Outcomes

- PGB and GBP will reduce pain severity (VAS) when used to treat CS.

- PGB and GBP will reduce disability severity (ODI) when used to treat CS.

- Personality traits and quality of life (HLoC) influence treatment outcomes with PGB and GBP in CS patients.

- When compared head to head, a difference exists between PGB and GBP in reducing pain severity and disability severity.

- When compared head to head, a difference exists between PGB and GBP in the frequency and severity of AEs.

1.9　　Thesis structure and outline

This research investigates two common pharmacological treatments for CS, namely PGB and GBP. The work is presented as a series of published papers in international and national journals. The thesis consists of seven chapters each with a different focus. The seven chapters are as follows:
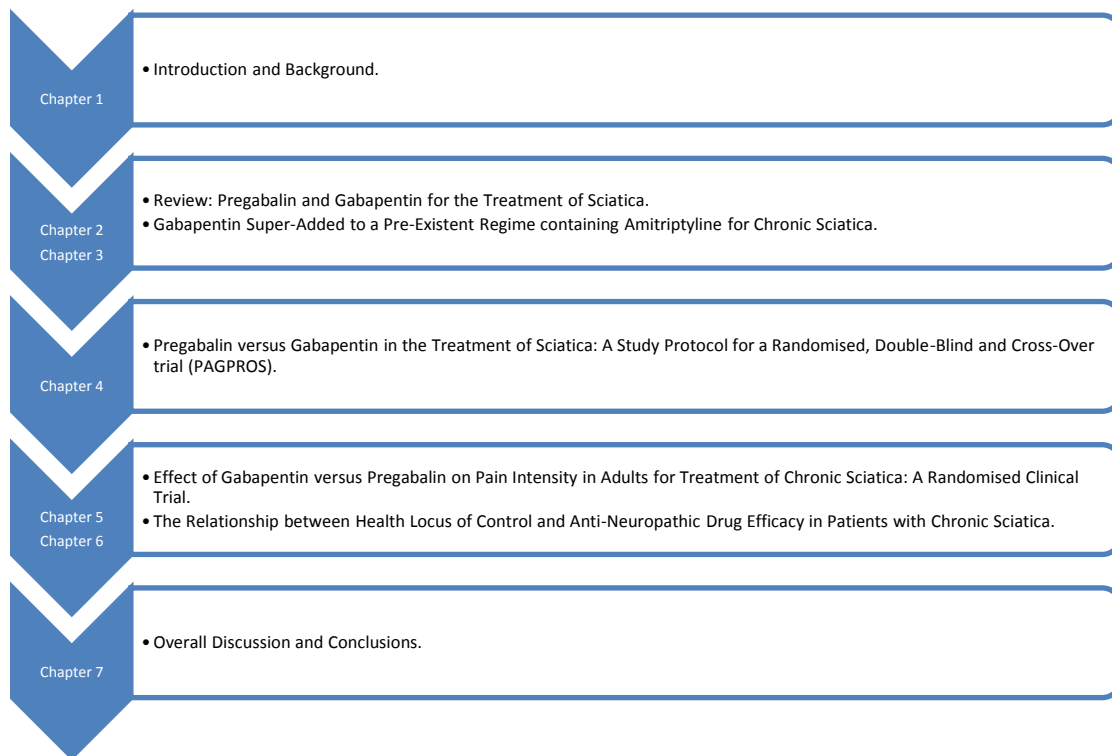
Figure 1.1 Thesis structure

Chapter 1 provides the context of the research. Justification for the research is outlined by defining NP and CS, describing the burden it places on society and outlining current treatments options and their AE profile. The significance of the research is described in terms of unmet needs. A rationale is given for the study design, which is based on the ability to detect superiority of either PGB or GBP. The clinical trial design is in line with internationally recognised principles for the conduct of clinical trials and was conducted in accordance with Good Clinical Practice (GCP) principles.

Chapter 2 investigates the literature. This review highlights a key conclusion that PGB and GBP for CS have been under-explored. Work in this chapter has been published in the *Journal of Clinical Neuroscience*, 2016, volume 26 pages 1-7. DOI 10.1016/j.jocn.2015.05.061

Chapter 3 investigates GBP treatment in a CS population attending a specialist spine clinic. This study highlights AEs and efficacy of GBP and provides useful information for the design and methodology for the clinical trial. This study has been published in the journal *Pain Medicine*, 2016, April, pages 1-5. DOI 10.1093/pm/pnw052

Chapter 4 investigates study design and methods, and address issues of recruitment and ethics, following CONSORT guidelines for the reporting of clinical trials. This study has been published in the journal *BMC Trials*, January 2019, 19:21 https://doi.org/10.1186/s13063-017-2400-y.

Chapter 5 investigates the head-to-head comparison of PGB and GBP in a randomised controlled trial. This study has been published in *JAMA Neurology*, published online October 15, 2018. http://Doi:10.1001/jamaneurol.2018.3077.

Chapter 6 investigates the relationship between treatment outcomes and personality. In this chapter, a HLoC survey is analysed to explore a relationship to medication effectiveness. This study has been submitted to the *Pain Medicine* journal.

Chapter 7 provides an overall discussion, draws conclusions and provides recommendations based on the findings of this research.

The style of the thesis is structured according to the James Cook University (JCU) reference style (American Psychological Association, APA 6) preferred by the College of Medicine and Dentistry. The JCU allows published journal papers to be included in the thesis. The inclusion of publications in this thesis means that different publications may contain the same or similar descriptions of concepts, test procedures and findings. Different referencing styles were employed as required by the journals in which the papers were published. Similarly, the spelling of some words might not be consistent throughout the thesis.

1.10   Summary

This thesis will explore the gap in knowledge that is needed for more effective and improved treatment options for CS and provide an overview of the most current treatment option between PGB or GBP. A randomised, double-blind and cross-over clinical trial was used to test the efficacy of both PGB and GBP in CS, with the results reported within chapter 5 of this dissertation.

Chapter 2   Review: Pregabalin and Gabapentin for the Treatment of Sciatica

'The scientific method actually correctly uses the most direct evidence as the most reliable, because that's the way you are least likely to get led astray into dead ends and to misunderstand your data'

Aubrey de Grey (1963–)

2.1   Background

Pain experienced by patients is a very broad term and to research in its entirety is beyond the scope of this work. Different mechanisms including social, mechanical and behavioural contribute to a dimension of experienced pain. However, if the experienced pain is caused by a specific condition such as chronic sciatica (CS), we can be more precise and robust in researching medications to alleviate this pain.

While undertaking a preliminary project on pain generally, a common theme started to emerge. The drugs pregabalin (PGB) and gabapentin (GBP) were captured in most of our data with a varied and unequal prescription to patients. On further exploration, both medications were being utilised for the same indication of CS. A brief snapshot of the non-parametric use of these two drugs for sciatica prompted further research. However, before this could proceed a review of the literature was needed.

Chapter 2 of this thesis, entitled "Review: Pregabalin and Gabapentin for the Treatment of Sciatica" is based on the manuscript published in the *Journal of Clinical Neuroscience.* The paper is inserted into this thesis with minor modifications. Only the formatting of section sub-headings and numbering of tables and figures have been modified from the original publication to match the thesis format. The referencing of the paper is retained in the original journal style.

Robertson K, Marshman L, Plummer D. (2016). Review: Pregabalin and Gabapentin for the Treatment of Sciatica. *Journal of Clinical Neuroscience.* 26: 1-7. DOI: 10.1016/j.jocn.2015.05.061

2.2 Abstract

Whilst PGB and GBP are both used to treat NP, their relative role in CS is unclear. Our aim was to extensively review the relative role of PGB and GBP in treating sciatica and specifically CS. The efficacy, adverse event (AE) profile and cost of PGB and GBP in NP states were reviewed with special reference to CS. N=11 articles matched the criteria: n=7 systematic reviews, n=1 retrospective cross-sectional study, n=1 placebo-controlled-crossover study, n=1 randomized placebo-controlled double-blind study and n=1 case report. GBP and PGB appeared to demonstrate comparable efficacy and AE. However, the amount and quality of evidence was low, and only indirect comparisons were available. Importantly, no direct 'head-to-head' study existed. Globally, costs varied widely (by up to x31) and unpredictably (PGB cheaper than GBP, or vice versa). Formulary regulator rulings were globally disparate: however, many exclusively favoured the more expensive drug (whether GBP or PGB). No studies assessed PGB-GBP interchange. Weak evidence suggests that efficacy and AE with GBP and PGB are probably similar: however, firm conclusions are precluded. Despite weak data, and having cited minor titration but definite cost advantages, NICE-UK favoured PGB over GBP. However, globally, costs vary widely and unpredictably: paradoxically, many Formulary regulators exclusively favour the more expensive drug (whether GBP or PGB). Given that no evidence supports unhindered PGB-GBP interchange, neither drug should probably be favoured. Prospective 'head-to-head' studies are urgently required to provide robust evidence-base for relative GBP/PGB use in CS.

2.3 Introduction

Anecdotally, both GBP and PGB have been widely used to treat NP states, including CS. However, the efficacy and AEs of GBP and PGB for the treatment of patients with CS have not been firmly established. Only two limited specific reviews exist. The first emanates from the UK National Institute for Health and Clinical Excellence (NICE-UK) [1]. The second is a recent systematic review, and meta-analysis, for the pharmacological treatment of sciatica by Pinto et al. [2]. Both could only make indirect comparisons between GBP and PGB, whilst the review of Pinto et al. was based on one study for each drug, both trials failed to satisfy accepted criteria for being a high-

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quality design [2, 3]. No review appears to have sufficiently examined the AEs and quality-of-life differences between the different preparations.

Sciatica or sciatic neuralgia, a common form of lumbosacral radiculopathy, is characterised by low back pain which radiates to the leg and which may be accompanied by sensory loss, motor weakness and/or reflex abnormalities. Sciatica is a symptom defined as well-localised leg pain, with a sharp, shooting or burning quality that approximates to the dermatomal distribution of the sciatic nerve down the posterior lateral aspect of the leg [2]. It is often associated with numbness or paraesthesia in the same distribution but typically extends beyond the limits of perceived pain in either a dermatomal or sclerotomal anatomical fashion [4, 5]. The term "sciatica" is used by clinicians in different ways; some refer to any leg pain referred from the back as sciatica; others prefer to restrict the term to pain originating from the lumbar nerve root. Others believe sciatica is a form of 'neuropathic' pain caused by compression or irritation of the roots or nerves that comprise the sciatic nerve [2,6]. CS is sciatica lasting at least 3 months. These definitional inconsistencies potentially confound analysis within and between studies.

A substantial proportion of patients with CS have persistent pain for two years or longer [2], which contributes to increased absence from employment and increased applications for work cover compensation. The annual prevalence of CS is estimated to be between 1.6% and 43% [6]. While guidelines provide clear and generally consistent recommendations for prescribing analgesics to treat non-specific low back pain, often the same guidelines are applied for the dissimilar diagnosis of CS, and more recently, non-evidenced based use of either PGB or GBP.

Chronic low back pain per se can often be managed with simple analgesic regimen that include paracetamol, non-steroidal anti-inflammatory agents (e.g. ibuprofen), or opioid analgesics (e.g. codeine or tramadol). CS, however, like most NP states, is often resistant to simple analgesic regimens [2, 6]. NP is typically managed by super-adding anti-convulsant drugs onto basic analgesic regimes: the drugs most commonly used are GBP or PGB. CS is therefore increasingly being treated with super-added GBP or PGB [2, 6]. Both are analgesics derived from Gamma-Aminobutyric Acid (GABA) that modulate the calcium-channel subunits, possibly decreasing neurotransmitter release that occurs in CS [2, 6].

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It is important to note that at some stage in the patient's management of CS, either PGB or GBP may constitute the next-line treatment offered: either as an alternative to surgery (with its greater risks), or as a penultimate step before committing towards surgery (with its greater risks). That is, patients may be offered either drug at a stage in their management where response to standard first-line analgesics has proven insufficient. However, the precise role of PGB or GBP in CS has been surprisingly under-explored [2, 7]. In consequence, individual prescribers have defaulted to a position of equipoise pending the outcome of direct, high quality research to rationalize the use of PGB or GBP in the treatment of CS [7].

The aim was to review the utility (i.e. efficacy, AE profile and cost) of PGB and GBP in NP states with special reference to CS.

2.4   Methods

Studies to be included in the review were identified using electronic searching of the PubMed/Medline, CINAHL and Cochrane databases from the earliest records to 14th March 2015. Key search and MeSH terms used included "Pregabalin", "Gabapentin", "Sciatica". Terms were selected based on the keywords and the title in the review which included the synonym's radiculopathy, nerve root compromise or compression, nerve root pain or entrapment, lumbosacral radicular syndrome, or pain defined as radiating below the knee. Terms were not used individually, but in combination in order to achieve focused results. Combinations included "Pregabalin AND Sciatica", Gabapentin AND Sciatica" and "Pregabalin AND Gabapentin AND sciatica".

The identified citations were refined to publications in English and studies carried out in human. Further refinement included studies limited to describing safety, efficacy and/or tolerability of PGB and/or GBP in CS. Studies that analysed other NP conditions in combination with sciatica were also included. Articles exploring GBP and PGB as combination treatments were excluded as well as trial protocols and post-surgical populations.

One reviewer screened all relevant titles and abstracts and excluded irrelevant papers. Two reviewers independently evaluated the full reports for eligibility. Discussion and consensus was used to resolve differences in assessment. To identify potential articles

missed by the electronic search, the bibliographies of the identified articles were analysed and any appropriate article based on title and abstract were also retrieved.

Decisions to include papers in this review did not depend on their quality. The goal was to present all published studies that met our inclusion criteria regardless of the design type and quality.

Formal meta-analytic methods were precluded because of the broad scope of adverse events and painful symptoms, the variety of measures used to assess AEs, and the different study definitions of pain. This review is a quantitative and semi qualitative synthesis of the relevant, representative, and evidence-based literature.

2.5   Results

Thirteen studies were identified in the initial search with 2 studies being excluded due to irrelevance [8, 9]. Eleven studies were included in the literature review that examined the safety, efficacy and/or tolerability of PGB and GBP for patients with sciatica. All eleven studies were included in this review. The studies included in the review were seven systematic reviews, one retrospective cross-sectional study, one placebo controlled crossover study, and one randomized placebo-controlled double-blind study and one case report. (Table 2.1)

Table 2.1 Studies included in the literature review

STUDY	DESIGN	OBJECTIVES	FINDINGS
Sumracki N et al (2012) [15]	Randomised, double-blind, placebo-controlled, three-way crossover study in unilateral sciatica	Tolerability and efficacy of Minocycline and Pregabalin	Although not significant once adjusting the P-value, the 28% (95% CI 0% to 56%) reduction of hyperalgesia in the affected leg prior to intradermal capsaicin by single oral dose minocycline is a novel finding that glial attenuation may be anti-hyperalgesia in humans.
Moore RA et al (2011) [8]	Systematic review of randomized double-blind studies in chronic neuropathic pain and fibromyalgia	Tolerability and efficacy of Gabapentin compared to placebo	Gabapentin was superior to placebo in 14 studies with 43% improving with Gabapentin and 26% with placebo; the NNT was 5.8 (4.8 to 7.2).
Wiffin PJ et al (2010) [9]	Systematic review of randomized trials for acute and chronic pain	Tolerability and efficacy of Gabapentin compared to placebo	The study in acute post-operative pain showed no benefit for Gabapentin compared to placebo for pain at rest. In chronic pain, the NNT for improvement in all trials with evaluable data is 4.3 (95% CI 3.5 to 5.7). Forty two percent of participants improved on Gabapentin compared to 19% on placebo.
Finnerup NB et al (2010) [10]	Systematic review of randomized, double-blind placebo controlled trials for neuropathic pain	Pharmacological management in neuropathic pain.	Tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors, the anticonvulsants Gabapentin and Pregabalin, and opioids are the drug classes for which there is the best evidence for a clinical relevant effect.

Straube S et al (2012) [13]	Systematic review of double blind trials compared with placebo for established acute postoperative pain in adults	Efficacy and tolerability of Single dose oral Gabapentin and placebo	At least 50% pain relief over 6 hours was achieved by 15% with Gabapentin and 5% with placebo. Significantly fewer participants needed rescue medication within 6 hours with Gabapentin than with placebo. About one third of participants reported adverse events with both Gabapentin and placebo. No serious adverse events occurred with Gabapentin.
Wiffen PJ et al (2005) [11]	Systematic review of randomized controlled trials for acute and chronic pain	Anticonvulsant drug's efficacy and tolerability	The only placebo-controlled study in acute pain found no analgesic effect of Sodium Valproate. Three placebo-controlled studies of Carbamazepine in trigeminal neuralgia had a combined NNT (95% confidence interval (CI)) for effectiveness of 2.5 (CI 2.0 to 3.4). A single placebo-controlled trial of Gabapentin in post-herpetic neuralgia had an NNT of 3.2 (CI 2.4 to 5.0).
Grice GR et al (2008) [18]	A Case report on sciatica	A report of Gabapentin usage for 2 patients.	The first was a patient was treated with many alternative drugs and, he was then prescribed Gabapentin his pain substantially improved, even after the first dose. The second patient was a 68-year-old treated with Gabapentin 100 mg at bedtime. Pain improved rapidly.
Gore M et al (2007) [12]	Retrospective cross-sectional study about painful peripheral neuropathic disorders	Usage patterns of common drugs for painful neuropathic disorders (PND's)	Use of medications with clinically demonstrated efficacy in PNDs was high. Average daily doses of select neuropathic pain-related medications among PND patients were lower than those recommended for neuropathic pain. The use and doses of evidenced-based neuropathic pain-related medications was low, and lower than the use of NSAIDs (a

			medication class with no proven efficacy for PNDs) in each group, suggesting possible sub-optimal neuropathic pain management among these patients.
Pinto et al (2012) [2]	Systematic review and meta-analysis of drugs for treatment of sciatica	Efficacy and tolerability of drug treatments for sciatica.	NSAIDs showed low evidence of efficacy (P<0.06). No NSAIDS displayed better effects than the other. Corticosteroids showed significant effects on pain (P<0.01).
			Gabapentin showed great efficacy compared to placebo (P<0.01), Topiramate showed no better effects than placebo. Combo of antidepressant + opioid had no significant effect compared with placebo.
			For all included studies, the median adverse events were 17% for active drugs and 11% placebo.
Burke SM et al (2010) [14]	Randomized double-blind placebo controlled study of Lumbar Discectomy	Tolerability and efficacy of Pregabalin compared to placebo	The decrease in VAS score at 3 months was greater in patients who received Pregabalin than those who received placebo. The Roland Morris disability score at 3 months was less in patients who received Pregabalin. Pregabalin administration was associated with greater pain tolerance thresholds in both lower limbs compared with placebo at 24 hours postoperatively.
Moore RA et al (2009) [16]	Systematic review of randomised double-blind trials in acute and chronic pain	Efficacy and tolerability of Pregabalin	There was no clear evidence of beneficial effects of Pregabalin in established acute postoperative pain. No studies evaluated Pregabalin in chronic nociceptive pain, like arthritis.

2.5.1 Efficacy: Gabapentin

2.5.1.1 Sciatica

The use of GBP to reduce pain has been extensively covered in systematic reviews. In a review and meta-analysis involving 23 studies for the drug treatment of sciatica, GBP showed greater efficacy in pain reduction compared to placebo in participants with sciatica (mean diff -26.6 (-38.3 to-14.9) [2].

