ANALGESIC INTERVENTIONS IN ACUTE AND CHRONIC PAIN

EVALUATING ANALGESIC INTERVENTIONS FOR ACUTE SURGICAL PAIN, PREVENTION OF PERSISTING POST-SURGICAL PAIN, AND CHRONIC LOW BACK PAIN.

By

HARSHA SHANTHANNA, MBBS, MSC

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Doctor of Philosophy
McMaster University

McMaster University DOCTOR OF PHILOSOPHY (2019)

Department of Health Research Methods, Evidence, & Impact

TITLE: Evaluating analgesic interventions for surgical pain; prevention of persisting post-surgical pain; and chronic low back pain.

AUTHOR: Harsha Shanthanna., MBBS, MSc
SUPERVISOR: Professor Lehana Thabane
NUMBER OF PAGES: xii, 94

LAY ABSTRACT

It is important to evaluate analgesic interventions to decrease pain, improve function, and lessen health care costs. In a randomized controlled trial of day surgery patients, we demonstrate that there are no differences between morphine and hydromorphone in achieving pain relief and common side effects. To prevent persistent post-surgical pain in patients having elective video-assisted thoracic surgery lobectomies, we performed a 2×2 factorial, feasibility randomized controlled trial, to compare N-methyl-D-aspartate antagonists versus placebo, and intravenous steroids versus placebo. We observe that appropriate protocol changes must be made before embarking on a larger trial. Finally, we report our systematic review and meta-analysis on the use of gabapentinoids in adult patients with chronic low back pain and observe that the existing evidence is small and not supportive, and the use of gabapentinoids for chronic low back pain merits caution.

ABSTRACT

Acute and chronic pain conditions cause significant patient distress, interference with daily activities, and increased health care costs. It is important to evaluate analgesic interventions to improve pain relief, function, quality of life, and also to prevent persisting pain after surgery. This thesis is a combination of studies evaluating analgesic interventions in the setting of acute surgical pain; prevention of persistent post-surgical pain; and chronic low back pain. In part 1, we report our comparison of morphine and hydromorphone in 402 ambulatory surgery patients, for their ability to achieve satisfactory analgesia with minimal emesis using a design of multicentre randomized controlled trial. We observed no differences in their analgesic potential and common side effects and note that appearance of side effects is likely to be idiosyncratic. In part 2, we report our 2×2 factorial feasibility trial to prevent persistent post-surgical pain in patients having elective video-assisted thoracic surgery lobectomies, comparing N-methyl-D-aspartate antagonists versus placebo, and intravenous steroids versus placebo. As our feasibility outcomes were not met, we suggest appropriate considerations for protocol changes before embarking on a definitive larger trial. In part 3, we report on our systematic review and meta-analysis assessing the effectiveness and safety of gabapentinoids (gabapentin and pregabalin) in adult patients with chronic low back pain. We observed that the existing evidence is small and there is minimal improvement in pain and other outcomes with potential for adverse events. We suggest that the use of gabapentinoids for chronic low back pain merits caution and there is need for large high-quality trials.

ACKNOWLEDGEMENTS

At the outset, I would like to thank Dr. Lehana Thabane for his excellent guidance, encouragement and advice. Lehana, you have always been so supportive and I have been fortunate to have you as my mentor ever since we met. I am sincerely thankful to my committee members, Drs. PJ Devereaux and Mo Bhandari for their support, guidance and inspiration. PJ, by being associated with you and your excellent research team, there were invaluable skills that I was able to learn and opportunities that I was able to make use of, all of which will go a long way in my research career.

I am truly thankful to Dr. Norm Buckley (former Chair, Department of Anesthesia), Dr. James Paul (present Chair, Department of Anesthesia), and Dr. Janet Farrell (Chief of Anesthesia, St. Joes) for their continued support and encouragement. I am thankful to my entire anesthesia, surgical and nursing colleagues who have wholeheartedly supported my research work all through these years. A very large thank you to all contributing patients to whom I am always indebted.

I would like to acknowledge the support of all the contributing individuals for the successful completion and publication of the included projects: Satisfactory Analgesia Minimal Emesis in Day Surgeries (SAME DayS); Preventing pAIn with NMDA antagonists – Steroids in Thoracoscopic lObectomy Procedures (PAIN-STOP); and Gabapentinoids in Chronic Low Back Pain.