2.5.1.2 Other Conditions

Additionally, a systematic review of 29 studies involving 3571 patients was performed in 2011 to analyse the effects of GBP in chronic NP and fibromyalgia. GBP was superior to placebo in 14 studies with 43% of patients improving with GBP and 26% with placebo; the number needed to harm (NNH) was 5.8 (4.8 to 7.2). Furthermore, using the IMPACT definition of substantial benefit, GBP was superior to placebo in 13 studies with 31% of patients improving with GBP compared to 17% with placebo [10].

In another systematic review of GBP use in acute and chronic pain, the study showed no benefit for GBP compared to placebo for pain at rest [11]. In chronic pain, the NNT for improvement in all trials with evaluable data is 4.3 (95% CI 3.5 to 5.7) with 42% of participants improving on GBP compared to 19% on placebo [11]. A larger systematic review examining 174 trials in NP showed that GBP had an overall number needed to harm (NNH) of 32.5 (18-222) when used as a treatment for a variety of NP disorders [12].

An earlier review for acute and chronic pain reported a single-placebo controlled trial of GBP in post-herpetic neuralgia had an NNT of 3.2 (CI 2.4 to 5.0). In the same review, for diabetic neuropathy NNT for effectiveness was 3.8 (CI 2.4 to 8.7) for the population treated with GBP [13].

In light of this evidence for GBP's utility, a cross-sectional study into painful neuropathic disorders found that average daily doses for GBP were commonly suboptimal for pain management among these patients [14].

However, for most of these systematic reviews, even when restricting inclusion to randomised, double-blind studies, the review incorporated a majority of trials with either an unclear or high risk of bias due to design flaws, differing measured outcomes, dosage variation and inconsistent conditions being treated.

2.5.1.3 Single Dose Gabapentin

Single-dose GBP was explored in a review consisting of 4 unpublished studies for acute postoperative pain in adults [15]. At least 50% pain relief over 6 hours was achieved by 15% of patients with GBP 250 mg and 5% with placebo; giving a Risk: Benefit of 2.5 (95% CI 1.2 to 5.0) and an NNH of 11 (6.4 to 35). Also noteworthy was that significantly fewer participants needed rescue medication within 6 hours with GBP 250 mg than with placebo [15].

The conclusions were that GBP appears to provide high level pain relief in about a third of people who take if for NP. Conversely, over half of those treated with GBP do not report worthwhile pain relief. Overall, evidence for using this drug in some conditions is low, which leaves the question as to why GBP works under some circumstances but not others. This finding precludes us confidently concluding that it actually works or not when treating patients with sciatica [2, 10].

2.5.2 Efficacy: Pregabalin

The reduction of neuropathic and sciatica pain has been less explored for PGB compared to GBP.

2.5.2.1 Sciatica

The use of PGB to reduce pain and time to loss of response (LOR) was reviewed in a meta-analysis involving 23 studies for the drug treatment of sciatica. Most patients with chronic lumbosacral radiculopathy responded to PGB therapy; however, time to LOR did not significantly differ between PGB and placebo [2].

A randomised, double-blind placebo controlled trial examined the effect of PGB on pain following lumbar discectomy in 40 participants. The decrease in pain score was greater at 3 months for the patients treated with PGB compared to placebo (p=0.08).

PGB was associated with greater pain tolerance thresholds in both lower limbs compared with placebo at 24 hours postoperatively [16].

In a randomised, double-blind, placebo-controlled, three-way cross-over study of 18 patients with unilateral sciatica, PGB did not reduce capsaicin-induced spontaneous pain. Importantly however, the design of the study was primarily focused on the activity of an alternative drug, Minocycline, in unilateral sciatica [17].

2.5.2.2 Other Conditions

A systematic review involving 174 studies of various NP conditions suggested that PGB is a member of a class of drugs in which there is best evidence for clinical effect. When the data was pooled, PGB displayed a number needed to harm (NNH) of 10.6 (8.7-14) which was approximately 3 times less than its comparator agent GBP. This tends to indicate that PGP has a higher adverse event rate [12].

A large systematic review which studied more than 70,000 participants concluded that there was no clear evidence of beneficial effects of PGB for acute pain. No studies included in the review explored chronic pain. The best (lowest) NNT for each condition for at least 50% pain relief over baseline (substantial benefit) for PGB compared with placebo was 3.9 (95% confidence interval 3.1 to 5.1) for post herpetic neuralgia, 5.0 (4.0 to 6.6) for painful diabetic neuropathy, 5.6 (3.5 to 14) for central NP, and 11 (7.1 to 21) for fibromyalgia [18].

Overall, the reviewed studies failed to satisfy accepted criteria for being a high-quality trial [3] and led to a generalised conclusion that individualisation of treatment with PGB is needed to maximise pain relief and minimise adverse effects. Patients with niche indications or where there is a contraindication to GBP AEs are often being prescribed PGB.

2.5.3 Adverse Events – Gabapentin

AEs in populations administering GBP or PGB were frequent, but mostly tolerable.

2.5.3.1   Sciatica

A large review and meta-analysis reported 2 from 25 patients treated with GBP experienced an AE including dizziness, somnolence, chest pain, fainting, dry mouth, constipation, weight increase, headache and peripheral oedema. However, the numbers of AEs were fewer compared to PGB. In this study, patients allocated to the placebo control arm reported no AEs [2].

2.5.3.2   Other Conditions

A study GBP for treating chronic NP and fibromyalgia, reported that 12% of patients withdrew from the study because of AEs when the dose was 1200mg or more. This compares with 8% for placebo giving a risk ratio of 1.4 (1.1 to 1.7). Somnolence, drowsiness, sedation, peripheral oedema and ataxia were the most common complaints from participants receiving GBP. All-cause withdrawals occurred in 20% of participants being treated with GBP compared to 19% receiving placebo (risk ratio 1.1, 0.9 – 1.2), and patients experiencing at least one AE was experienced by 66% of GBP patients and 51% on placebo (risk ratio 1.3, 1.2-1.4)10. Of these mentioned AEs, 4% on GBP and 3.2% on placebo were considered to be serious [10].

Another review examined the utility of GBP in acute and chronic pain, with the authors reporting the NNH for each episode of major harm from GBP usage. Major harm was considered to be any effects that lead to participants withdrawing from the study. The resultant NNH for major harm was not statistically significant, however for minor harm, the authors report a NNH of 3.7 (2.4 to 5.4). The most common AEs were dizziness (24%), somnolence (20%), headache (10%), diarrhoea (10%), confusion (7%) and nausea (8%) [11].

2.5.3.3   Single dose Gabapentin

Single dose GBP was compared to placebo for established acute postoperative pain in adults. A low-quality review which included four unpublished studies showed 28% of patients taking GBP experienced at least one AE compared to 32% for placebo. The relative risk for treatment with GBP was 0.91 (95%CI 0.66-1.3). No serious AEs were reported with GBP use; however, there was a report of "heart arrest" occurring one day after study completion. Withdrawals from the study were limited, with only 3/370 participants receiving GBP leaving the study due to fever [15].

2.5.4 Adverse Events – Pregabalin

2.5.4.1 Sciatica

The AEs of PGB were reported in a randomised double-blind placebo controlled study when used to treat pain following lumbar discectomy. Visual disturbances occurred in 2/18 patients in the PGB group, however these were self-limiting and resolved within 4 hours in all cases. Somnolence and dizziness were also reported in patients receiving PGB [16].

In a small randomised double-blind cross-over study where PGB was used as a control, 14 of the 18 participants (78%) experienced AEs following PGB treatment. These events included dizziness, nausea and tiredness. However, these events were reported retrospectively at the end of the study [17].

A large systematic review and meta-analysis which included studies using treatments for sciatica reported that 31 from 110 patients allocated PGB experienced at least one AE including dizziness, somnolence, chest pain, fainting, dry mouth, constipation, weight increase, headache and peripheral oedema. A greater number of AEs were reported with the usage of PGB [2]. Additionally, the systematic review found that patients allocated to the placebo control arm, did not report a single AE [2].

2.5.4.2 Other Conditions

Conclusions about the frequency of AEs associated with PGB could not be reported in a study for acute and chronic pain, because these events were not recorded in all studies. Consequently, the authors had to perform dose-dependent adverse event analysis with the results showing there is no link between a higher dose and greater adverse outcome. The only reported AEs were somnolence and dizziness [18].

The rate and type of reported AEs varied substantially between drugs and between trials of the same medication.

2.5.5 Costing and National Formulary Listing – Pregabalin and Gabapentin

The cost of each drug varied widely between countries (Table 2.2): e.g., costs for GBP varied by a factor of 31 between the UK and USA (from $8.43 to $263.32). The cost of each drug also varied unpredictably between countries (Table 2.2): e.g. in Australia, PGB ($51.71 for 56 150mg capsules) was more expensive than GBP ($29.13 for 100 400mg capsules), whilst in New Zealand GBP was more expensive than PGB. Moreover, costs for both drugs were markedly more expensive (by a factor of 6 for GBP) in New Zealand compared to Australia ($173.56 for GBP and $115.51 for PGB).

Paradoxically, most nations (4/7) for which data could be easily obtained solely favoured the more expensive drug (whether GBP or PGB) (Table 2.2). For example, New Zealand and Singapore listed only GBP, whilst Australia and Europe listed only PGB: in all cases, the more expensive drug (Table 2.2). By contrast, USA, UK and Canada listed both drugs. However, the criteria required to obtain GBP in USA and Canada were more stringent than with PGB: thus, PGB was still favoured in these countries. Interestingly, in the USA, where both drugs were listed, PGB and GBP were both comparable in cost (PGB: $221.86 for 56 150mg capsules compared to GBP: $263.32 for 100 400mg capsules): a similar situation prevailed in Canada. However, whilst cost comparability between PGB and GBP also prevailed in Europe, only PGB was listed in Europe (22). Finally, whilst both PGB and GBP were listed in some UK hospitals, PGB was markedly more expensive (by a factor of 13) than GBP.

2.6   Discussion

Only 2 limited specific reviews which account for the role of PGB or GBP in CS exist. The first emanates from NICE-UK which recommended a variety of treatment modalities for the relief of pain associated with neuropathic conditions [1]. NICE-UK guidelines state that there is evidence for the efficacy of PGB and GBP for treating NP disorders, including CS: however, "adverse effects should be discussed with each patient, and weighed against potential benefits". Whilst both PGB and GBP were considered efficacious, NICE-UK nevertheless favoured PGB over GBP for 3

main reasons: 1) lower number needed to treat (NNT) values from meta-analysis comparisons, 2) simpler dosing and titration regime with PGB and 3) cost-effectiveness over GBP.

However, when considering NICE-UK guidelines, it is important firstly to note that they were derived only from indirect comparisons of weak power. Furthermore, NNT values were quoted which are open to bias, and for which confidence intervals cannot be reliably determined. Regarding dosing, the regime for PGB – whilst simpler (i.e. twice daily dosing) – is not majorly different from GBP (thrice daily). Furthermore, whilst GBP should be titrated with delayed dosage increments (e.g. 4 days), many now also consider that, in order to offset AEs, PGB should similarly be introduced in "low and slow" incremental fashion. On this view, the advantages of PGB titration seem exaggerated. Finally, it is important to note that costs for either PGB or GBP vary widely and unpredictably globally (Table 2.2). Thus, while NICE-UK considered PGB more cost effective, the converse is true in other countries: e.g. GBP is substantially cheaper in Australia than PGB. Despite the latter, and somewhat surprisingly, only PGB is subsidised on the Australian PBS: this presumably reflecting the influence of NICE-UK guidelines.

The second, and most recent, systematic review, and meta-analysis concerning drug treatment per se for CS is that of Pinto et al. [1]. However, only one study each for GBP and PGB was included. The appraisal and conclusions of the study highlighted the low quality of extant trials, and the fact that the best primary management for CS remained unclear: especially regarding GBP and PGB. The review of Pinto et al. showed significant efficacy for GBP without any comment on PGB. Our review, by contrast, examines 11 studies in which PGB or GBP were used to treat NP including CS.

Inconclusive evidence for either PGB or GBP in the treatment of CS and NP conditions is reflected worldwide by significant disparity in the rulings of individual Formulary regulators. For example, GBP is currently available on the PBS in Australia and some hospitals in the UK only for epilepsy: it is not listed for NP. PGB, by contrast, is subsidised on the Australian PBS for NP. The Food and Drug Administration (FDA) in the USA, along with Health Canada, have adopted similar reimbursement criteria to that of the Australian PBS: notwithstanding, both GBP and

PGB can be accessed in the USA and Canada via special access schemes (if patients satisfy stringent criteria for NP). In marked contrast, GBP is listed for use in both partial seizures and NP throughout Europe. The rulings of Formulary regulators have therefore been inconsistent, and dependent upon the individual body.

Our review has confirmed the absence of any adequately powered direct 'head-to-head' trial comparing GBP and PGB. Formulary regulators have therefore globally used indirect comparisons to inform listing decisions. Such indirect comparisons possess numerous limitations: including differing patient demographics, primary outcomes and pain measurement scales. Based on NICE-UK guidelines, weak evidence suggests that efficacy and AE profiles of PGB and GBP in CS are probably similar: however, firm conclusions are necessarily precluded. NICE-UK noted, as one factor in favouring PGB over GBP, that PGB had distinct pharmacokinetic advantages: including higher bioavailability, more rapid absorption and increased binding affinity. However, such factors are secondary, and had only gained eminence owing to a lack of firm evidence for primary factors (i.e. efficacy and AE profiles).

The lack of firm evidence for the use of either PGB or GBP in CS has, in consequence, permitted global inconsistency in the rulings of individual Formulary regulators regarding drug preference. Given that NICE-UK guidelines were ultimately largely influenced by cost considerations, one might have expected that similar considerations would also account for the wide disparity found in Formulary regulator rulings. However, paradoxically, most countries for which data could be easily obtained have solely favoured the more expensive drug (whether GBP or PGB) (Table 2.2). Some Nations (UK, USA and Canada) appear to have accepted a degree of equipoise, in agreement with current evidence, and have listed both drugs. Particularly in the UK, free interchange between PGB and GBP is therefore also possible. However, whilst USA and Canada listed both drugs, the criteria required to obtain GBP are more stringent than with PGB: thus, PGB is still favoured in these countries. In marked contrast, free interchange between PGB and GBP has become thwarted in Australia, New Zealand, Europe and Singapore. Whilst NICE-UK noted cost effectiveness to secondarily justify a bias toward PGB, cost

cannot explain the Formulary regulator rulings in these countries where solely the more expensive drug was listed.

In Australia, the recent addition of PGB to the PBS for neuropathic pain (2013) has created a conflict in that some long-standing users of GBP, who were previously controlled on GBP, were subsequently forced to either incur greater costs, or to switch to PGB (with, potentially less utility). The Australian Pharmaceutical Benefits Advisory Committee rejected applications to subsidise GBP for the treatment of neuropathic pain on the grounds of lack of evidence in the proposed population (i.e. clinical trial data did not reflect the population covered by the proposed PBS restriction) and uncertain cost-effectiveness in this patient group. However, prescribing authorities in Europe appear to have taken a different view (Table 2.2).

Table 2.2 National Formulary Regulator rulings and costs across nations.

Country	Gabapentin	Pregabalin
Australia [22]	NL ($29.13)	L ($51.71)
New Zealand [23,24]	L ($173.56)	NL ($115.51)
Canada [25,26]	L ($110.32)	L ($140.01)
Europe [19,27]	NL ($147.32)	L ($182.76)
USA [28,29]	L ($263.32)	L ($221.86)
Singapore [30,31]	L ($174.06)	NL (not available)
UK [32,33]	L ($8.43)	L ($113.31)

Abbreviations: L listed, NL not listed for NP

Currency: $US

*Price is reflective of Pregabalin 150mg capsules quantity 56 and Gabapentin 400mg capsules quantity 100.

NB: Listing generally equates with favoured, that is, more difficult to obtain the "not listed" drug. In some countries e.g. (Australia), this means that the listed drug is subsidised and that not listed drugs will incur greater cost to the patient.

The SPORT study [20] showed that many patients with CS will spontaneously improve in the medium term with non-operative management: every attempt should be made to avoid a potentially unnecessary operation. Given that some patients may benefit from either PGB or GBP (but not both), free interchange between PGB and GBP should be facilitated and not obstructed (as it is in many countries). However, given that no evidence supports unhindered PGB-GBP substitution; free interchange should not be forced as has occurred in countries like Australia, where many patients have been forced to interchange GBP with PGB. Based on current evidence, neither drug should probably be favoured.

2.7   Conclusion

Weak evidence suggests that efficacy and AE with GBP and PGB are probably similar: however, firm conclusions are precluded. Despite weak data, and having cited minor titration but definite cost advantages, NICE-UK favoured PGB over GBP. However, globally, costs vary widely and unpredictably: paradoxically, many Formulary regulators exclusively favour the more expensive drug (whether GBP or PGB). Given that no evidence supports unhindered PGB-GBP interchange, neither drug should probably be favoured. Prospective 'head-to-head' studies are urgently required to provide robust evidence-base for relative GBP/PGB use in CS.

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Chapter 3 Gabapentin Superadded to a Pre-Existent Regime Containing Amitriptyline for Chronic Sciatica

'I have found that most people are willing to accept physical pain and limitation rather than acknowledge and deal with the mental and/or emotional pain that might have caused it."

Tobe Hanson

3.1 Background

Only 2 previous studies have assessed Gabapentin (GBP) use in chronic sciatica (CS): both by the same author, and one from a journal which has since become defunct. In all previous studies, participants were required to cease all prior pain medication, and were denied any background therapies (some of which had probably proven beneficial). Furthermore, the study designs for these studies did not permit the full assessment of adverse events (AEs): hence AEs were either not reported, or were very brief.

Chapter 3 of this thesis, entitled "Gabapentin Super-added to a Pre-Existent Regime Containing Amitriptyline for Chronic Sciatica" is based on the manuscript published in the Journal *Pain Medicine*. The paper is inserted into this thesis with minor modifications. Only the formatting of section sub-headings and numbering of tables and figures have been modified from the original publication to match the thesis format. The referencing format of the paper is retained in the original journal style.

> **Robertson K**, Marshman L. (2016). Gabapentin Super-Added to a Pre-Existent Regime Containing Amitriptyline for Chronic Sciatica. *Pain Medicine.* April:0: pages 1-5. DOI: 10.1093/pm/pnw052

3.2   Abstract

Setting: There is currently a gross lack of evidence base guiding the medical management of CS. Only scant previous studies have assessed GBP in CS. Extrapolating NICE-UK guidelines, prescribing authorities often insist on trialling anti-depressants (e.g. Amitriptyline, AMP) as first-line for neuropathic pain states, like CS. When super-adding second-line agents, such as GBP, NICE-UK encourages overlap with first-line agents to avoid decreased pain-control. No study has reflected this practice.

Objective: Evaluate efficacy and AE of GBP super-added to a pre-existent regime containing AMP for CS.

Subjects and Methods: Prospective cohort of patients with unilateral CS attending a specialist spine clinic. Eligible patients had experienced partial benefit to a pre-existent regime containing AMP: none had significant AE. No drugs other than GBP were added or discontinued (the latter was considered inequitable) for 3 months. Visual Analogue Pain Score (VAS), Oswestry Disability Index (ODI) and AE were recorded.

Results: *Efficacy*: in 56% (43/77) there were reductions in VAS (5.3±3.6→2.8±2.7, P<0.0001) and ODI (42.8±31.1→30.7±25.2, P=0.008). *AE*: Eighty-two AE (23 types) were reported in 53% (41/77). Efficacy was less in those with AE: a trend existed for a lesser reduction in VAS (2.0±2.4 v 3.0±2.7, P=0.08) which proved significant for ODI (8.1±11.4 v 16.7±18.2, P=0.01). Thirty-four per cent (26/77) discontinued GBP: all within 1 week (i.e. during titration).

Conclusion: This was the first prospective cohort study of GBP super-added to a pre-existent regime containing AMP for CS, as per routine clinical practice and NICE-UK principles. Super-added GBP demonstrated further efficacy over the previous regime in 56%: however, AE were frequent (53%) and diverse (23 types); and 34% abruptly discarded GBP. Although AE were associated with decreased efficacy, 37% nevertheless tolerated GBP despite AE.

3.3 Introduction

Neuropathic pain (NP), arising from diverse conditions such as trauma, infection degeneration or idiopathic in origin, is one of the most difficult types of pain to treat [1]. Chronic sciatica (CS: i.e. sciatica present for more than 3 months), due to compression or irritation of lumbo-sacral roots, is assumed to represent NP [2, 3]. A recent editorial [4], and a systematic review [3], have both highlighted the gross lack of evidence base guiding the current medical management of CS.

Anti-depressants, such as tri-cyclic antidepressants (TCAs: e.g. amitriptyline AMP), are widely used to treat NP; including CS. Based on 'moderate-quality' evidence, NICE UK reported TCA efficacy over placebo for NP [4]. However, based on 'high-quality' evidence, TCAs were also significantly more likely to produce AEs than placebo. Extrapolating NICE-UK guidelines, prescribing authorities (e.g. Australian Therapeutic guidelines, ATG) often insist on trialling TCAs first for NP, prior to introducing second-line agents. Limited information, however, is available regarding TCA use specifically in CS. In one rare cross-over study, Nortriptyline – alone, or combined with Morphine – demonstrated no significant benefit over placebo [6].

Anticonvulsant anti-neuropathic agents, such as GBP, are also widely used to treat NP; including CS. Based on 'moderate-to-high-quality' evidence, NICE UK noted efficacy of GBP over placebo for NP [4]. However, based on 'high-quality' evidence, GBP – like TCAs – was also significantly more likely to produce AEs than placebo. At the time of this study, Australian prescribing authorities (e.g. ATG) recommended anti-neuropathic agents as second-line agents for NP, even though NICE-UK did not actually favour TCAs over anti-convulsant as first-line agents (or vice versa). However, when introducing second-line agents, NICE-UK did encourage "overlap" with first-line agents and pre-existent regimes, to avoid decreased pain-control [4]. In consequence, many patients in routine practice are co-prescribed both AMP and GBP in a sequential manner for control of NP or CS.

Only 2 previous studies have assessed GBP use in CS [5, 6]. However, neither study was representative of routine clinical practice: participants were required to cease all prior pain medication, and were denied any background therapies. Whilst imperative for pure scientific study, such practice conflicts with routine clinical

practice; and is contrary to NICE-UK guidelines as aforementioned. Moreover, study designs did not permit full assessment of the frequency and type AE. AE were also under-reported in the studies reported by NICE-UK when compared to routine clinical practice and National Formularies.

Given methodological problems encountered previously, our study maintained representativeness as per NICE-UK guidelines by including background therapies (including first-line AMP) with GBP use in CS. In addition, this work faithfully recorded the frequency and type of AE, in order to validate and quantify anecdotal evidence of considerable AE emanating from routine clinical practice.

3.4   Methods

A cohort of patients attending a specialist spine clinic in an Australian public hospital were prospectively studied between Dec 2010-Dec 2012. This coincided with the period when only GBP was subsidised by the hospital authority (PGB was not available on the Australian Pharmaceutical Benefit Scheme, PBS, until March 2013).

3.4.1   Inclusion Criteria

All study participants were over 18yrs old, had unilateral CS for a minimum of 3 months due to lumbo-sacral root compression proven on MRI. All were being actively considered for surgery: however, consistent with good medical practice, all non-operative angles were being explored first. Furthermore, subsidised GBP was only available as second-line treatment after first-line treatment with AMP. Eligible participants were taking paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) as part of a pre-existent regime, in which codeine-based analgesia was only taken 'as required'. As recommended by the prescribing authority, all patients were also taking AMP in low dose (10-50mg) once daily: none, however, had suffered significant AE with their pre-existent regime. GBP was titrated to each pre-existing regime for 3 months: initially 300mg once daily for 4 days, 300mg twice daily for a further 4 days, and thereafter 300mg thrice daily (as per Australian Therapeutic guidelines) [7]. Further 300mg increments were tried, as appropriate, in the same fashion to optimise efficacy: however, no patient took more than 1.8g per day. No other drugs were added or discontinued during this interval. The VAS, ODI and AE

were recorded. The local HREC approval was obtained for the study and agreed to waive individual consent.

All patients were fully informed of the possible types of AE associated with GBP, as listed in the Australian Medicines Handbook (AMH) (8), prior to participation. As a result, all patients who had previously tried, but discarded, AMP because of AE were subsequently found to be also disinclined to take GBP. Because of this, and because all other patients were already taking AMP in a pre-existent regime prior to specialist clinic referral, it was not possible to obtain a control arm in which either AMP or GBP could be prospectively prescribed alone. It was considered inequitable to ask patients to cease a pre-existent regime which had already proven partially beneficial (with no reported AE). AE and outcome measures were routinely recorded at regular clinic attendances at 3 monthly intervals.

3.4.2 Exclusion Criteria

Patients were excluded if they were taking other anti-depressants, other opiate preparations or other anti-convulsant. Patients were also excluded if they had previously tried GBP, had chronic renal failure, had an active unstable psychiatric condition (including alcoholism), had previously failed spinal surgery, had bilateral sciatica or cauda equina syndrome, infection, tumours, malignancy, known osteoporosis, significant confounding hip or knee pathology or were pregnant.

3.4.3 Statistics

Efficacy was defined as a reduction in VAS and ODI. Microsoft Excel and IBM SPSS version 19 were used to analyse data. Data was checked for normality and appropriate parametric or non-parametric tests performed. Baseline characteristics, reduction of pain and ODI scores were compared using Fisher's exact/Chi Square for dichotomous variables and t-test or Mann Whitney U test for continuous variables. Results are reported as statistically significant when p-values are <0.05.

3.5 Results

Data was available on all patients (n=77) in this prospective cohort. Demographic data is recorded in (Table 3.1). Once daily AMP dosage regimes were: 10mg in n=69

(90%), 25mg in n=7 (9%) and 50mg in only n=1 (1%). Total daily doses of GBP were 900mg in n=71 (92%), and 1.2-1.8g in n=6 (8%).

3.5.1   Efficacy

In 56% (43/77) there were reductions in VAS (5.3±3.6→2.8±2.7, P<0.0001) and ODI (42.8±31.1→30.7±25.2, P=0.008) (Table 3.1). Improvement was less in those with AE: a trend existed for a lesser reduction in VAS (2.0±2.4 v 3.0±2.7, P=0.08) which, however, proved significant for ODI (8.1±11.4 v 16.7±18.2, P=0.01). Total daily doses of GBP were 900mg in n=41, and 1.2-1.8g in n=2 in those with efficacy. Of those with efficacy, n=39 were taking AMP-10mg, n=4 were taking AMP-25mg, n=0 were taking AMP-50mg. There was no significant difference between those with and without efficacy regarding the use of codeine-based analgesia 'as required' (22/43, 51% v 20/34, 59%: P=0.57).

3.5.2   Adverse Events

Eighty-two AEs (23 types) were reported in 53% of patients (41/77) (Table 3.1).

Table 3.1 Patient characteristics – total population

Description	Value	P – value (if applicable)
Total population – n (%)	77 (100)	-
Age (years) - mean (range)	57 (21 – 89)	-
Sex, n (%)		
Male	32(42)	-
Female	45(58)	
Adverse Events – n (%)	41(53)	-
Efficacy - n (%)	42(55)	
Ceased Treatment <1wk – n (%)	26 (34)	-
VAS		
Start – mean (SD)	5.31 (3.64)	<0.0001
Finish – mean (SD)	2.83 (2.72)	
ODI		
Start – mean (SD)	42.84 (31.12)	0.008
Finish – mean (SD)	30.74 (25.19)	

As Table 3.2 lists, the most common AEs were amnesia (8/82, 9.8%), dizziness (8/82, 9.8%), confusion (7/82, 8.5%), and ataxia (6/82, 7.3%). Sixteen per cent (12/77) continued with GBP with no efficacy and no AE (Figure 3.1).
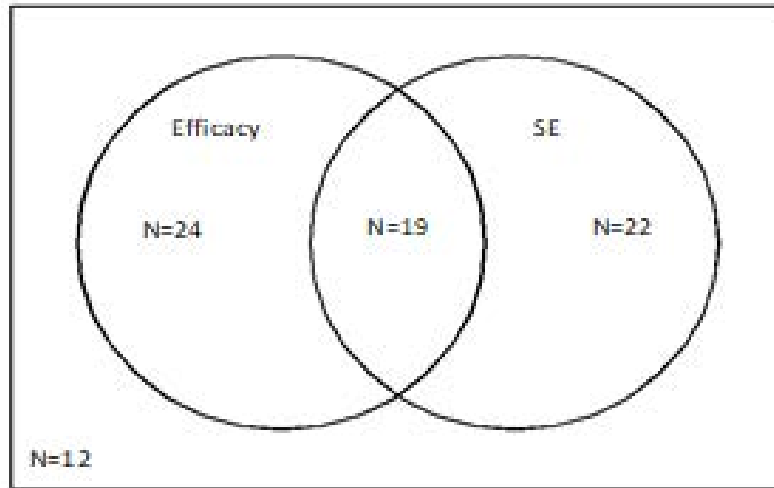
Figure 3.1 Venn diagram: efficacy versus side effects

AEs were recorded in n=23/41 (56%) of females and n=18/41 (44%) males: a similar distribution pertained in those without AE (n=22/36 [61%] females, and n=14/36 [39%] males) (P = 0.66). Total daily doses of GBP were 900mg in n=37 (90%), and 1.2-1.8g in n=4 (10%). Of those with AE, n=39 (95%) were taking AMP-10mg, n=2 (5%) were taking AMP-25mg and n=0 (%) AMP-50mg. Of those without AE, n=30 (83%) were taking AMP-10mg, n=5 (14%) were taking AMP-25mg and n=1 (3%) AMP-50mg. There was no significant difference between those with and without AE regarding the use of codeine-based analgesia 'as required' (20/41, 49% v 20/36, 56%: P=0.46).

Table 3.2 Adverse events experienced by population

Description	Frequency	Proportion of population with side-effect (%)
Dizziness, Vertigo	11	27
Drowsy, sedation, retardation	9	22
Decrease Memory	8	20
Confusion	7	17
Dry Mouth, Heart Burn, Decreased taste	6	15
Ataxia	6	15
Lethargy	5	12
Bowel Disturbance	5	12
Rash, Weight Gain	5	12
Nausea, Vomiting, Headache	5	12
Euphoria, Tingling	4	10
Diplopia,	3	7
Psychiatric Disturbance	3	7
Auditory Hallucination	2	5
Aggression	2	5
Sleepwalking	1	2
TOTAL	**82**	

3.5.3   Gabapentin Cessation

Thirty-four per cent (26/77) discontinued GBP: all within 1 week (i.e. during titration). Of those who ceased GBP, n=24/26 (92%) had AE. N=2 (8%) ceased because they had experienced no efficacy and because they had "expected" AE. Of those who ceased GBP, n=5/26 (19%) had reported efficacy with AE. N=4/43 (9%) with efficacy ceased GBP because of AE. Total daily doses of GBP were 900mg in n=24, and 1.2-1.8g in n=2. Of those who ceased GBP, n=1 was taking AMP-25mg, and n=1 was taking AMP-50mg.

3.6   Discussion

Our study results showed super-added GBP demonstrated further efficacy in 56% of patients: however, AEs were frequent (53%) and diverse (n=23); and 34% abruptly discarded GBP. The first prospectively randomised placebo-controlled study reported using GBP used unconventional outcome parameters (e.g. a Likert-type scale was used to assess pain instead of the VAS) and specifically did not use the ODI (the 'Gold standard' to assess disability with low back conditions) [5]. In addition, the proportion reporting efficacy was not established since patients who did not tolerate even basal doses of the drug were withdrawn from the study. Blinding between GBP and placebo also remained uncertain, thus questioning the integrity of allocation concealment given that GBP must be introduced incrementally. Additionally, GBP requires an adequate trial of more than two months as per National Formularies, which would have been difficult to complete where high doses are required [7]. Finally, as aforementioned, AEs were recorded in only 8% (i.e. a much lower proportion than that recorded using GBP in other NP states) despite doses of up to 3600mg GBP having been administered [5, 9]. A second study in the literature examining GBP was a prospective open-label non-comparative study that did use the VAS and ODI: however, the study did not mention AE at all [6].

Prospective cohort studies, such as ours, maintain representation because all patients were necessarily recruited. In our study, all patients were taking a pre-existent regime which had included AMP, as enforced by the prescribing authorities (Queensland Health Medicines Advisory Committee, QHMAC, and the Pharmaceutical Benefit Advisory Committee, PBAC). At the time of the study, subsidised GBP was not available for first-line treatment in CS. Such a regime containing AMP had already proven partially effective, as reflected in moderate baseline scores for both VAS (5.3±3.6) and ODI (42.8±31.1). Furthermore, no patient studied had reported significant AE on their pre-existent regime. Because patients were already taking AMP, and because those who had previously tried (and failed) AMP were disinclined to take GBP, it was not possible to obtain a control arm in our study in which either AMP or GBP could be prospectively prescribed alone. Furthermore, it was considered inequitable to ask patients to cease a pre-existent regime which had already proven partially beneficial solely to ensure a statistically

sound study. Indeed, this would have been against NICE-UK guidelines, where "overlap" with first-line agents and pre-existent regimes is encouraged precisely to avoid decreased pain-control.

3.6.1 Efficacy

Our results are compatible with previous studies where only GBP was used to treat other NP states. For example, NICE-UK concludes that "patients taking GBP were significantly more likely to report at least 50% pain reduction and global improvement compared with patients taking placebo (moderate-to-high-quality evidence)". This is comparable to the 47% reduction in VAS seen in our study. However, the lower improvement in ODI (28%) observed in our study, by contrast, initially appeared divergent. Nevertheless, as we subsequently discuss, both the VAS and (especially) the ODI were adversely affected by AE in our study. Excluding those with AE, both scores were rendered compatible with the NICE-UK statement. This suggests that GBP when added to a pre-existent regime containing AMP in CS exhibits remarkably similar efficacy to that when GBP is prescribed alone in other NP states.

3.6.2 Adverse Events

An important aspect of our study was the complete documentation of AE. National formularies (e.g. Australian Medicines Handbook (AMH), British national Formulary (BNF), European Pharmacopoeia) report no less than 16 types of AE associated with GBP in general use described as "common" (fatigue, sedation, dizziness, ataxia, tremor, diplopia, nystagmus, amblyopia, amnesia, abnormal thinking, hypertension, vasodilation, peripheral oedema, dry mouth, weight gain and rash), as well as a further 4 types described as "rare" (jaundice, movement disorders, myoclonus and allergic reactions) [8, 10, 11]. In marked contrast, regarding GBP use in non-CS NP states, NICE UK noted only 3 types of AE: i.e. dizziness, somnolence (moderate-quality evidence) and fatigue (low-quality evidence). Indeed, regarding sedation and gait disturbance, NICE-UK reported "no significant differences" between patients taking GBP and patients taking placebo (very-low-quality evidence).

The 2 previous studies reported by Yildirim et al. [5, 6] also reported AEs that were both; lower frequency and diversity of type, compared to our study. However, it should be noted that that an undisclosed proportion of patients "who did not tolerate even basal doses of the drug" were immediately withdrawn from the study of Yildirim et al.: data from this subset was therefore unavailable [5]. Moreover, Yildirim et al. later stated that a further n=7/23 (30%) had ceased GBP throughout the study period, compared to 34% in our study. Given that the vast majority of patients who ceased GBP in our study (i.e. 92%) had suffered AE, it is very likely that the actual incidence of AE in the study of Yilidrim et al. had been grossly under-reported.

3.6.3 Gabapentin Cessation

An important aspect of our results (and others) was that of GBP cessation. Regarding GBP use in other NP states, NICE UK reported that patients taking GBP were "significantly more likely to withdraw from treatment because of adverse effects" compared with patients taking placebo (moderate-quality evidence). As noted above, both studies by Yildrim et al. referred to a population of patients "who did not tolerate even basal doses of the drug". Thus, it is implicit in both studies that a definite proportion ceased GBP potentially at an early stage, such as during the initial GBP titration period. Our results were more explicit. Given the slow manner in which GBP is incrementally introduced, such findings suggest that many patients discard GBP before any efficacy could possibly have accrued. Nevertheless, of those who ceased GBP, n=5/26 (19%) had reported efficacy, but with AE. Overall, n=4/43 (9%) with efficacy had ceased GBP because of AE. Indeed, of those who ceased GBP, n=24/26 (92%) reported AE. Thus, the principal reason for abrupt GBP cessation related to either the development, or anticipation, of AE: not a lack of efficacy. In this latter regard, n=2 (8%) ceased because they had experienced no efficacy, and because they had "expected" AE.

3.6.4 Interaction of Adverse Events with Efficacy

Probably the most interesting aspect of our study was that the occurrence of AE was associated with decreased GBP efficacy. The statistically significant effect of AE on ODI may be associated with the fact that, as aforementioned, the overall mean ODI

improvement (28%) was somewhat lower than that expected from studies where GBP was used in other NP states using other measures. ODI improvement in those without AE was 39%: this proportion approaches that observed following spinal fusion for CS (49.5%) [12]. VAS improvement likewise improved from 47% in those with AE, to 62% in those without AE.

It is not immediately clear from our study as to why AE were associated with decreased GBP efficacy. Adverse psychological factors, associated with having experienced AE, could conceivably have impacted negatively upon pain perception. However, our study cannot provide any definite mechanism for the result observed.

3.7 Conclusion

This was the first prospective cohort study of GBP super-added to a pre-existent regime containing AMP for CS. The study was therefore representative of clinical practice, and in accord with NICE-UK principles. Super-added GBP demonstrated further efficacy in 56%: however, AE were frequent (53%) and diverse (n=23); and 34% abruptly discarded GBP. Such findings also endorse the study's representation. Although AE were associated with decreased efficacy, 37% nevertheless tolerated GBP despite AE.

3.8 References

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Chapter 4   Pregabalin versus Gabapentin in the Treatment of Sciatica: A Study Protocol for a Randomised, Double-Blind and Cross-Over Trial (PAGPROS)

'Doubt is a pain too lonely to know that faith is his twin brother."

Khalil Gibran

4.1   Background

This protocol presents the design and rationale for a double-blind, double-dummy, randomised, cross-over trial comparing the efficacy of Pregabalin (PGB) to Gabapentin (GBP) in chronic sciatica (CS). Due to the variability in regular dosage frequency between the medications (PGB = twice daily and GBP thrice daily), the design and implementation of this trial was complex. Thus, "PAGPROS" represents the first head-to-head study to determine the relative role of either PGB or GBP in the evidence-based medical management of CS. However, in addition to efficacy, PAGPROS also determines the frequency and severity of adverse events (AEs) with PGB or GBP. Thus, PAGPROS examines the 'efficacy *v* AE trade-off' with each drug.

Chapter 4 of this thesis, entitled "Pregabalin versus Gabapentin in the Treatment of Sciatica: A Study Protocol for a Randomised, Double-Blind and Cross-Over Trial" is based on the manuscript published in the journal *BMC Trials*. The paper is inserted into this thesis with minor modifications. Only the formatting of section sub-headings and numbering of tables and figures have been modified from the original publication to match the thesis format. The referencing of the chapter retains the original journal style.