Special thanks to Toni Tidy and the entire anesthesia research team for their invaluable support and contribution. Jessica Vincent, thank you so much for your support and expertize in the PAIN STOP trial, and for helping us navigate through the various bumps we had on our way.

I am sincerely thankful to the following funding agencies and grants that have supported me and the included studies over the last 5 years: CIHR RCT mentoring grant (2015); AbbVie New Investigator Award in Anesthesia-Canadian Anesthesiologists' Society (CAS) (2014); Carl Koller Memorial research grant-American Society of Regional Anesthesia and Pain Medicine (2016); Michael DeGroote Institute of Pain Research and Care grant (2016); and CAS career scientist award (2018).

Lastly, I am very thankful to my parents and family; my wife Prathiba and daughters Ahana and Anupama for being there for me at all times and supporting me throughout this journey.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

- ANOVA: Analysis of variance
- ARI: Absolute Risk Index
- AS: Ambulatory Surgeries
- ASRA: American Society of Regional Anesthesia and Pain Medicine
- BMI: Body Mass Index
- BPI: Brief Pain Inventory
- CAS: Canadian Anesthesiologists' Society
- CI: Confidence Interval
- CIHR: Canadian Institute Of Health Research
- CLBP: Chronic Low Back Pain
- CONSORT: Consolidated Standards Of Reporting Randomized Trials
- CPSP: Chronic Post-Surgical Pain
- CRF: Case Record Form
- CS: Central Sensitization
- DN: Douleur Neuropathique
- DSU: Day Surgery Unit
- EMU: Equivalent Morphine Units
- EORTC: European Organization for Research and Treatment of Cancer
- FDA: Food and Drug Agency
- FM: Fibromyalgia
- GB: Gabapentin
- GIC: Global Impression of Change
- GRADE: Grading of Recommendations, Assessment, Development and Evaluation
- HADS: Hospital Anxiety Depression Scale
- HM: Hydromorphone
- IASP: International Association for the Study of Pain
- IBD: Irritable Bowel Syndrome
- IMMPACT: Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
- IQR: Inter Quartile Range
- ITT: Intent to treat
- IV: Intravenous
- LTFU: Loss to Follow Up
- M-H: Mantel-Haenszel

- M: Morphine
- MED: Morphine Equivalent Dose
- MI: Myocardial Infarction
- MINS: Myocardial Injury after Non-Cardiac Surgery
- NAS: Numerical Analogue Scale
- NHS: National Health Service
- NMDA: N-methyl D aspartate
- NNT: Number Needed to Treat
- NP: Neuropathic Pain
- NRS: Numerical Rating Scale
- NSAIDS: Non-Steroidal Anti Inflammatory Drugs
- ON: Ontario
- OR: Odds ratio
- OR: Operating room
- PACU: Post-Anesthetic Care Unit
- PAIN STOP: Preventing pAIn with NMDA antagonists-Steroids in Thoracoscopic lObectomy Procedures
- PCA: Patient Controlled Analgesia
- PCS: Pain catastrophizing scale
- PG: Pregabalin
- PONV: Post-Operative Nausea Vomiting
- PPSP: Persisting Post-Surgical Pain
- QoL: Quality of Life
- RA: Research assistant
- RCT: Randomized Control Trial
- RoB: Risk of Bias
- RR: Relative Risk
- SAME DayS: Satisfactory Analgesia Minimal Emesis in Day Surgeries
- SAME: Satisfactory Analgesia Minimal Emesis
- SD: Standard deviation
- SMD: Standardized Mean Difference
- VAS: Visual analogue scale
- VATS: Video Assisted Thoracic Surgery
- VDS: Verbal descriptive scale
- WHO: World health organization
- WMD: Weighted Mean Difference

DECLARATION OF ACADEMIC ACHIEVEMENT

Chapter 1: This chapter is unpublished and H. Shanthanna is the sole author.

Chapter 2: This chapter is published in the journal *BMJ Open*. H. Shanthanna conceived the study question and was involved in the study as a primary investigator and drafted the chapter manuscript. Contribution of other authors is highlighted within the chapter.