> **Robertson K,** Marshman L, Hennessy M, Harriss L, Plummer D. (2017). Pregabalin versus Gabapentin in the Treatment of Sciatica: A Study Protocol for a Randomised, Double-Blind and Cross-Over Trial. *BMC Trials*: January 19:21 https://doi.org/10.1186/s13063-017-2400-y

4.2   Abstract

Background: There is currently an absence of high grade evidence regarding the treatment of CS. Whilst GBP and PGB are both currently used to treat CS, equipoise exists regarding their individual use. In particular, no head-to-head study of GBP and PGB in CS exists. Despite equipoise, most countries' formulary regulation authorities typically favour one drug for subsidy over the other: this hinders interchange wherever the favoured drug is either ineffective or not tolerated.

Primary Aim: To compare head-to-head the efficacy of PGB versus GBP for CS by outcomes on Visual Analogue Scale (VAS) and Oswestry Disability Index (ODI).

Methods: Prospective, randomised, double-blind, double-dummy cross-over study. Included patients were over 18 years, and suffer unilateral CS with radiological confirmation of corresponding neural compression/irritation. Pregnant women, those with major organ disease, or creatinine clearance <60ml/min were excluded. Patients continued their current pain medication at study onset conditional upon dosage consistency during the prior 30 days. Each drug was titrated up to target dose (GBP: 400-800mg tds, PGB: 150-300mg bd) and taken for 8 weeks. The first drug was then ceased: however, cross-over occurred after a 1-week washout period. Drug efficacy was assessed by the visual analogue scale and Oswestry Disability Index. The Health Locus of Control (HLoC) Scale and AE frequency/severity determined psychological functioning. Assuming the hypothesis that one drug will display a superior effect, the sample size required is n=38 with 80% power and 5% type 1 error rate. Results were analysed via intention- to-treat methodology.

Discussion: This study establishes the efficacy of PGB compared with GBP in reducing pain for people with CS and leads to greater understanding of the treatment options available.

Trial Registration Number: Australian and New Zealand Clinical Trial Register: 12613000559718 (registered 17.05.13)

4.3   Introduction

Sciatica or sciatic neuralgia, a common form of lumbosacral radiculopathy, is characterised by low back pain which radiates to the leg and which may be accompanied by sensory loss, motor weakness and/or reflex abnormalities. Sciatica is a symptom defined as well-localised leg pain, with a sharp, shooting or burning quality that approximates to the dermatomal distribution of the sciatic nerve down the posterior lateral aspect of the leg [1]. It is often associated with numbness or paraesthesia in the same distribution but typically extends beyond the limits of perceived pain in either a dermatomal or sclerotomal anatomical fashion [2, 3]. The term "sciatica" is used by clinicians in different ways; some refer to any leg pain referred from the back as sciatica; others prefer to restrict the term to pain originating from the lumbar nerve root. Others believe sciatica is a form of 'neuropathic' pain (NP) caused by compression or irritation of the roots or nerves that comprise the sciatic nerve [1, 4]. CS is sciatica which has been present for more than 3 months despite active conservative management, including physical therapy. CS may complicate previous chronic low back pain: however, it may also present purely as an isolated phenomenon [1, 4].

The annual prevalence of CS varies widely (1.6-43%) with male predominance [4]. CS accounts for 5% of low back pain presenting to primary care and 30% of sufferers have persistent pain for greater than 12 months [4]. Of these 30% presenting to primary care, 20% are already out of work and 5-15% require surgery. Over half of CS sufferers will have pain 4 years post diagnosis with the socio-economic cost per country per year is estimated at \$128million in hospital care, \$730million for absenteeism and \$708million for disablement [5].

Anti-depressants such as tri-cyclic antidepressants (TCAs: e.g. Amitriptyline AMP) are widely used to treat NP including CS, first line after failure of simple analgesics. Based on 'moderate-quality' evidence, The National Institute for Clinical Excellence –United Kingdom (NICE-UK) reported TCA efficacy over placebo for NP [6]: however, based on 'high-quality' evidence, TCAs were also significantly more likely to produce AE than placebo. Extrapolating NICE-UK guidelines, prescribing authorities (e.g. Australian Therapeutic guidelines, ATG) often insist on trialling TCAs first for NP, prior to introducing second-line agents. Limited information,

however, is available regarding TCA use in CS. In one rare cross-over study, Nortriptyline – alone, or combined with Morphine – had no significant benefit over placebo [6].

Anticonvulsant anti-neuropathic agents such as GBP and PGB are also widely used to treat NP, including CS. Based on 'moderate-to-high-quality' evidence, NICE UK noted efficacy of these agents over placebo for NP [6]. Australian prescribing authorities (e.g. ATG) recommend anti-neuropathic agents as second-line agents for NP, even though NICE-UK did not actually favour TCAs over anti-neuropathic as first-line agents (or vice versa). However, when introducing second-line agents, NICE-UK states that "overlap" with pre-existent regimes should be considered to avoid decreased pain-control [6]. A recent literature review provides individual efficacy of PGB and GBP over placebo for CS, however when compared head to head no firm conclusions can be made [7].

In summary, CS, like most NP states, often proves resistant to simple analgesic regimes (including paracetamol, non-steroidal anti-inflammatory agents, or opioids) and recommended first line TCA's [1, 4]. Instead, the drugs most commonly used currently in both CS and NP are GBP or PGB (1, 4). PGB and GBP are both analogues of gamma-aminobutyric acid (GABA), a substance known to modulate calcium-channel subunits. Both GBP and PGB may therefore possibly act by decreasing neurotransmitter release associated with central sensitisation in both CS and NP.

As with NP, there is currently an absence of high-grade evidence regarding the medical treatment of CS [1, 6]. No adequately powered direct 'head-to-head' trials comparing either PGB or GBP with other drugs are extant [1, 6]. Indirect comparisons, using placebo as the common comparator, have been published: however, each have presented differing patient populations, differing primary outcomes, as well as differing pain measurement scales [6]. A recent review concluded, albeit based on weak evidence, that efficacy and AE with GBP and PGB were probably similar [7].

Notwithstanding, citing minor titration but definite cost advantages, NICE-UK nevertheless favoured PGB over GBP [6]. However, costs for either PGB or GBP

vary widely globally. Moreover, costs vary unpredictably (i.e. PGB more expensive than GBP, or vice versa) on a global basis [7]. Despite this, formulary regulation authorities in most countries have, like NICE-UK, favoured one drug over the other. Furthermore, and somewhat paradoxically, formulary regulation authorities in most countries have typically favoured the more expensive drug: whether GBP or PGB [7]. For example, GBP is currently available on the PBS in Australia and some hospitals in the UK only for epilepsy: it is not listed for NP. PGB, by contrast, is subsidised on the Australian Pharmaceutical Benefits Scheme (PBS) for NP. The Food and Drug Administration (FDA) in the USA, along with Health Canada, have adopted similar reimbursement criteria to that of the Australian PBS: notwithstanding, both GBP and PGB can be accessed in the USA and Canada via special access schemes (if patients satisfy stringent criteria for NP). In marked contrast, GBP is listed for use in both partial seizures and NP throughout Europe. The rulings of formulary regulators have therefore been inconsistent, and dependent upon the individual body. Such action hinders interchange wherever the favoured drug is either ineffective or not tolerated [7]. Given that no evidence supports unhindered PGB-GBP interchange, and that no study has directly challenged GBP and PGB head-to-head, neither GBP nor PGB should probably be favoured given current evidence [7].

Prospective 'head-to-head' studies are therefore urgently required to provide robust evidence-base for GBP or PGB use in CS [4]. Both medications have previously displayed efficacy when compared to placebo [1, 8, 9]. We therefore present a protocol for the first study to assess GBP and PGB directly head-to-head in CS.

4.4   Objectives

4.4.1   Primary Objective and Outcome

To demonstrate if either GBP or PGB demonstrates superiority over the other in terms of efficacy for the treatment of patients diagnosed with CS.

The co-primary outcome is leg pain intensity using the Visual Analogue Scale (VAS) measured at baseline and at weeks 4, 8, 10, 14 and 18. The participants were asked to rate their average leg pain over the last 24hours out of 10, with zero representing 'no leg pain', and 10 representing the 'worst pain imaginable [10].

The co-primary outcome is the Oswestry Disability Index (ODI) Questionnaire [10], measured at baseline and at weeks 4, 8, 10, 14 and 18, to assess disability. The Health Locus of Control (HLoC) survey was used at baseline and at weeks 4, 8, 10, 14 and 18 to assess participants decision making processes as we have identified compliance with these medications being low [10].

4.4.2   Secondary Objective and Outcome

To demonstrate if one drug (i.e. either GBP or PGB) demonstrates superiority over the other in terms of the frequency and severity AEs in the treatment of CS.

The key secondary outcome was the record of frequency and severity of AEs. Details of AE will be collected at weeks 4, 8, 10, 14 and 18. The most common AE of PGB are dizziness and somnolence [11]. The most common AEs of these medications are dizziness (27%), drowsiness (22%) and decreased memory (20%) [10].

4.5   Methods

PGB and GBP prospective clinical trial for the treatment of sciatica (PAGPROS) is a double-blind, randomised, double-dummy, cross-over trial comparing PGB to GBP in the treatment of CS (Figure 4.1).
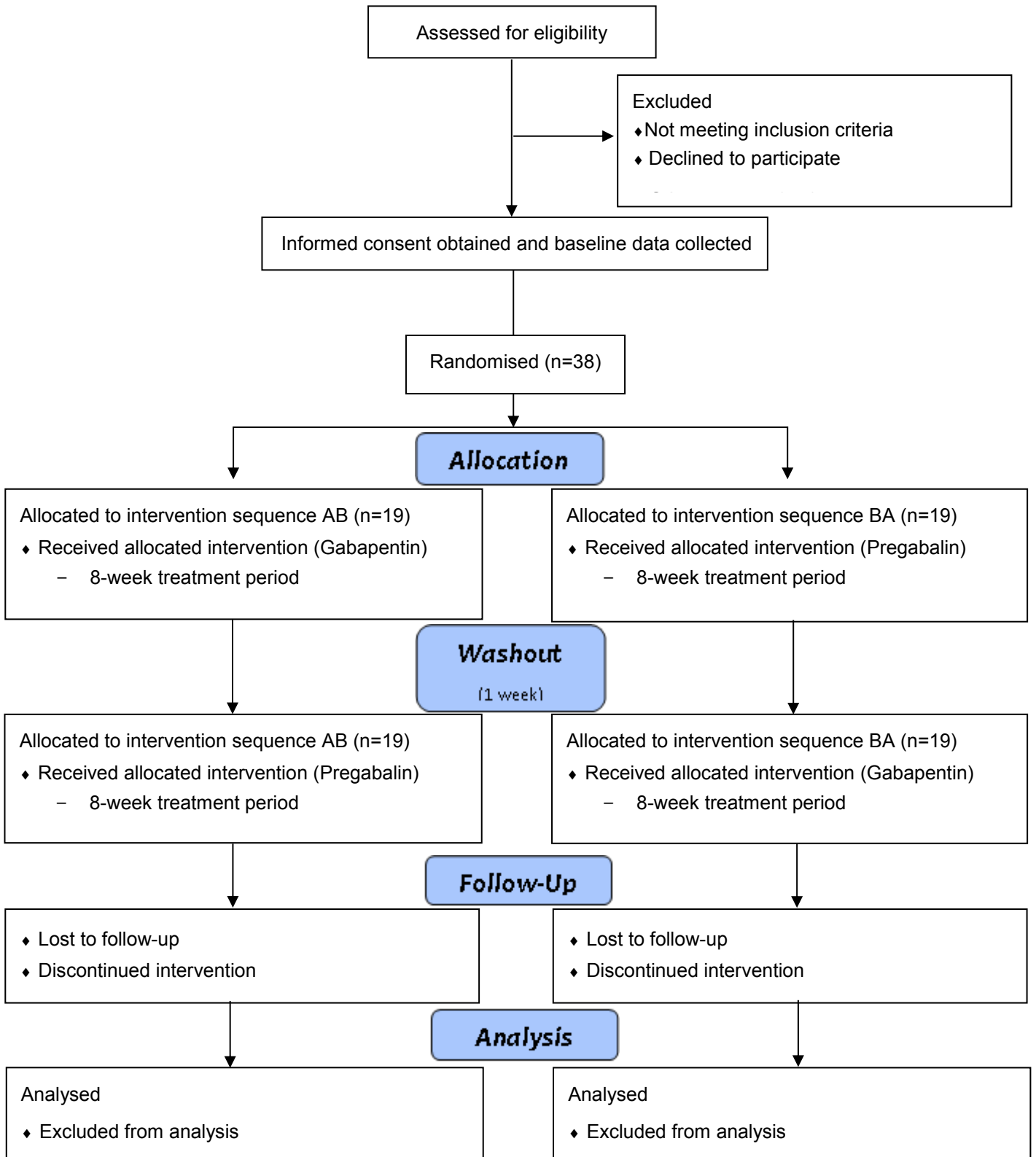
Figure 4.1 CONSORT Flow Diagram for PAGPROS

Ethics approval was obtained from the local HREC, and the study has been registered (Australian and New Zealand Clinical Trial Registry (ANZCTR) 12613000559718). The study protocol follows the SPIRIT statement [12] and a CONSORT diagram are provided (Figure 4.1).

4.5.1 Participants and Recruitment

Participants were recruited from attendance at a specialist neurosurgery clinic in a large tertiary hospital located in Townsville Australia, who had unilateral CS. The study specialists comprising consultant neurosurgeons performed a medical evaluation to gain relevant medical and medication history, and screened the patient against the eligibility criteria. This initial intervention included baseline scores for VAS, ODI and HLoC. The patient was then directed to the trial pharmacist who remained independent of the treating team, for consenting and signature of the informed consent document.

Patients were deemed eligible if they meet all the following criteria:

- Pain radiating into one leg only to, at, or below knee level

- Magnetic Resonance Imaging (MRI)/Computed Tomography (CT) confirmed sciatica caused by a degenerative condition (e.g. degenerative disc disease, bone spur growth, degenerative scoliosis)

- Naïve to PGB and GBP usage

- Age 18 years or older

- Sufficient understanding of the English language or interpretation assistance available to complete the study treatment and assessments.

Concomitant medication including analgesics and Central Nervous System (CNS) depressants (Paracetamol, NSAIDS, and Opioids) could be continued as long as the medication dose has been stable 30 days prior to the start of the study.

Patients were excluded if they meet any of the following criteria:

- Pregnant or breastfeeding women; or females planning conception during the study period

- Patient history or laboratory results that suggest the presence of inherited neuropathy, or neuropathy attributable to other causes (hypothyroidism, B12 deficiency, connective tissue disease, amyloidosis, toxic exposure)

- Major organ system disease; diabetic cardiovascular autonomic neuropathy with abnormality in sympathovagal balance; baseline postural hypotension of more than 20mm Hg

- Specific contraindications to PGB or GBP (allergy to, or significant renal impairment). PGB and GBP are both predominantly renally excreted, so patients with an estimated creatinine clearance of<60 ml/minute will be excluded

- Other neurologic medications such as serotonin reuptake inhibitors (Paroxetine, Fluoxetine), Dual (serotonin and noradrenaline) reuptake inhibitors (Venlafaxine), benzodiazepines, anticonvulsant medications (Valproic acid, Carbamazepine), antipsychotic medications (Clozapine, Olanzapine, Risperidone) or bipolar disorder medications (Lithium)

- People with a diagnosis of cancer; dementia, severe mental illness or other condition which will significantly reduce the ability to consent and/or fully undertake the program.

- Diabetic and /or HIV-related neuropathies.

If a patient is eligible, the unblinded independent trial pharmacist gained informed consent and notified the research team. The participant was then randomised and the pharmacist dispensed and counselled on the study medications, and arranged visit appointments with reminders. At this point, baseline data was confirmed by the pharmacist as collected at the first visit, or subsequently via telephone, before the participant commenced the study medication. Following baseline data collection, the researcher informed the participant to break the seal on the medication pack and

commence the study medicine as per the dosage instructions. At this point the participant was considered to have been included into the study.

To ensure consistency, the study researchers ensured that the protocol was followed, and that Good Clinical Practice was monitored. General practitioners were able to refer community patients into the trial, via a trial specialist hotline contact number, whereby the patient is screened by a study specialist to ensure consistency of enrolments.

4.5.2   Randomisation and Blinding

The trial pharmacist (un-blinded) generated a randomisation code using a computer-derived permuted block with varying block size sequence. Manufacturing and preparation of the medication capsules were performed by an external Good Manufacturing Practice (GMP) accredited facility. The unblinded pharmacist was involved in the preparation of the medication kits as per the randomisation schedule. The sequence was a 2x2 sequential design where participants received PGB first, then subsequently GBP (or vice versa) in a double-blinded fashion. Due to the variability in regular dosage frequency between the medications (PGB = twice daily, GBP = thrice daily) study medication packs contained 3 bottles each correlating to the dosage times of morning, lunch, and night, to maintain blinding. Medication packs pertaining to the PGB arm have a placebo incorporated as the lunch time dose with all medications being indistinguishable. The randomisation schedule remained concealed from other researchers. Placebo capsules had an identical appearance to the active capsules. The randomisation process ensured concealed allocation and blinding of the specialist, the participant and the outcome assessor.

4.5.3   Study Treatment

Participants were randomised to commence treatment on either PGB or GBP. Because of the cross-over methodology, participants had the opportunity to experience both PGB and GBP and we predicted little or no carry-over effects (medium or long term) after the washout period. We believe the incorporation of standalone placebo arm is unethical in trials where participants with moderate to severe pain are recruited.

The starting dose of PGB was 150mg once daily for the first week. This was then titrated to the participant's optimal dose, up to a maximum of 300mg twice daily, depending on their progress and tolerability at each dose level. The starting dose for GBP was 400mg once daily for the first week. This was then titrated to the participant's optimal dose, up to a maximum of 800 mg thrice daily, depending on their progress and tolerance at each dose level. These doses were based on national recommendation from the Australian Medicines Handbook [11]. In the standard study dosing regimen (Table 4.1), a 4-week titration period, after which the maximum tolerated dose for each participant will be maintained for 4 weeks before the first study medication is ceased preparing for washout. The washout period between treatment phases lasted 1 week which was sufficient for these medications as they possess a short half-life (5-7 hours). The dosage of either PGB or GBP could be amended at any stage in PAGPROS based upon efficacy and/or AE by communication between the study specialist and the study pharmacist. The maximum treatment period was 8 weeks [13].

Table 4.1 PAGPROS medication titration schedule

Week	Pregabalin	Total Daily Dose
1	1 x 150mg capsule in the morning	150mg/day
2	1 x 150mg capsule three times a day (middle dose is placebo)	300mg /day
3 -8	2 x 150mg capsules three times per day (middle dose is placebo)	600mg/day
Week	Gabapentin	Total Daily Dose
1	1 x 400mg capsule in the morning	400mg/day
2	1 x 400mg capsule three times per day	1200mg/day
3-8	2 x 400mg capsules three times per day	2400mg/day

The titration and dosage regime was based on recommendations from clinical practice and medication guidelines such as the Australian Medicines Handbook and product Prescribers Information. Both medications have the potential for adverse neurological side effects and hence a slow ascent in dose contributed to mitigating this risk for participants and increasing compliance on the trial. Simultaneously prior to washout, the dosage was gradually reduced instead of an abrupt halt further

decreasing the likelihood of medication misadventures for the participants (and increasing compliance).

In addition to PGB or GBP, participants could continue concomitant medications (including analgesics) if the dosage has been stable for 30 days prior to commencing the study period. These concomitant medications were closely monitored and recorded as part of the case report form. Medicines for NP include antidepressants, selective serotonin and noradrenaline re-uptake inhibitors, topical lignocaine and other anticonvulsant medications [14]. Note that this practice is entirely consistent with NICE-UK guidelines which states that, when super-adding second-line agents for analgesic control (such as GBP and PGB), "overlap with first-line agents is encouraged to avoid decreased pain-control". To our knowledge, only one prospective cohort study has reflected this practice with GBP in CS [14]. However, participants should not take concomitant medication that could result in an adverse interaction with PGB or GBP, including medicines that might increase the risk of excessive sedation (for example, benzodiazepines) [11]. No other pain interventions were permitted throughout the period of study: if considered necessary, then such patients were withdrawn from PAGPROS.

Participating in PAGPROS was completely voluntary and participants could stop taking part at any time without explanation or prejudice. Ceasing to participate in PAGPROS may be considered, for example, wherever participants wish to explore the possibility of other treatments, including other medications or interventions (see above). In some cases, participants may find that the starting dose of either PGB or GBP, whilst efficacious, produces unwanted AE [10]. In such cases, a lower dose may be required: at least for a period of time. Because this cannot be accommodated within the current PAGPROS protocol, such patients were removed from the study and data analysed as per intention-to-treat (ITT) principles: however, they could still form part of a prospective cohort for parallel study.

4.5.4   Data Collection

Data collection was conducted by the study researchers via telephone, email or online at baseline (before medication commencement) and at weeks 4, 8, 10, 14 and 18. Week 10 data collection acted as the cross-over secondary baseline for

analysis purposes. Data was entered into Case Report Forms by dedicated trained staff. Each participant received up to seven face-to-face or telephone consultations with the trial pharmacist to commence treatment, monitor progress and adjust the dose of the study medication over the 8-week treatment periods. These visits incorporated a medical evaluation and collection of primary and secondary outcomes. Participants received usual neurosurgical care independent of, and parallel to, PAGPROS.

The use of prior and continued analgesic medicines were collected at baseline. Adherence to study medication was documented through a self-reported daily medication diary and by counting the returned medicine, compared to the prescribed regimen as recorded by the trial pharmacist. Participants were asked to return used and unused study medications at each visit.

4.5.5   Data Integrity and Analysis

The integrity of trial data was monitored by regularly scrutinising data files for omissions and errors. Double data entry was performed of the primary and key secondary outcomes. The source of any inconsistencies explored and resolved. Electronic data stored on a secure server and paper copies located in a locked cabinet. Data was only accessible by researchers, and participant confidentiality maintained through secure password protected data storage, during and post-PAGPROS.

Data was de-identified prior to statistical analysis and performed on an intention-to-treat basis. Normality of data distribution assessed, and appropriate parametric (Students t-test or ANOVA) or non-parametric tests (Wilcoxon signed rank, Wilcoxon rank sum) for between-groups differences performed. Statistical significance assessed at $P<0.05$. Subgroup analysis may be implicated and considered as PAGPROS develops. Time to event analysis undertaken using Kaplan Meier estimates on the week 8 and week 18 VAS scores. Missing data handled by a single imputation method whereby the last observation will be carried forward and used as a surrogate for the missing value. This method is the favoured approach for replacing missing data as it is conservative, yields an appropriate estimate of variation in outcome and is unlikely to bias towards the alternative hypothesis [15].

An alternative approach to missing data may be use of a longitudinal mixed-effects model incorporated into the analyses.

4.5.6 Sample Size

We hypothesize that over an 8-week treatment period GBP will reduce pain on the VAS scale by an average of 4.5 points from (7.5 to 3.0) as per historical literature [16]. We predict PGB to show at least the same benefit. We hypothesize that PGB will display superiority over GBP by at least 20% better relative reduction in VAS score with a resultant reduction of 5.4 (7.5 to 2.1) points from baseline. This 20% relative reduction is based on the average reduction of pain symptoms compared to placebo for indirect comparisons [1, 16]. Relative reduction will be used as it is often more impressive, and also to allow for the instance of a lower than expected event rate which would lower the absolute risk reduction.

If the true difference in mean both arms of the study means is 0.9, with a standard deviation of 1.2, to detect this 20% relative decrease in pain between GBP and PGB we will need to study 30 patients (15 per treatment arm) in order to reject the null hypothesis with 80% power. The type 1 error probability associated with this test of the null is 0.05. Assuming a 20% drop-out rate the total sample size will be 38 patients (19 per treatment arm). We have chosen this large effect size and conservative standard deviation based on anecdotal and specialists experience with this cohort of patients. The benefits of the cross-over methodology are evident with the small sample size required, due to each participant acting as their own controls. If this was a conventional parallel study design, sample size would be approximating to 100 participants. We conservatively estimate that if two people can be recruited per week the study duration will be approximately 1.5 years.

4.5.7 Adverse Events and Monitoring

Potential risks of both PGB and GBP have been well studied due to its use in neuropathic conditions. These risks have been minimised by our exclusion criteria. Any AEs were monitored weekly during follow-up phone-calls and examinations. Close monitoring of other neurological pain medications occurred with patient diaries. AEs were quantified in a latest meta-analysis and given the rare AEs of both

medications and its likely effectiveness; the potential benefits outweigh the risks in this study [17].

During the recruitment period a monitoring visit was applicable. The responsible monitor was a specialist neurosurgeon not involved in the conduct of the trial and is Chair of the Hospital patient safety committee. The purpose of monitoring is to:

- Ensure that the study is conducted according to the protocol and applicable guidelines and regulations

- Verify source data against data on the CRF and database

- Check the security of stored data

- Confirm that the consent process, approved by the HREC have been followed and view a random sample of original signed consent forms

- Review all serious adverse events.

Interim data monitoring took place in-house for review of safety and AEs. The trial could be stopped if more harm to patients is shown. The Pocock boundary could be used as the stopping rule, where after each set of 2n patient responses to a total of "K" looks at the data. This is a group sequential approach where the critical boundary ($p < 0.018$) will be set at each look.

An AE is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study even if the event is not considered to be related to the investigational drug. Any serious adverse event (defined as an event that is life threatening, results in death, hospitalisation, or significant disability) were reported immediately to the relevant authorities (study monitor, ethics committee, data safety monitoring board). If a potential relationship was suspected between the study drug and serious adverse event, then un-blinding to treatment allocation was indicated and the participant withdrawn from PAGPROS.

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant or require therapy. The occurrence of adverse events was sought by non-directive questioning of the patient

at each visit during the study. AEs were also detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test or other assessments.

All AEs were recorded with:

- Severity grade – mild, moderate, severe.

- Relationship to investigational drug – suspected/not suspected

- Duration

- Continuation to a serious adverse event (SAE).

All AEs are treated appropriately. The action taken to treat the AE was recorded. A serious adverse event (SAE) is defined as:

- Fatal or life-threatening

- Results in persistent or significant disability/incapacity

- Constitutes a congenital anomaly/birth defect

- Requires inpatient hospitalisation or prolongation of existing hospitalisation.

To ensure patient safety, every SAE regardless of suspected causality, occurring after the patient has provided informed consent and until 7 days after the patient has stopped study participation, was notified by expedited reporting to the Townsville Hospital and Health Service Human Research Ethics Committee.

4.5.8   Modification of the Protocol

Any modifications to the protocol that may impact on the design and conduct of the study required a formal protocol amendment. Such amendment was agreed upon by the study investigators and approved by the local ethics committee prior to implementation. Once approved, the changes communicated to the relevant parties.

4.6   Discussion

The PAGPROS protocol presents the design and rationale for a double-blind, double-dummy, randomised, cross-over trial comparing the efficacy of PGB to GBP in CS. Due to the variability in regular dosage frequency between the medications (PGB = twice daily, GBP = thrice daily) study medication packs contained 3 bottles each correlating to the dosage times of morning, lunch, and night, so as to maintain blinding. Medication packs pertaining to the PGB arm had placebo incorporated as the lunch time dose with all medications being indistinguishable.

Thus, PAGPROS represents the first head-to-head study to determine the relative role of either PGB or GBP in the evidence-based medical management of CS. However, in addition to efficacy, PAGPROS also determined the frequency and severity of AE with PGB or GBP. Thus, PAGPROS determined the 'efficacy v AE trade-off' with each drug, and whether differences in compliance rates result in consequence. For example, in a prior study with GBP in CS, 31% patients ceased GBP within one week of treatment [10]. Moreover, efficacy was significantly less in those who suffered AE in that study [10].

PAGPROS employs the HLoC questionnaire to assess psychological functioning with PGB or GBP in CS. In particular, PAGPROS explores the prognosis of each drug relating to questionnaire outcomes relating to patient's insight into their psychological dysfunction. Thus, PAGPROS determines deficits and provides not actually reported as AE by the patients themselves. This proves an important aspect of the study. For example, a prior prospective cohort study with GBP in CS revealed that, of 23 different AE types amongst 53% patients, more than half could have adversely affected the ability to drive a motor vehicle safely, or even to maintain employment [10].

Finally, the double-blind cross-over design of PAGPROS provides guidance regarding the implications of any potential need to substitute one drug for the other. For example, PAGPROS determines whether AE experienced with one drug is also observed with the other: i.e. in the same patient, in close temporal succession after cross-over. This proves especially important should PAGPROS demonstrate a between-groups null effect regarding efficacy. However, PAGPROS shows

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significant efficacy to one drug, yet no efficacy to the other. Despite a lack of evidence-base, many formulary regulation authorities world-wide typically favour one drug for subsidy over the other [4]. This hinders interchange wherever the favoured drug is either ineffective or not tolerated [4]. The nature of PAGPROS' design directly assesses the utility of cross-over between PGB and GBP, and therefore enables formulary regulation authorities to make more informed therapeutic decisions than at present.

Recruitment commenced in early 2016, with data collection completed by late 2018. The allocation concealment and double-blind design minimises bias, while data collection processes ensure data quality and integrity. The trial team has extensive experience in the design, conduct and reporting of clinical trials. Results of the study are disseminated via publications and presentations.

4.7 Potential Weaknesses of PAGPROS

4.7.1 Treatment Duration

PAGPROS permits a 4-week titration period, after which the maximum tolerated dose for each participant will then be maintained for 4 weeks. The duration of individual drug study is, therefore, 8 weeks. In some rare cases, this might be considered insufficient time to test efficacy at optimum dose [10]. Furthermore, since, anecdotally, some patients develop tolerance to AE incurred with either PGB or GBP, the study period may also be too short to detect AE tolerance.

4.7.2 Dosages

Given the restricted doses and study time available in PAGPROS, it is not possible to introduce either drug in 'low and slow' fashion [4]. Since the latter potentially off-sets the development of AE, PAGPROS may therefore potentially over-estimate AE with either drug. However, at least with GBP, there exists some control, in that a prospective cohort study found AE in 53% patients with CS [10].

4.7.3   Maintenance of Background Therapies Including Prior Analgesia

This may affect both efficacy and AE development: potentially increasing both. However, note that this practice is entirely consistent with NICE-UK guidelines [6, 10]; and, indeed, standard clinical practice. NICE-UK guidelines state that, when super-adding second-line analgesic agents (such as GBP and PGB), "overlap with first-line agents is encouraged to avoid decreased pain-control" [6]. To our knowledge, only one prospective cohort study has reflected this practice, using GBP in CS [10].

4.8   References

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Chapter 5   Effect of Gabapentin versus Pregabalin on Pain Intensity in Adults for Treatment of Chronic Sciatica: A Randomised Clinical Trial

'It is during our darkest moments that we must focus to see the light.'

Aristotle

5.1   Background

We performed a stringent single-site study using robust definitions of chronic sciatica (CS). It is important to note that at this stage in the patient's management, either Pregabalin (PGB) or Gabapentin (GBP) would be the next treatment routinely offered: either as an alternative to surgery (with its greater attendant risks), or as a penultimate step before committing to surgery. That is, patients will be offered either drug at this stage in their management irrespective of whether they actually participate in the study. It is also important to note that a position of equipoise genuinely exists regarding which drug (i.e. PGB or GBP) to prescribe in this situation. We believe that we had a responsibility to establish the best treatment option for the benefit of all CS patients.

Chapter 5 of this thesis, entitled "Effect of Gabapentin versus Pregabalin on Pain Intensity in Adults for Treatment of Chronic Sciatica: A Randomised Clinical Trial" is based on the manuscript published in *JAMA Neurology*. The paper is inserted into this thesis with minor modifications. Only the formatting of section sub-headings and numbering of tables and figures have been modified from the original publication to match the thesis format. The referencing format of this chapter retains the original journal style.

> **Robertson K,** Marshman L, Plummer D, Downs E. (2018). Effect of Gabapentin versus Pregabalin on Pain Intensity in Adults for Treatment of Chronic Sciatica: A Randomised Clinical Trial. *JAMA Neuro.* Published online October 15, 2018. http://doi:10.1001/jamaneurol.2018.3077

5.2   Abstract

Importance: Optimal pharmacological treatment for CS is currently unclear. While GBP and PGB are both currently used to treat CS, equipoise exists. Never-the-less, pharmaceutical regulation authorities typically subsidise one drug over the other. This hinders interchange wherever the favoured drug is either ineffective or ill-tolerated.

Objective: To assess 'head-to-head' GBP vs PGB for the treatment of CS.

Design: A pre-planned interim-analysis of a randomised, double-blind, double-dummy cross-over trial of PGB versus GBP in CS, at half the estimated final sample size, was performed.

Setting: Single-centre, tertiary referral Australian public hospital.

Participants: Patients attending a specialist neurosurgery clinic in a large tertiary hospital, with unilateral CS, were considered for trial recruitment. CS was defined as pain lasting for at least 3 months radiating into one leg only to, at, or below the knee level. Imaging (MRI, with or without CT) corroborating a root-level lesion concordant with symptoms and/or signs was determined by the trial clinician. Inclusion criteria also included patients being naïve to both GBP and PGB, patients 18 years of age or older.

Interventions: Randomly assigned participants received GBP (400-800mg thrice-daily) then PGB (150-300mg twice-daily), or *vice versa*, each taken for 8 weeks. Cross-over followed a 1-week washout.

Main Outcome(s) and Measure(s): The primary outcome was pain intensity (10-point Visual Analogue Scale, VAS) at baseline and 8 weeks. Secondary outcomes included: disability (Oswestry Disability Index ODI), and severity/frequency of adverse events (AE).

Results: N=20 underwent randomisation. This equated to n=40 drug and patient episodes. N=2 were excluded. Both GBP (P<0.0001) and PGB (P=0.002) displayed significant VAS-reduction, and ODI-reduction (P<0.001 for both). 'Head-to-head', GBP showed superior VAS-reduction (GBP:1.72±1.17 *v* PGB:0.94±1.09, P=0.035)

irrespective of sequence order: however, ODI-reduction was unchanged. PGB-AE were more frequent (PGB=31 v GBP=7, P=0.002): especially when PGB was taken first (P<0.001). 'Central Nervous system' PGB-AE were significantly more *severe* (P<0.05). AE significantly reduced GBP ODI-efficacy.

Conclusion and Relevance: PGB and GBP were both significantly efficacious. However, GBP was superior, with fewer/less severe AE. GBP should be commenced *before* PGB to permit optimal cross-over wherever PGB may ultimately be warranted.

Trial Registration: Australian and New Zealand Clinical Trial Register: 12613000559718: http://www.anzctr.org.au/

5.3 Introduction

CS, like other neuropathic pain (NP) states, is often resistant to simple treatment regimens [1, 2]. CS is sciatica lasting more than 3 months [3]. NP states are typically managed by super-adding anti-convulsant drugs onto simple drug regimens. The drugs most commonly used are GBP or PGB. CS, has therefore been increasingly treated with super-added GBP or PGB [1, 2, 4]. PGB and GBP are both analogues of gamma-aminobutyric acid (GABA), a substance known to modulate calcium-channel subunits. Both GBP and PGB may therefore possibly act by decreasing neurotransmitter release associated with central sensitisation in both CS and NP.

Optimal pharmacological treatment for CS is unclear. In particular, the precise role of the two principal drugs, PGB or GBP, in treating CS has been surprisingly under-explored [5].

Thus, while GBP and PGB are both currently used to treat CS, a position of equipoise appears to exist regarding which to choose [6]. Notwithstanding, pharmaceutical regulation authorities across different countries typically subsidise one drug over the other. This hinders interchange wherever the favoured drug is either ineffective or not tolerated. Paradoxically, in many countries, the drug favoured for subsidy has actually been the more expensive: regardless whether PGB or GBP was chosen [6].

A prospective randomised placebo controlled trial recently demonstrated a null effect for PGB in treating 'sciatica'. However, this study included patients recruited from multiple sources, and who suffered from both acute and chronic sciatica: sub-group analysis specifically targeting CS was not performed [7]. Perhaps more importantly, no adequately-powered direct 'head-to-head' study, which has compared PGB with any drug (including GBP), exists.

Our study therefore represents the first prospective randomised cohort of patients with CS to comprehensively assess the 'head-to-head' efficacy of PGB and GBP, the associated frequency and severity of AE, and the impact of PGB-GBP interchange.

5.4 Methods

5.4.1 Trial Design and Oversight

The study design used was a prospective, single-centre, double-blind, randomised, double-dummy, cross-over in patients with CS (Figure 4.1). The trial was conducted in accordance with the SPIRIT statement and procedures following Good Clinical Practice (GCP) principles [8]. The trial protocol has been published previously and is available in open access full text [9]. The trial was initiated by the investigators and funded by an internal hospital grant. No drug company had any involvement in drug supply, trial conduct or manuscript review.

5.4.2 Eligibility and Recruitment

Patients attending a specialist neurosurgery clinic in a large tertiary hospital, with unilateral CS, were considered for trial recruitment. CS was defined as pain lasting for at least 3 months [3] radiating into one leg only to, at, or below the knee level. Imaging (MRI, with or without CT) corroborating a root-level lesion concordant with symptoms and/or signs was determined by the trial clinician. Inclusion criteria also included patients being naïve to both GBP and PGB, patients 18 years of age or older, and patients with a sufficient understanding of English (or an available appropriate interpreting service) to complete the study treatments and assessments. Concomitant medications (including analgesics) could be continued as long as the

dose was stable 30 days prior to the start of the study. No more than 2 dose modifications were permitted throughout the study period.

Patients were excluded from the trial if they: were pregnant, breastfeeding or women planning conception during the study period; had a history or diagnostic results which suggested an inherited neuropathy, or neuropathy attributable to other causes (hypothyroidism, B12 deficiency, connective tissue disease, amyloidosis, toxic exposure); had a major organ system disease; had cardiovascular autonomic neuropathy; had baseline postural hypotension of more than 20mm Hg; had specific contraindications to PGB or GBP (allergy to, or significant renal impairment); had cancer, dementia, severe mental illness or other condition which would significantly reduce their ability to consent and/or fully undertake the program; were unlikely to comply with study procedures (e.g. those with high opiate/opioid tolerance, inconsistent clinic attendances etc.). Since PGB and GBP are both predominantly renally excreted, patients with an estimated creatinine clearance of<60 ml/minute were also excluded.