Chapter 3: This chapter is published in the journal *British Journal of Anaesthesia*. H. Shanthanna was the primary investigator and contributed to study design, trial registration, supervised the study conduct, interpretation of data analysis and drafted the manuscript. Contribution of other authors is highlighted within the chapter.

Chapter 4: This chapter is being prepared for a journal submission. H. Shanthanna was the primary investigator and contributed to writing the protocol, applying for regulatory approvals, study conduct and supervision, and also drafted the chapter manuscript. Contribution of other authors is highlighted within the chapter.

Chapter 5: This chapter has been published in the journal *BMJ Open*. H. Shanthanna was the lead investigator and contributed to study idea, protocol, registration of the review, and as the lead author of the manuscript. Contribution of other authors is highlighted within the chapter.

Chapter 6: This chapter has been published in the journal *PLOS Medicine*. As the primary investigator, H. Shanthanna contributed to the conduct of the review and analysis, ensured data integrity, interpretation of data analysis and drafted the chapter manuscript. Contribution of other authors is highlighted within the chapter.

Chapter 7: This chapter is unpublished and H. Shanthanna is the sole author of this chapter.

Chapter 1: Introduction to Thesis

"No doubt Pain as God's megaphone is a terrible instrument".
C.S. Lewis, *The Problem of Pain*

Pain is a universal human experience. As a physiological sensation, its function is to protect an individual from bodily harm. However, pain is not a pleasant experience and the word 'pain' is associated with physical and emotional distress, and helplessness. Throughout human history, people have attempted to understand pain, which is derived from the Latin word called poena (punishment). Well known Greek philosophers Aristotle and Plato believed pain to be an emotion and not a sensation. Rene Descartes, who wrote the Treatise of Man (1664), is credited with the specificity theory of pain and to the recognition that pain happens due to a disturbance that is passed down along nerve fibers until it reaches the brain. This led to the foundations of subsequent understanding and transformed the perception of pain from a spiritual experience to a physical sensation. The International Association for the Study of Pain (IASP) came out with their first definition of pain in 1979, as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"[1]. What sets out pain from other physiological sensation is the subjective nature of effects resulting from an actual or potential tissue damage. The experience of pain is thus a uniquely personal experience. Although, access to pain treatment is considered a fundamental human right across the world, it is important to acknowledge that a major gap exists between our understanding of the pathophysiology of pain and its adequate management[2]. Inadequate treatment of pain not only leads to individual physiological and psychological suffering, it also impacts the patient's family and the society as a whole. Need for better treatment of pain is observed both with the acute and chronic pain settings. Among factors leading to inadequate pain treatment, lack of available evidence-based interventions is an important limitation[3]. This sandwich thesis consists of three parts, each of which separately deals with an assessment of an analgesic intervention, in a particular context and patient population. In the following paragraphs, I summarize the background, the primary objective and methodology of each of these investigations.

Contents of the Thesis

Part 1: The pathophysiology of pain is relatively better understood for acute pain conditions than for chronic pain. Still, 30-40% of surgical patients suffer from inadequately treated pain, worldwide[3]. In a 2008 survey of 1490 patients in Netherlands, 41% of patients had moderate to severe pain on the first day of surgery, despite the presence of an acute pain protocol[4]. As there has been a significant increase in the proportion of ambulatory surgeries, it is important to address the aspect of postoperative analgesia in this group of patients. Day surgeries pose unique challenges as patients are discharged home on the same day. Pain and postoperative nausea-vomiting (PONV) are the leading factors affecting its quality of services[5,6], affecting the recovery, discharge, and overall satisfaction of day surgery patients[7,8]. For the management of postoperative pain, multimodal analgesia is frequently employed. Despite efforts to increase the use of other options, opioids have remained the primary modality in moderate to severe pain, especially for surgeries involving abdomen and pelvic structures, wherein effective

regional analgesic choices are limited[9]. Although opioids are potent analgesics, their use is akin to a double-edged sword, as they cause several side effects such as drowsiness, sedation, PONV, itching and respiratory depression. In such a scenario, it is important for a clinician to choose an opioid that is clinically superior, based on patient important outcomes. *In chapter 2*, we describe the burden of pain and PONV in day surgery patients and the use of opioids for treating postoperative pain. We note the limitations of existing evidence with respect to choosing between morphine versus hydromorphone, as the opioid of choice in the immediate postoperative period, and describe our methods to compare the two opioid medications. *In chapter 3*, we report the results of our multicentre, randomized control trial (RCT) of morphine versus hydromorphone in day surgery patients, with the primary objective of comparing the proportion of patients with Satisfactory Analgesia and Minimal Emesis during their stabilisation in post anesthetic care unit (PACU).