5.4.3   *Randomisation and Blinding*

The trial pharmacist (un-blinded/independent) generated the randomisation code using a computer-derived permuted block with varying block size sequence. Manufacturing and preparation of the medication capsules was performed by an external GMP accredited facility. The un-blinded pharmacist was involved in preparing medication kits according to the trial randomisation schedule. Treatment was allocated according to a 2x2 sequential design where participants received PGB first, then subsequently GBP (or vice versa) in a double-blinded fashion. Due to the variability in regular dosage frequency between the medications (PGB = twice daily, GBP = thrice daily) study medication packs contained 3 bottles, one for each dosage time (morning, lunch, and night) in order to maintain blinding. Medication packs for the PGB arm had a placebo incorporated as the lunch time dose such that both drug regimens were indistinguishable. The randomisation schedule remained concealed from other researchers. The randomisation process ensured concealed allocation and blinding of the specialist, the participant and the outcome assessor during recruitment, data collection and analysis.

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5.4.4   Trial Regimen and Procedures

All patients were fully informed of the possible types of AE associated with either GBP or PGB, as listed in the AMH [11], prior to participation. Participants were randomised to commence treatment on either PGB or GBP. As a result of the cross-over design, participants had the unique opportunity to experience both PGB and GBP in succession. Because of the one-week washout period, carry-over effects (medium or long term) were considered improbable. Participants received standard neurosurgical care independent of, and parallel to, the trial.

The starting dose of PGB was 150mg once daily for the first week. This was titrated to the participant's optimal dose, up to a maximum of 300mg twice daily, depending on their progress and tolerance at each dose level. The starting dose for GBP was 400mg once daily for the first week. Likewise, this drug was titrated to the participant's optimal dose, up to a maximum of 800 mg thrice daily, depending on their progress and tolerance at each dose level. These doses are based on national recommendations from the Australian Medicines Handbook [10]. In the standard study dosing regimen, there was a 4-week titration period, after which the maximum tolerated dose for each participant was maintained for 4 weeks before the first study medication was ceased for washout. The washout period between treatment phases lasted for 1 week: this was deemed sufficient for these medications since they both possess a short half-life (5-7 hours). The dosage of either PGB or GBP could be amended at any stage in the trial based upon efficacy and/or AE by communication between the study specialist and the study pharmacist. The maximum treatment period was 8 weeks for each medication [11].

Participants could continue concomitant medications (including analgesics) throughout the study period, given the stipulations stated above. Such concomitant medications were closely monitored and recorded as part of the case report form. Note that this practice is entirely consistent with NICE-UK guidelines, which state that, when super-adding second-line agents for analgesic control (such as GBP and PGB), "overlap with first-line agents is encouraged to avoid decreased pain-control". To our knowledge, only one prospective cohort study has reflected this practice, with GBP in CS [12]. However, participants did not take concomitant medications that were contraindicated because of a known interaction with PGB or GBP [10]. No other

pain interventions were permitted throughout the period of study: if considered necessary, such patients were withdrawn from the trial.

5.4.5   Outcomes and Data Collection

The primary outcome was leg pain intensity using the Visual Analogue Scale (VAS). Participants were asked to rate their average leg pain over the last 24 hours out of 10, with zero representing 'no leg pain', and 10 representing the 'worst pain imaginable' [4]. A clinically important minimum difference of 1.5 points was chosen based on previous literature [13].

The key secondary outcome was the Oswestry Disability Index (ODI) questionnaire [4], to assess disability where scores range from 0 to 100, with higher scores indicating greater disability. The clinically important difference is represented by 10 points [14].

Details of AE were collected throughout the course of the trial and were noted as a description including a 0 to 10 score for both frequency and severity, whereby an increasing number denotes a higher frequency or severity. Outcomes were assessed at baseline, then at weeks 4, 8, 10, 14 and 18. Baseline, week 8, 10 and 18 were considered the primary time points for the primary outcome which represented the start and finish of each medication.

Data collection was conducted by the study researchers from telephone, email or online. Week 10 data collection served as the cross-over secondary baseline for the purpose of analysis. Data was entered into Case Report Forms by dedicated trained staff.

Adherence to study medication was documented through a self-reported daily medication diary, and by counting the returned medicine.

5.4.6   Statistical Analysis

It was estimated that a sample of 38 patients would be required to provide the trial with 80% power to detect a conservative minimum between-treatment difference of 0.9 points in the pain score on the 10 point scale at week 8 and 18, and to detect a

clinically important between-treatment difference of 10 points on the ODI at the same assessment interval. These assumptions included a standard deviation (SD) of the difference between the two same values for the same patient of 1.2 points (given a cross-over study design) and a two-sided alpha level of 0.05. The estimated sample size would also allow for a drop-out rate of 20%.

Because of our study representing the first 'head-to-head' trial between PGB and GBP, an interim analysis was planned at 50% sample size to assess AE and efficacy, and to confirm trial viability. No formal stopping rules were used due to the lack of previous 'head-to-head' data enabling the pre-setting of boundaries. Instead, the investigators and independent trial monitor would make a judgment based on AEs and outcomes in the primary measure. Missing data was handled by a single imputation method whereby the last observation is carried forward and used as a surrogate for the missing value. This is the favoured approach for replacing missing data as it is conservative, yields an appropriate estimate of variation in outcome and is unlikely to bias towards the alternative hypothesis [15].

Data was de-identified prior to interim statistical analysis and performed on an 'intention-to-treat' basis. Unadjusted mean ± SD were calculated and presented for descriptive statistics of the population. Normality of data distribution was assessed, and the appropriate t-tests performed for between-groups differences including repeated measures linear models. Binary variables were tested using Chi-square analysis. Statistical significance was set at a two-sided P value of less than 0.05. The frequency and severity of AE were reported descriptively with calculated mean ± SD based on unadjusted mean scores of patients. Data imputations were not required since less than 5% of the primary outcome data were missing. Analyses were performed using both Microsoft Excel and SPSS statistical software version 22.

5.5   Results

N=20 participants underwent randomisation from March 2016 to March 2018. This equated to n=40 drug and patient episodes. N=2 were excluded. N=10 were allocated to receive GBP followed by PGB, and n=10 PGB to receive followed by GBP (Figure 4.1). After randomisation, 2 patients were excluded from analysis.

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Both drop-outs had been randomised to the 'GBP-then-PGB' sequence. One patient had failed to collect study medication and was subsequently lost to follow-up. Each participant reached maximal dosing for the medications with <10% requiring any dose reductions (either temporary or permanent).

The total trial population (n=18) experienced efficacy in VAS-reduction and ODI-reduction with the medication regimes. Two-thirds (n=12, 67%) of the population reported at least one AE while in the trial. Over half of the population (n=10) where taking concomitant paracetamol alone or in combination with codeine, while one third of the population were stable on a background opioid before and during the trial (Table 5.1).

Table 5.1 Patient characteristics – total population

Description	Value	P – value (if applicable)
Total population – n (%)	18 (100)	-
Age (years) - mean (range)	57 (22 – 80)	-
Smokers - n (%)	5 (28)	-
Alcohol intake – n (%)	12 (67)	-
Male	11(61)	0.230
Female	7(39)	
Adverse events – n (%)	12(67)	-
Efficacy - n (%)	18(100)	-
Concomitant medications – n (%)		
NSAIDS	3 (17)	-
Paracetamol (+/- codeine)	10 (56)	-
Opioid	6 (33)	-
Antiepileptic/anticonvulsant	1 (5)	-

5.5.1 Efficacy

At the end of an 8-week treatment period, a significant VAS-reduction was recorded for both GBP (7.54 ± 1.39 to 5.82 ± 1.72, $P<0.0001$) and PGB (7.33 ± 1.30 to 6.38 ± 1.88, $P=0.002$) (Table 5.2). A significant ODI-reduction was also observed at 8 weeks for both GBP (59.22 ± 16.88 to 48.54 ± 15.52, $P=<0.001$) and PGB (59.22 ± 13.24 to 50.44 ± 16.58, $P<0.001$) (Table 5.2).

When unadjusted mean differences in VAS-reduction were compared 'head-to-head', GBP proved superior (GBP 1.72 ± 1.17 versus PGB 0.94 ± 1.09, $P=0.035$) (Table 5.2). However, when unadjusted mean differences in ODI-reduction were compared 'head-to-head', no significant difference was found (GBP: 10.66 ± 9.90 versus PGB: 8.78 ± 8.86, $P=0.63$) (Table 5.2).

Table 5.2 Efficacy for total population.

Gabapentin		
VAS		
Start – mean ± SD	7.54 ± 1.39	<0.001
Finish – mean ± SD	5.82 ± 1.72	
ODI		
Start – mean ± SD	59.22 ± 16.88	<0.001
Finish – mean ± SD	48.54 ± 15.52	
Pregabalin		
VAS		
Start – mean ± SD	7.33 ± 1.30	0.002
Finish – mean ± SD	6.38 ± 1.88	
ODI		
Start – mean ± SD	59.22 ± 13.24	<0.001
Finish – mean ± SD	50.44 ± 16.58	
Head-to-head		
VAS		
Drug GBP – mean difference ± SD	1.72 ± 1.17	0.035
Drug PGB – mean difference ± SD	0.94 ± 1.09	
ODI		
Drug GBP – mean difference ± SD	10.66 ± 9.90	0.631
Drug PGB – mean difference ± SD	8.78 ± 8.86	

*efficacy defined as reduction in VAS and/or ODI from both PGB and GBP

5.5.2 Adverse Events

Thirty-eight AEs (21 types) were reported in 12/18 (67%) of patients at some stage in the study. The most common AEs overall were dizziness (5/38, 13%), drowsiness (5/38, 13%) and nausea (4/38, 11%). There were significantly more AEs associated with the PGB arm than with GBP (n=31 v n=7, P=0.002) (Table 5.3, Table 5.4, Table 5.5).

Table 5.3 Adverse events experienced by population

PREGABALIN

Description	Prevalence (No. of recordings)	Proportion of population with AE (%)
Nausea, Vomiting, Headache	7	39
Bowel Disturbance	5	28
Diplopia, Dysarthria	5	28
Dizziness, Vertigo	4	23
Drowsy, sedation	3	17
Lethargy, numbness	2	11
Dry Mouth	1	6
Alertness	1	6
Weight Gain	1	6
Erectile Dysfunction	1	6
Psychiatric Disturbance	1	6
TOTAL	**31**	

GABAPENTIN

Description	Prevalence (No. of recordings)	Proportion of population with AE (%)
Drowsy, sedation	3	17
Dizziness, Vertigo	2	11
Nausea, Vomiting, Headache	1	6
Alertness	1	6
Total	**7**	

SUMMARY

	Gabapentin	**Pregabalin**	**P-value**
Count (N)	7	31	0.002
Frequency (Mean)	4.71	5.51	0.83
Severity (Mean)	4.57	6.03	0.71

*frequency and severity measured on a scale of 1 to 10 with 10 being the worst possible score.
NB: The same participant may have experienced multiple adverse events of different descriptions.

Table 5.4 Interchangeability of Gabapentin and Pregabalin

Description	SEQUENCE		P-value
	GBP to PGB	PGB to GBP	
Patients (n)	8	10	-
Adverse events			
Drug 1 (n)	3	21	**-**
Drug 2 (n)	10	4	**-**
VAS			
Drug 1 mean reduction (range)	1.35 (0.5-2.9)	1.43 (0.1-4.2)	0.62
Drug 2 mean reduction (range)	0.33 (0.0-0.7)	2.01 (0.6-5.5)	**0.01**
P-value	<0.01	0.34	
ODI			
Drug 1 mean reduction (range)	11.25 (0-30)	12.4 (2-28)	0.31
Drug 2 mean reduction (range)	4.25 (0-12)	10.2 (0-30)	0.24
P-value	0.14	0.36	

Table 5.5 Relationship of efficacy with adverse events

Description	COHORT		P-value
	With AEs	Without AEs	
Patients (n)	12	6	-
VAS			
Gabapentin mean reduction (range)	1.63 (0.5-5.5)	1.88 (1.0-2.9)	0.91
Pregabalin mean reduction (range)	1.09 (0.1-4.2)	1.23 (0.0-2.6)	0.81
P-value	0.27	0.08	
ODI			
Gabapentin mean reduction (range)	9.33 (0-30)	13.33 (0-30)	**0.04**
Pregabalin mean reduction (range)	10.66 (2-28)	5.00 (0-12)	0.18
P-value	0.79	0.09	

When the per-patient recorded AEs were clustered based on body system affected, into central nervous system (CNS), respiratory, gastrointestinal and genitourinary, both GBP and PGB demonstrated predominantly 'CNS' AE. However, PGB was associated with more severe central nervous system AE than GBP (P=0.01).

5.5.3 Interchangeability

A total of 8 patients completed the 'GBP-then-PGB' sequence, while 10 patients completed the 'PGB-then-GBP' sequence (Table 5.4). Table 5.4 clearly shows that GBP demonstrated superior efficacy in VAS-reduction irrespective of the sequence order. Specifically, in the 'GBP-then-PGB' sequence, there was a significantly greater mean VAS-reduction associated with GBP than with PGB (GBP:1.35 v PGB:0.33, P<0.01). Likewise, in the 'PGB-then-GBP' sequence, there was a significantly greater mean VAS-reduction with GBP (PGB:0.33 vs GBP:2.01, P=0.01).

However, ODI severity was not significantly reduced by cross-over (Table 5.4). Notably, both PGB and GBP demonstrated a clinically important mean ODI-reduction at the start of treatment (PGB:12.4 and GBP:11.25), with only the 'PGB-then-GBP' sequence continuing the trend of a mean clinical important result solely for GBP (PGB:4.25 and GBP:10.20).

Table 5.5 shows that sequence order affected AE only with PGB. Thus, while GBP-AE occurred at similar frequency irrespective of sequence order, PGB-AE were significantly affected by sequence order. Specifically, PGB-AE were doubled when PGB was prescribed first. Thus, AE in the 'PGB-then-GBP' sequence was GBP: n=3 and PGB: n=21 compared to GBP: n=4 and PGB: n=10 in the 'GBP-then-PGB' sequence.

5.5.4 Reduced Disability (ODI) Efficacy in those with Adverse Event

Table 5.5 shows that AE specifically tended to affect ODI severity only with GBP. Specifically, efficacy was significantly less in those with AE (P=0.04, Table 5.5).

5.6   Discussion

PAGPROS protocol required the Independent Data Monitor to review data after 50% of participants were recruited. The predetermined criteria for stopping the trial was a significant difference in recurrence rates or incidence of AE between groups. Simultaneously, the trial would have considered to be stopped if any superiority was observed between the medications.   After consultation in March 2018, the Independent Data Monitor made a recommendation to the investigators that stopping the trial early was justified.

This pre-determined interim analysis of PAGPROS showed that, while PGB and GBP were both significantly efficacious in reducing pain intensity in patients with CS, GBP was superior when compared 'head-to-head'. Moreover, GBP was associated with fewer and less severe AE irrespective of the sequence order. However, while PGB and GBP were both significantly efficacious in reducing pain-associated disability (ODI), neither was superior when compared 'head-to-head'.

PAGPROS was adequately powered to detect a conservative difference between medications of 0.9 points out of 10 on the pain intensity score. The authors acknowledge the current clinically important treatment effect of 1.5 points out of 10 for pain intensity, and 10 points out of 100 for disability severity. Our results showed that GBP was the only medication to show a clinically important difference in VAS-reduction (mean: 1.72±1.17) and ODI-reduction (10.66±9.90). Compliance with the medication regimen was high based on patient diaries and pill containers returned at each visit. Our selection criteria were based on an established definition of CS with one specialist neurosurgeon involved in screening and recruitment for consistency. The dose of the medications was adjusted using an increasing titration schedule with AE monitoring according to National Formulary recommendations [10].

The 'cross-over' methodology chosen for this trial provides many advantages and particularly strengthens the study findings. In clinical trials, a 'cross-over' design should be limited to a disease which is both chronic and stable, and for which treatments should not result in a total cure but, instead, only alleviate the condition. CS, and treatment with either PGB or GBP, satisfied both these criteria: particularly considering that PGB and GBP are currently considered equivalent. PAGPROS

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therefore achieves a more efficient comparison of treatments than is possible with a parallel trial design. Any potential disadvantage relating to a 'carryover effect' between medications in sequence was obviated by having set the washout period to more than 6 half-lives of either PGB or GBP (effectively, 1 week).

Notably, PAGPROS showed that PGB-AE were more frequent and severe when PGB was taken first prior to GBP. This suggests that GBP may in some way 'sensitize' tissues such that, despite subsequent wash out, tolerance to PGB-AE was significantly enhanced. If so, then putative PGB-induced 'sensitisation' did not appear to affect tissue tolerance to GBP: GBP-AE were significantly lower irrespective of sequence order. Given these findings, PAGPROS suggests that GBP should be commenced before PGB to permit optimal cross-over wherever PGB may ultimately be warranted.

5.7   Conclusion

PGB and GBP were both significantly efficacious. However, GBP showed a modest superiority and tolerability. Therefore, GBP should be considered before PGB to permit optimal cross-over.

5.8   Limitations

5.8.1   Low Recruitment Frequency

Reflects the difficulty associated with recruiting patients with CS who have not already been prescribed either PGB or GBP by practitioners in either primary or tertiary care.

5.8.2   Treatment Duration Effects

The duration of the study for each participant is 8 weeks. In some rare cases, this might be considered insufficient time to test efficacy at the optimum dose [4].

5.8.3   Treatment Dosages

Given the restricted doses and study time available in PAGPROS, it was not possible to introduce either drug in 'low and slow' fashion. Since the latter potentially

off-sets the development of AE [4], PAGPROS may therefore potentially over-estimate AE with either drug. Moreover, the maximal dose of gabapentin prespecified in the study design is lower than what can be prescribed, and was compared to the maximal dose of pregabalin.

5.8.4 Maintenance of Background Therapies Including Prior Analgesia

This may affect both efficacy and AE development: potentially increasing both. However, note that this practice is entirely consistent with NICE-UK guidelines [4, 16]; and, indeed, standard clinical practice.

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Chapter 6   The Relationship between Health Locus of Control and Anti-Neuropathic Drug Efficacy in Patients with Chronic Sciatica

'The best preparation for tomorrow is doing your best today'.

H. Jackson Brown, Jr.

6.1   Background

Recent studies [4-7] have demonstrated that cognitive and psychological factors are significant in the development and persistence of neuropathic pain (NP) conditions. We explore the use of a Brazilian–Portuguese adapted Health Locus of Control (HLoC) survey for patients receiving medication treatment intervention for chronic sciatica (CS), with the hypothesis that patients with a higher external locus of control will have poorer medication efficacy outcomes and thus will negatively influence the prognosis of CS.

Chapter 6 of this thesis, entitled "The Relationship between Health Locus of Control and Anti-Neuropathic Drug Efficacy in Patients with Chronic Sciatica" is based on the manuscript submitted to the *Pain Medicine* journal. The paper is inserted into this thesis with minor modifications. Only the formatting of section sub-headings and numbering of tables and figures have been modified from the original publication to match the thesis format. The referencing of this chapter retains the original journal style.

> **Robertson K,** Plummer D, Marshman L, (2018). The Relationship between Health Locus on Control and Anti-Neuropathic Drug Efficacy in Patients with Chronic Sciatica. *Pain Medicine* (submitted 12.10.2018).

6.2   Abstract

Setting: Psychological and personality factors may be significant in the development and persistence of NP, such as CS. Specifically, patients with an 'external' HLoC orientation reportedly experience poorer medication efficacy with NP. HLoC-scores ('internal'/'chance'/'external') measure a patient's sense-of-control over their own health, and their ability to influence outcomes.

Objective: To investigate any relationship between HLoC and efficacy with PGB and GBP in CS.

Subjects and Methods: The study formed part of a recently-published novel prospective randomised controlled double-dummy cross-over 'head-to-head' trial of PGB and GBP in CS. An adapted HLoC questionnaire, Visual Analogue Scale (VAS) and Oswestry Disability Index (ODI) were administered. HLoC-scores were used to prospectively dichotomize: 1) patients predominantly with 'internal'-HLoC scores 2) patients predominantly of 'external'-HLoC scores.

Results: Across n=38 drug-patient episodes, 'external'-HLoC was correlated with baseline ODI. Within each HLoC group, GBP and PGB both displayed significant VAS and ODI reductions at each interval. However, when VAS and ODI were averaged over the entire study, 'external' HLoC significantly improved only ODI with GBP, not PGB. Further, 'external'-HLoC was correlated with decreased improvement in VAS and ODI solely with PGB, not GBP. After cross-over, patients taking PGB progressed to a higher 'external'-HLoC level. PGB alone demonstrated a significant positive correlation between 'external'-HLoC and VAS (r=0.62, p=<0.05).

Conclusion: CS patients with an 'external'-HLoC showed a higher disease disability. This affects anti-neuropathic drug efficacy. Specifically, CS patients with personality traits of an external locus nature, were less likely to benefit from treatment with PGB. Moreover, HLoC can shift and should not be taken as a fixed value.

6.3　Introduction

Sciatica is a form of radicular pain characterised by buttock or hamstring discomfort which typically radiates to below knee level. It may also be accompanied by sensory loss, motor weakness and reflex diminution in the affected lower limb. Sciatica is caused by either compression, or irritation, of the roots or nerves which together form the sciatic nerve [1, 2].

However, the term "sciatica" is used by clinicians in different ways; some refer to any leg pain originating from the back as sciatica; others prefer to restrict the term to pain originating from the lumbar nerve root. Others believe sciatica is a form of NP which is bundled with other NP such as chronic low back pain (CLBP) [1, 2]. CS is persistent sciatica for more than 3 months otherwise refractory to conservative measures [3].

The annual incidence of CS is estimated to be between 1.6% and 43% [2]. A large proportion of patients with CS suffer persistent pain for two years or longer [1], which contributes to absence from employment and workers compensation claims. While clinicians adopt guidelines to provide general recommendations for prescribing analgesics to treat CS, the associated cognitive and psychological factors which affect the outcomes of treatment are not well understood.

Recent studies have demonstrated that cognitive and psychological factors are significant in the development and persistence of NP conditions [4-7]. The HLoC is one of the most frequently investigated patient decision-making frameworks in neuropathic conditions [5, 6, 8, 9] and is defined as the perceived control the individual has over his or her own health [4, 10].

HLoC can be classified as internal (individuals believe that they are responsible for their own health outcomes), external (the belief that other people are responsible for health outcomes) or by chance (the belief that health relies on chance) [4, 10, 11]. Individuals with an 'external' locus of control reportedly allow their clinicians to take a more paternalistic approach, with the patient participating less in treatment decisions. Individuals with a higher 'internal' locus of control prefer to participate in treatment decisions, and be part of an active alliance between the clinician and the patient [4, 10, 11].

Studies of HLoC in patients with CLBP have shown that a bias towards an 'external'-HLoC negatively influences the prognosis of CLBP [5, 8], and has an increased association with depression [7]. Conversely, people with CLBP who have an 'internal' HLoC show lower levels of disability after treatment when compared to individuals with an external HLoC [8]. Although these correlations of locus of control to disease outcome have been studied for CLBP, these studies are both dated and not specific to the condition of CS. To date, there has been no study to examine the locus of control for CS patients and association to medications.

The present study aimed to test these theories in a population with CS who were enrolled in a previously published prospective randomised controlled double-dummy cross-over trial of PGB and GBP use in CS [12]. The HLoC scale, developed by Wallston et al [11], is frequently used for patients with NP [5, 8]. This questionnaire has three subscales, which measure the internal, external and chance health locus of control of the participant [4, 10, 11]. Recently, a Brazilian–Portuguese version of an adapted HLoC scale was developed and validated for use specifically in NP [13].

We used the adapted HLoC scale for patients receiving medication for CS to test the hypothesis whether patients with a higher external HLoC experience a poorer efficacy and outcome after treatment with GBP or PGB.

6.4 Objective

To investigate the relationship between HLoC scores and efficacy of medication interventions (PGB versus GBP) as measured by changes in a Visual Analogue Score (VAS) and in the Oswestry Disability Index (ODI)

6.5 Methods

The study was performed as part of a prospective randomised controlled double-dummy cross-over trial of PGB and GBP in CS [14]. Participants were randomised in a double-blinded fashion to a treatment regime. Either GBP or PGB was continuously taken until a planned one-week washout period, after which participants were crossed over to the other drug. Participants were monitored by the trial pharmacist to ensure compliance with the medication regime and collection of data. Efficacy was assessed by recording VAS and ODI [15]. The ODI is the 'gold

standard' for measuring disability associated CLBP [15]. On the ODI, 0-20 equates to 'minimal disability', 21-40 'moderate disability', 41-60 'severe disability', 61-80 'crippled' and 81-100 'bed-bound'. Adverse events (AE) to either drug was also systematically documented.

The adapted HLoC scale was administered to consenting participants of the clinical trial. The validity of the adapted HLoC scale has been previously demonstrated [13]. The scale is composed of 18 items divided into 3 loci-of-control subscales, which are 'internal' locus (6 items, questions 1, 6, 8, 12, 13, 17), 'chance' (6 items, questions 2, 4, 9, 11, 15, 16), and 'external' locus (6 items, questions 3, 5, 7, 10, 14, 18). Responses were recorded using a 6-point Likert-type rating scale, with a value of 1 indicating "strongly disagree" and a value of 6 indicating "strongly agree." Summed subscale scores ranged from 6 to 36. The higher the participant scores for each subscale, the greater the locus of control on that dimension.

The adapted HLoC questionnaire (appendix 1) was administered at baseline (before medication commencement and at weeks 8 (pre-washout), week 10 (secondary baseline) and week 18. The data for internal, chance and external sub scales of the questionnaire where collated and averaged for each participant.

Averaged scores for each subscale in the HLoC questionnaire was used to prospectively dichotomize two study sub-groups: Group 1 'predominantly internal locus', and Group 2 'predominantly external locus'. Between group means of 'Internal'/'Chance' and 'External'/'Chance' were calculated and used to distribute, and thus eliminate the chance subscale evenly.

The score on the VAS and ODI was collected for each participant at four-time points: T0, T1, T2 and T3. Time-point T0 and T1 relates to start and end of the first drug treatment respectively. Following a planned 1-week washout, T2 and T3 correspond to the start and finish of treatment with the second drug. Randomisation was used to determine which drug came first for each participant. The HLoC was assessed at these same time points in an interview format and thus permits correlation with VAS and ODI. Averaged changes in VAS and ODI were calculated for each patient as a marker of pain and disability respectively. A positive averaged reduction in VAS and/or ODI would be taken as reflecting efficacy of the respective medication.

Descriptive statistics include frequency distribution for categorical variables (gender and disability level), and mean and standard deviation for continuous variables (age, ODI) as seen in table 6.1. Statistical analysis of data was undertaken using SPSS version 22 software. Comparisons between two independent groups were performed with the independent samples t-test. Pearson's correlation coefficient was calculated to examine the association between pain and disability with the HLoC variables. A P-value <0.05 was considered statistically significant.

6.6   Results

The parent clinical trial was ceased because the planned interim analysis demonstrated superiority of GBP over PGB (12). N=20 participants underwent randomisation.   This equated to n=40 drug and patient episodes. N=2 were excluded. N=10 were randomised to receive GBP followed by PGB, and n=10 to PGB followed by GBP. After randomisation, 2 patients were excluded from analysis. Both drop-outs had been randomised to the 'GBP-then-PGB' sequence. Data was available on 18 patients for this secondary analysis as previously published [12]. Further allocation into groups saw 10 patients analysed as belonging in the "internal locus" group and 8 in the "external locus" group respectively. Total population demographic data are shown in Table 6.1.

Table 6.1 Demographic characteristics of patients with chronic sciatica

Description	N	%
Total population	18	100
Gender		
Male	12	66
Female	6	34
Level of ODI		
Minimal disability	Nil	0
Moderate disability	4	23
Severe disability	5	28
Crippled	8	44
Bed-bound	1	5
	Mean + SD	
Age (years)	57.11	16.50
ODI		
T0	59.22	16.89
T1	48.55	15.53
T2	59.22	13.25
T3	50.44	16.58
VAS		
T0	7.54	1.39
T1	5.82	1.72
T2	7.32	1.30
T3	6.38	1.88

6.6.1   Pain Severity

Pain severity was significantly reduced by each drug within each group at the end of each treatment (P=<0.05). Furthermore, pain severity (VAS) at baseline time points T0 and T2 and at end-of-treatment timepoint T1 were the same in both 'internal HLoC' and 'external HLoC' groups (P=>0.05) (Table 6.2). However, pain severity at end-of PGB treatment timepoint T3 was significantly different between 'internal HLoC' and 'external HLoC' groups, with PGB having a higher VAS score for pain (P=<0.05).

6.6.2 Disability Severity

ODI at timepoint T0 showed significant disparity, with "external"-HLoC patients demonstrating a higher ODI (P=<0.05) (Table 6.2). This timepoint correlates to the start of GBP treatment. All remaining ODI timepoints between groups were not significantly different. ODI severity within each group was significantly reduced by each drug (P=<0.05).

Results for average medication efficacy between groups showed variabilities (Table 6.2). There was no difference for internal locus patient's outcome scores for either VAS or ODI for either medication. Conversely, a significant difference, both within group and between groups, was observed for external locus patients, who experienced a reduced outcome from PGB in both VAS and ODI (P=<0.05).

6.6.3 Health Locus of Control Effect with Interchange

A total of 8 patients completed the 'GBP-then-PGB' sequence, while 10 patients completed the 'PGB-then-GBP' sequence (table 6.4). Table 6.4 shows that a significant shift occurred in the 'external' locus subscale after treatment with PGB when GBP was the predecessor. No other significant different shifts were observed locus of control scales between the drug sequences.

6.6.4 Health Locus of Control Correlation with Efficacy

The relationship between subscales of HLoC with pain severity (VAS) and ODI at each time point for the total population is shown in table 6.3. A significant positive relationship was found between the external HLoC and VAS after PGB (r=0.62, p=<0.05). There were no other significant correlations between the 'internal' and 'chance' HLoC factors with either VAS or ODI.

Table 6.2 Results of medication efficacy according to pre-defined Health Locus of Control study group.

Description	Group 1 Internal Locus (n = 10)	Group 2 External Locus (n= 8)	P value
Demographics			
Age years - (Mean SD)	58.3 (13.04)	55.6 (20.93)	0.988
Gender - (Male %, n)	60%(6)	63%(5)	1.00
Smoker (%,n)	30%(3)	25%(2)	1.00
Alcohol intake (%,n)	50%(5)	88%(7)	0.151
Ethnicity (%,n)			
- Caucasian	80%(8)	62%(5)	-
- Italian	10%(1)	25%(2)	-
- ATSI	10%(1)	13%(1)	-
Pain Severity (VAS)			
T0 –baseline	7.39 (1.76)	7.73(0.81)	0.560
T1 – End Gabapentin	5.59 (2.06)	6.13 (1.27)	0.454
P-Value	**0.003**	**<0.001**	
T2- baseline 2	6.86 (1.47)	7.91 (0.80)	0.073
T3 – End Pregabalin	5.52 (2.04)	7.46 (0.91)	**0.026**
P-Value	**0.012**	**0.003**	
Disability Severity (ODI)			
T0 –baseline	53.00 (19.62)	67.00(8.55)	**0.028**
T1 – End Gabapentin	48.20(17.24)	49.00(14.26)	0.757
P-Value	**0.006**	**0.001**	
T2- baseline 2	58.20 (15.18)	60.50 (11.25)	0.596
T3 – End Pregabalin	45.80 (19.14)	56.25 (11.28)	0.076
P-Value	**0.003**	**0.018**	
Treatment Outcomes			
Average VAS reduction			
Gabapentin	1.80 (1.44)	1.61 (0.80)	0.812
Pregabalin	1.34 (1.35)	0.45 (0.30)	**0.042**
P-Value	0.435	**0.004**	
Average ODI reduction			
Gabapentin	4.80 (4.35)	18.00(10.19)	**0.005**
Pregabalin	12.40(10.19)	4.25 (3.91)	**0.008**
P-Value	0.052	**0.014**	

*considered statistically significant – P=<0.05

Table 6.3 Correlation between Health Locus of Control and ODI, VAS for the total
population

Description	Internal Pearson's r	Chance Pearson's r	External Pearson's r
Pain Severity (VAS)			
T0 –baseline	0.06	0.10	0.20
T1 – End Gabapentin	0.03	0.17	0.23
T2- baseline 2	-0.12	0.22	0.36
T3 – End Pregabalin	-0.16	0.33	**0.62***
Disability Level (ODI)			
T0 –baseline	-0.29	0.28	0.38
T1 – End Gabapentin	0.09	0.26	0.19
T2- baseline 2	0.10	0.43	0.19
T3 – End Pregabalin	-0.15	0.34	0.33

*considered statistically significant – P=<0.05

Table 6.4 Interchangeability and effect on Health Locus of Control

GBP to PGB (n=8)	HLoC Subscale		
	Internal	Chance	External
T0 (avg)	21.2	16.6	21.4
T1 (avg)	21.0	16.1	21.2
WASHOUT			
T2 (avg)	21.6	15.3	22.7
T3 (avg)	21.3	16.7	22.7
P-value (drug 1 vs drug 2)	0.41	0.63	**0.01**

PGB to GBP (n=10)	HLoC Subscale		
	Internal	Chance	External
T0 (avg)	21.5	17.8	20.4
T1 (avg)	22.4	17.4	20.5
WASHOUT			
T2 (avg)	22.4	16.7	21.6
T3 (avg)	21.9	17.8	21.2
P-value (drug 1 vs drug 2)	0.79	0.54	0.38

*considered statistically significant – P=<0.05

6.7   Discussion

This present study supplements a recently published clinical trial which compared GBP and PGB efficacy and adverse events (AE) in CS [12]. The PAGPROS trial results revealed that GBP was more effective than PGB for treating CS, and that GBP was associated with fewer and less severe AE. In accordance with another prior study [3], AE were significantly associated with decreased ODI efficacy; specifically, with GBP [3, 12]. Importantly, AE with PGB were both more frequent and severe when PGB was trialled first [12]. This potentially suggested that GBP may 'prime' tissues against PGB-related AE. The overall study conclusion was therefore that GBP should be considered before using PGB in CS [12]. Notably, this conclusion is contrary to current NICE UK guidelines regarding PGB and GBP [16].

However, in addition to assessing such core outcomes, in the current study we also examined whether certain personality characteristics could, in turn, influence treatment outcomes. The HLoC score was used as a surrogate marker for 'personality': notably, for whether the patient was more oriented towards 'self-control' ('internal' HLoC) or whether, instead, they were more susceptible to allowing others to take control of their health ('external' HLoC). To our knowledge, this is one of the first studies to explore such an association between HLoC and medication efficacy, AE or tolerance in patients with CS.

Analysis showed that patients with higher baseline 'external' HLoC score also had a higher baseline ODI. Because the ODI is self-rated, one possible interpretation is that those with an 'external' HLoC potentially over-estimated their degree of CS-related disability. However, another possibility is that CS of a severity which causes greater disability, over time, potentially encourages or predisposes patients to move more towards an 'external' HLoC score. That is, over time, persistent pain and disability may lead to an attrition of 'self-control'. On this scheme, therefore, HLoC may be more 'dynamic' than is often assumed.

As with the PAGPROS Trial results [12], within each HLoC group, GBP and PGB both displayed significant VAS and ODI reductions at each pre-determined time interval.   However, those with a higher 'external' HLoC experienced less improvement in either VAS or ODI while taking PGB. This suggests that treatment

outcomes with PGB may, to some degree, be influenced by personality or psychological factors. Furthermore, following cross-over, patients taking PGB also appeared to progress from a lower to a higher 'external' HLoC category. Interestingly, while CS may affect HLoC change over time, the latter result suggests that drugs such as PGB may be associated with more rapid HLoC change. This further supports the possibility that HLoC status may be more 'dynamic' than is often assumed.

Despite the fact that GBP and PGB both displayed significant VAS and ODI reductions at each pre-determined time interval, when VAS and ODI were averaged over the entire study period, only the 'external' HLoC group demonstrated significantly improved ODI and only with GBP. No ODI improvement was demonstrated with PGB. Further, VAS was significantly correlated with 'external' HLoC solely with PGB. Thus, VAS increased with the degree of 'external'-HLoC solely with PGB. Given the progression from a lower to a higher 'external' HLoC category in those taking PGB, such results not only support the PAGPROS data (i.e. that GBP is superior to PGB in CS) [12], they also raise the possibility that at least some of this superiority may relate to personality factors, such as those manifest in a dynamic HLoC.

Ultimately our results show that drug efficacy influences HLoC, and that HLoC can shift. Therefore, HLoC should not always be considered to be static. The reasons for shifting HLoC scores in individual participants over time are not clear however three possibilities include: First, participants with higher external HLoC scores at baseline were more likely to demonstrate more severe disability; that is, the greater the disability, the more likely they were to look to external factors, such as clinicians, to exercise control over their health. Perhaps, this finding is not so surprising as people with more severe disease may well have reached a stage where they are increasingly looking to others for answers. The second possibility relates to the impact of adverse events from the drugs, in that, treatment outcomes (esp. with PGB) are at least partly influenced by personality/psychological factors, perhaps mediated by experiencing adverse events. Finally, there seems to be a paradoxical effect with GBP where those with greater internal HLoC scores showed less improvement in disability scores than those with external HLoC, perhaps because

they tended to be less disabled in the first place. Despite each of these findings reaching statistical significance, it is possible that they are no more than statistical artefacts. On the other hand, for a carefully designed clinical trial, our findings do raise the possibility that clinical trials (and treatments) can be influenced by personality factors, even when the trials are double-blinded and procedures robust.

Our study emphasizes the importance of patient's perceptions regarding anti-neuropathic drug regimens for CS. It especially suggests that 'patient profiling', particularly regarding HLoC [17, 18], should be integral to shared decision making; at least regarding anti-neuropathic drug regimens for CS. With recent literature generally emphasizing the importance of patient involvement in the decision-making progress [5, 8], such a view makes sense.

6.8   Conclusion

CS patients with an 'external'-HLoC showed a higher disease disability. This affects anti-neuropathic drug efficacy. Specifically, CS patients with personality traits of an external locus nature, were less likely to benefit from treatment with PGB. Moreover, HLoC can shift and should not be taken as a fixed value.

6.9   References

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Appendix 1 – Adapted Health Locus of Control Survey

Instructions

Each item below is a belief statement about your medical condition with which you may agree or disagree. Beside each statement is a scale which ranges from strongly disagree (1) to strongly agree (6). For each item we would like you to circle the number that represents the extent to which you agree or disagree with that statement. The more you agree with a statement, the higher will be the number you circle. The more you disagree with a statement, the lower will be the number you circle. Please make sure that you answer **EVERY ITEM** and that you circle **ONLY ONE** number per item. This is a measure of your personal beliefs; obviously, there are no right or wrong answers.

Scoring range

Subscale	Possible Range	Items
Internal	6-36	1,6,8,12,13,17
Chance	6-36	2,4,9,11,15,16
External	6-36	3,5,7,10,14,18

1. Strongly Disagree (SD)
2. Moderately Disagree (MD)
3. Slightly Disagree (D)
4. Slightly Agree (A)
5. Moderately Agree (MA)
6. Strongly Agree (SA)

Questionnaire

Question	SD	MD	D	A	MA	SA
If my sciatica pain worsens, it is my own behaviour, which determines how soon I will feel better again						
As to my sciatica pain, what will be will be						
If I see my doctor regularly, I am less likely to have problems with my sciatica pain						
Most things that affect my sciatica pain happen to me by chance						
Whenever my sciatica pain worsens, I should consult a medically trained professional						
I am directly responsible for my sciatica pain getting better or worse						
Other people play a big role in whether my sciatica pain improves, stays the same, or gets worse						
Whatever goes wrong with my sciatica pain is my own fault						
Luck plays a big part in determining how my sciatica pain improves						
In order for my sciatica pain to improve, it is up to other people to see that the right things happen						
Whatever improvement occurs with my sciatica pain is largely a matter of good fortune						
The main thing, which affects my sciatica pain is what I myself do						
I deserve the credit when my sciatica pain improves and the blame when it gets worse						

Following a doctor's orders to the letter is the best way to keep my sciatica pain from getting any worse						
If my sciatica pain worsens, it is a matter of fate						
If I am lucky, my sciatica pain will get better						
If my sciatica pain takes a turn for the worse, it is because I have not been taking proper care of myself						
The type of help I receive from other people determines how soon my condition improves						

Chapter 7   Overall Discussion and Conclusions

'The great art of life is sensation, to feel that we exist, even in pain.'

Lord Byron

7.1   Introduction

This thesis reviewed the literature on Pregabalin (PGB) and Gabapentin (GBP) for managing chronic sciatica (CS). In addition, a series of studies were undertaken to provide evidence of differences in treatment outcomes between these two medications. This concluding chapter will summarise the findings and offer clinical recommendations and possible future directions for the utilisation of PGB and GBP in the treatment of CS.

7.2   Summary

The overall aim of this research was to investigate the pharmacological management of CS, including utilisation, AEs and efficacy of two key pain medications, PGB and GBP. Our expectation was that both drugs would have positive treatment outcomes, but that there may be a difference between the two in terms of pain severity, disability severity and/or adverse events. To test these possibilities, this work was operationalised into three main parts the main findings of which are as follows:

Part One: A review of the literature regarding current evidence on the use of PGB and GBP in CS.

This thesis comprehensively reviewed the available literature on the use of PGB and GBP in CS and other neuropathic pain (NP) states. It was found that no direct head-to-head evidence was available, and equally that there was no recent high-quality research to guide clinical practice. We already knew of only 2 limited specific reviews which accounted for the role of PGB and GBP in CS. The first emanates from NICE-UK guidelines which in turn recommends a variety of modalities for treating neuropathic conditions [9]. Interestingly, NICE-UK state specifically for CS "adverse events should be discussed with each patient, and weighed against potential

benefit". While both drugs are considered efficacious, NICE-UK favours PGB based on weak indirect comparisons of previous research. The second and most recent review only included one study for each GBP and PGB [11]. The authors of this work concluded that the best management for CS remained unclear.

Our review by contrast included eleven studies specific for PGB and GBP in CS and NP conditions. Our main conclusion was that there is a global lack of consistency among individual formulary regulators regarding treatment preference. Our review confirmed the absence of any adequately powered direct head-to-head trials comparing PGB to GBP for the treatment of CS.

Part Two: Compile evidence based on retrospective data on the efficacy and AE profiles of PGB and GBP when used to treat CS.

The second part of this thesis compiled evidence and clinical experience with these drugs by employing retrospective data collection. Given the methodological problems encountered in previous studies (identified in part one), we set out to maintain representativeness in line with gold standard guidelines (NICE-UK) by analysing the effects of the super-addition of GBP with background therapies in CS. In addition, we set out to systematically record the frequency and type of AEs to validate and quantify anecdotal evidence of AEs emanating from routine use of GBP in the first instance.

This research found compatible results with previous studies where GBP was efficacious in pain and disability reduction. Interestingly, our work specifically highlighted the effect AEs had on treatment outcomes. In fact, one-third of our cohort aborted the medication during the first week. Probably the most noteworthy aspect of this work, was the occurrence of AEs and association with decreased GBP efficacy. It was not immediately clear from this study as to why AEs were associated with decreased efficacy. Adverse psychological factors accompanying an AE could conceivably impact negatively on pain perception. However, this study could not provide any definite mechanism for the result observed and thus prospective randomized clinical trials are necessary.

Part Three: Determine the efficacy of PGB and GBP when used to treat CS. Sub analysis to examine HLoC in patients being treated with PBG and GBP for CS.

The final part of this thesis was to assess head to head PGB and GBP when used to treat CS. We hypothesised that both medications have positive outcomes based on the previous work in parts one and two of this thesis. Nevertheless, we anticipated a clinical difference might exist in specific criteria such as pain and disability severity along with frequency and severity of AEs. As part of the trial, we also took the opportunity to examine whether certain personality characteristics influenced treatment outcomes. To our knowledge, this work represents the first prospective head to head clinical trial to comprehensively assess the two drugs, as well as examine the impact of interchange, and to explore the association between medication efficacy and personality traits in clinical trials.

Notably, the clinical trial showed a difference between the drugs at the pre-planned interim analysis stage. GBP was superior to PGB when compared head-to-head for pain reduction (VAS), and was associated with fewer and less severe AEs. The superiority was consistent for GBP irrespective of drug sequence. Interestingly, there was no difference observed when compared head-to-head for reducing disability (ODI). Conspicuously, the research showed that PGB AEs were greater in frequency and severity when it was the drug taken first in the sequence prior to GBP. This result raises the possibility that GBP may sensitize tissues such that, despite a theoretically adequate wash-out, susceptibility to PGB AEs was increased. However, the same results were not observed when PGB was taken first. Given these findings, it might be prudent to commence with GBP before using PGB to permit optimal cross-over wherever PGB be ultimately be warranted.

Our research additionally examined the relationship between personality traits and treatment outcomes. We highlight a significant difference in treatment outcome with an external HLoC personality score. These patients tended to have better results with GBP than PGB, and a subsequent positive correlation and reduced pain reduction with PGB. Furthermore, a patient presenting with this self-control subtype was more likely to have a higher disease severity. Our work has unearthed the dynamic nature of HLoC and we recognise that the HLoC may well be more labile

than is often assumed and should not be considered a fixed value. Furthermore, our results show while it is widely accepted that personality can affect treatment outcomes, we uncovered evidence that personality traits might also play a role in clinical trial outcomes. This is particularly relevant for conditions that may take a heavy psychological toll (such as severe pain states) and in trials with small sample sizes despite otherwise 'textbook-style' randomisation.

7.3   Conclusions and Clinical Recommendations

The following conclusions have been drawn and recommendations made:

1. Until now, no direct high-quality research existed to guide treatment choice between PGB and GBP for CS. Further studies building on the work in this thesis are needed to consolidate and provide a consistent message to prescribers and formulary regulators.

2. GBP and PGB were both efficacious at reducing pain and disability for CS. At an individual level, both drugs were significantly efficacious at reducing VAS and ODI scores. No literature exists on their relative efficacy by other scales of measurement (i.e. not VAS or ODI). In this situation, caution should be given to the choice of drug and we would recommend the approach taken by the NICE-UK guidelines **"adverse events should be discussed with each patient, and weighed against potential benefit"**.

3. There is a difference in treatment outcomes between GBP and PGB when prescribed for CS. On average, GBP is superior in reducing pain severity and has less frequent and severe AEs. Moreover, GBP has favourable interchange results with no loss of efficacy and consistently lower AEs when compared to PGB. This result is the cornerstone of our research. In the absence of any other contraindication, we recommend GBP prescription before trying PGB.

4. Patients with an external self-control personality type are likely to present with an initial higher disability severity. Additionally, patients with an external self-control personality type more likely to benefit from GBP rather than PGB. This result further adds to the evidence of a difference in response observed

between the two drugs. We recommend initiating treatment with GBP as this drug was advantageous in both personality types.

7.4   Strengths and Limitations of this Thesis

Each study within this thesis has included a discussion of the methodological strengths and limitations of the research conducted. The following paragraphs describe more broadly the strengths and limitations of the thesis.

The first strength of this thesis is the use of a consistent and robust definition of CS. Having the research conducted within a single-centre under the guidance of a singular specialist provided a coherent link between the individual studies that have made up this thesis by publication. The use of a single specialist lens unifies the studies in this thesis. This approach is also principally useful as CS is commonly conflated with other forms of chronic low back pain and may not be well managed pharmacologically. This is particularly important with a current under-representation of CS studies worldwide [6].

The other strength of the work in this thesis is that the studies included are supported by robust methodology for interventional research and contain carefully constructed objectives. In addition, our review adopted an all-comers approach and can be stated to be most comprehensive in terms of methodology, allowing for the inclusion of experimental, non-experimental, and varying quality studies to broadly understand the phenomenon explored. In our review, unlike systematic reviews, clinical experience of the researcher was used to test the validity of the studies and determine their usefulness in practice. Each study that has been published in this thesis has also undergone the rigorous peer review process. Careful supervisory oversight was also provided by experienced researchers and clinicians.

There are a number of limitations associated with this thesis. The first is that the research was conducted with patients located at one regional Australian hospital, and as such the results may not be as generalisable to other jurisdictions with different regulators and methods of health provision, or with a different cultural or socioeconomic composition. The articles extracted for the review were managed using 2 reviewers and pre-defined criteria. However, the ability to replicate the same extraction are limited by the constantly evolving content available online. Limitations

also exist due to the cross-sectional design of our retrospective research in chapter 3, where trends over time in pain severity and disability function were unable to be determined. Selection bias is also a possible limitation in this study due to the cross-sectional nature of design. Another limitation of this thesis includes the nature of the survey and questionnaire tools used in the clinical trial. The HLoC questionnaire is a self-reported tool which reflects the patients perceived locus of control at particular points in time, rather than their measured locus of control.

7.5   Directions for Future Research

This work was exploratory in nature and, although these initial results are promising, further research is needed to corroborate these findings and translate them into real-world practice. Firstly, similar works to our clinical trial with a much larger sample size are needed to test our results. The design of future research can play an important role in improving the quality, and address the deficit in evidence in this area. Methodological quality of future studies needs careful attention. This includes data reporting, follow-up periods and the examination of the length of time patients have lived with sciatica, motivation and additional cognitive behaviour assessments.

Secondly, in Australia, the recent addition of PGB to the PBS for NP (2013) has created a conflict in that some long-standing users of GBP, whose pain was previously well controlled on GBP, were subsequently forced to either incur greater costs, or to switch to PGB (with, potentially less efficacy). The Australian Pharmaceutical Benefits Advisory Committee rejected applications to subsidise GBP for the treatment of NP on the grounds of lack of evidence in the proposed population (i.e. clinical trial data did not reflect the population covered by the proposed PBS restriction) and uncertain cost-effectiveness in this patient group. The SPORT study[16] showed that many patients with sciatica will spontaneously improve in the medium term with non-operative management: every attempt should be made to avoid a potentially unnecessary surgical procedures. Given that some patients may benefit from either PGB or GBP (but not both), free interchange between PGB and GBP should be facilitated and not obstructed (as it is in many countries).

Last, our results confirm the serious impact that CS has and how advanced disease responds poorly to oral pharmaceutical intervention. Perhaps the focus should shift more to acute sciatica and early intervention and investigating a potentially effective treatment at this early stage of disease. Simultaneously, exploration of alternative classes of drugs or combinations of therapies should be considered due to the high cost of PGB and GBP. A study published in the *Journal of Pain* [6] showed a clinically important difference with the combination Buprenorphine plus PGB with no increased risk of serious adverse events. However, the authors do conclude that combining medicines may give greater pain relief compared to single-ingredient medicines, but the lack of studies and overall low quality of evidence limit any formal recommendation [6].

7.6 Summation

The burden of CS is considerable and optimally effective pharmacological intervention is paramount. However, the choice between PGB or GBP was unclear due to a state of equipoise in our knowledge. In this context, this research has achieved four important outcomes; (i) made a significant original contribution to the body of knowledge about optimal treatment of CS using PGB and GBP, (ii) documented the difference between PGB and GBP when used to treat CS, (iii) explored the association of cognition and personality on treatment outcomes, and (iv) provided evidence based recommendations that can be translated into clinical practice.

7.7 References (for chapter 1 and 7)

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Appendices

Appendix A: PAGPROS Consent Form

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Appendix B: PAGPROS Patient Information Sheet

Queensland
Government

Townsville
Hospital and Health Service

JAMES COOK
UNIVERSITY
AUSTRALIA

PARTICIPANT INFORMATION SHEET

Pregabalin and Gabapentin Prospective trial for the Treatment of Sciatica: A Randomised, Double-Blind, Cross-over study.
(PAGPROS)

Background: Sciatica is a form of 'neuropathic' pain caused by compression or irritation of the roots or nerves around your spine. Chronic sciatica is 'neuropathic' pain present for more than 3 months. Chronic sciatica can be with previous chronic low back pain (CLBP), although it may appear entirely on its own.

Most types of this pain can often be managed with simple pain medications that include paracetamol, non-steroidal anti-inflammatory agents (e.g. brufen), or opioid analgesics (e.g. codeine or tramadol). Sciatica however is often resistant to such simple regimes. Therefore, sciatica is often managed by adding special pain medications together. In particular, 2 common pain medications for sciatica include gabapentin (GBP) or pregabalin (PGB) which are added on top of your existing regime to help control the pain.

Clearly, adding strong pain medications together could produce complications: indeed, some side effects have been experienced in some patients when either GBP or PGB is added. Nevertheless, despite these side effects, these medications work very well to reduce pain and therefore people tend to keep taking them.

The precise role of PGB or GBP in chronic sciatica has been surprisingly poorly explored. Furthermore, no study has examined GBP and PGB "head-to-head": to see which is better, or which has less side effects. We plan to perform this study to find out which drug is better for you in terms of reducing your pain and the side-effects experienced (if any).

How this study will affect you: At this stage in your management of chronic sciatica, one of either PGB or GBP would ordinarily be offered: either as an alternative or as a step before committing to surgery (with its greater risks). At present, we simply do not know whether one drug is better for you, or whether they are both the same. We are therefore in a position where the next stage in your management would consist of a random choice between PGB and GBP. We therefore have a duty to perform this in a scientific manner: to establish correctly whether one drug is better, or whether they are both the same, for the benefit of all.

Side effects may be experienced in an unknown number of patients taking either PGB or GBP: these are listed below. However, because you may already be taking other drugs for your pain, it is not known whether these side effects with PGB or GBP are due to an interaction with your other 'pain' drugs.

For this reason, we will ask you whether it is ok to record your current medications throughout the trial. We would like to know if any side effects or adverse events occur and the possible cause.

The study is being conducted by Dr Laurence Marshman (Consultant Neurosurgeon) and Mr Kelvin Robertson (Consultant Pharmacist) and will contribute knowledge in the best treatment options for people suffering from Sciatica. This study will contribute to a Doctor of Philosophy degree being undertaken at James Cook University Townsville.

What is involved if you agree?
If you agree to participate in the study, we will try to measure:

1. Your sciatic pain levels before and during treatment with Gabapentin and Pregabalin, and
2. Record and measure any side effects and adverse reactions you experience, and
3. Explore your decision making process about pain medications by a short questionnaire.

You will be invited to attend 7 visits at no extra cost to you. During the visits you will receive questionnaires to complete and have basic medical assessments. These tests will be performed by experienced specialists in pain and psychology. Each visit should take approximately 30 minutes of your time and will be conducted at The Townsville Hospital pain clinic. The study team will be available to give more detailed explanation of experimental protocols, answers and explanations to all of your questions during any time point of the study or outside of these visits. We will also conduct regular phone calls to field any queries you may have through out the trial.

It is important to note that during the course of the study you will be receiving a proven effective medication for the reduction of pain experienced with sciatica. This medication will be supplied free of charge. We are not

using any pretend or placebo tablets. Our aim is to determine which medication acts more effectively with less side-effects for patients with sciatica. Our dedicated study pharmacist will be available at any time point for medication related questions.

As with all medications, patients may experience side-effects that can be untoward. Because we are using medications in our study this presents a risk to participants that side-effects may occur. Below are the common side-effects that you may experience if you agree to participate in the trial;

GABAPENTIN

Common Side-effects (affect 1 in 10 people who take this medication)	What can I do if I experience this?
Feeling drowsy, tired, unsteady or dizzy, blurred vision and other eyesight problems	If any of these happen, do not drive or use tools or machines
Headache	Ask your pharmacist to recommend a suitable painkiller
Feeling or being sick, indigestion, stomach ache	Try eating smaller meals and stick to simple foods
Constipation	Try to eat a well-balanced diet and drink plenty of water each day
Dry Mouth	Try chewing sugar-free gum or sucking sugar-free sweets
Infections, flu-like symptoms, increased appetite, flushing, Increased blood Pressure, changes in weight, changes in emotions or mood, fits, movement difficulties, feeling shaky, difficulty sleeping, tingling feelings, vertigo, breathing difficulties, cough, gum changes, bruises, muscle or joint pains, impotence, swollen foot or ankles	If any of these become troublesome, speak with your Doctor.

PREGABALIN

Common Side-effects (affect 1 in 10 people who take this medication)	What can I do if I experience this?
Feeling dizzy, tired or sleepy / Blurred or double vision	If any of these happen, do not drive or use tools or machines
Dry Mouth	Try chewing sugar-free gum or sucking sugar-free sweets
Feeling or being sick, wind	Stick to simple meals – avoid rich and spicy food
Constipation	Try to eat a well-balanced diet and drink plenty of water each day
Headache	Ask your pharmacist to recommend a suitable painkiller
Increased appetite, mood changes, feeling confused or irritable, difficulties sleeping, reduced sexual desire, feeling unsteady or shaky, loss of concentration, vertigo (spinning sensation), swollen feet or ankles	If any of these become troublesome, speak with your Doctor.

Do I have to take part?
Taking part in this study is completely voluntary and you can stop taking part in the study at any time without explanation or prejudice. You may also withdraw any unprocessed data from the study. If you decide to withdraw, this will not affect your current/future treatment at the hospital

The research may involve blood sampling and if you feel distress from this or if you have any ethical or religious concerns about this, you can refuse to take part in the research. During the study you will be provided with advice on any question of your interest. Please feel free to contact the principal investigator or co-investigator if you have any questions regarding the study. It is unlikely that you will feel any distress during this study, however, if you do feel distressed please let the researchers know and you may also contact the hospitals Care link service on 1800 052 222.

Your responses and contact details will be strictly confidential. The results from the study will be used in research publications and scientific conferences. You will not be identified in any way in these publications.

If you have any questions about the study, please contact – Dr Laurence Marshman or Mr Kelvin Robertson

If you have any concerns regarding the ethical conduct of the study, please contact: Human Ethics, Research Office The Townsville Hospital, Townsville, Qld, 4811 Phone: (07) 4433 1111 (TSV-ethics-committee@health.qld.gov.au)   2

PAGPROS – PICF version (3) 29.10.15.

Visit schedule:

Time(start of week)	0	1	2	3	4	5	6	7	8	9	10
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Supply of drug		X				X					
HLOC Survey	X									X	WASHOUT
Visual analogue scale (Pain)	X									X	
Oswestry Disability Index test	X									X	

Time(start of week)	11	12	13	14	15	16	17	18	19
Informed Consent									
Inclusion/Exclusion Criteria									
Supply of drug	X				X				
HLOC Survey	X								x
Visual analogue scale (Pain)	X								X
Oswestry Disability Index test	X								X

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Appendix C: Ethical Approvals

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Appendix D: Funding Approvals

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