Part 2*:* There is increasing recognition of a not so uncommon state of persisting pain after a successful surgery. This state of persistent post-surgical pain (PPSP) is defined as the pain which develops or increases after a surgical procedure and it affects 10-50% of the surgical population[10,11]. Thoracic surgeries have a high risk of PPSP, affecting 25—60% of patients[12]. The pathophysiology of PPSP is full clear. However, it is likely that several surgical and patient factors independently influence the development of PPSP as a result of changes involving peripheral and central sensitization that happens during surgery[13]. N-methyl D-aspartate receptors have been observed to play a central role in the development of pathological pain and many of these changes can be potentially altered by NMDA antagonists[14]. Similarly, subclinical changes of neuro-inflammation[15,16] may result in neuropathic pain that persists beyond the healing period. Although the context of surgery allows us to intervene to minimize the chances of PPSP, existing strategies have not been effective at preventing PPSP[17] and presently, there is no established effective method of preventing PPSP after thoracic surgery. As NMDA antagonists and steroids can modify pain pathways, and inflammatory-immune pathways, they carry the potential to prevent the development of PPSP. Since these agents act through different biological mechanisms, and we are unaware of any biological reason for a negative interaction, it is appropriate to study their effects in a factorial design. By including all patients for both interventions, factorial design RCT's are more efficient to test 2 different interventions, using a smaller sample size and making better use of study resources, in comparison to a parallel group RCT[18]. In chapter 4, we report our feasibility 2×2 factorial trial comparing NMDA antagonists versus placebo and IV steroids versus placebo, in patients having elective video-assisted thoracic surgery (VATS) lobectomies, with an aim to establish the feasibility of a large multi-centre trial. In the introduction to this chapter, we describe the potential etiological considerations and the need to look at interventions in preventing PPSP in patients having thoracic surgery. We also review the existing evidence to support our rationale for considering NMDA antagonists and steroids, as interventions to prevent PPSP in a larger RCT.

Part 3: Chronic Low Back Pain (CLBP) is very common, with a lifetime prevalence between 51 and 80%[19]. It causes significant pain, suffering, impairment of daily activities, and decreased quality of life[20]. Among chronic conditions CLBP has been noted to be the leading cause of years lived with disability[21]. The pathophysiology of CLBP is unclear in a majority of patients. Gabapentinoids (pregabalin and gabapentin) belong to the class of antiepileptic medications and act at the α-2 delta2 subunit of presynaptic voltage-dependent calcium channels, there by modulating pathologically enhanced neurotransmission in the primary afferent neurons[22]. Both of them are approved for use in neuropathic pain conditions[23,24]. Despite unclear evidence, the use of gabapentinoids (pregabalin and gabapentin) for chronic pain conditions have increased over the years[25]. This is a cause for concern as gabapentinoids have been associated with adverse effects[26], and misuse[27], and many of these indications are off-label[28]. *In chapter 5*, we describe the burden of CLBP and its etiological and treatment considerations. We also summarize the limitations of existing evidence when it comes to use of analgesic medications, apart from reporting our methodology to review the existing evidence on the use of gabapentinoids for CLBP. Our primary objectives were to assess the pain relief and safety. *In chapter 6*, we report on our systematic review and meta-analysis of RCTs assessing the benefits and safety of using gabapentinoids in CLBP.

In chapter 7, we discuss the findings arising out of all the previous chapters, in the context of our entire thesis. We propose considerations for future research and clinical practice.

PART 1: Analgesic Intervention in Acute Surgical Pain

Chapter 2: The need to evaluate the most effective opioid for day surgeries causing moderate to severe pain-a protocol for a randomized control trial

Introduction

Over the last few decades, there has been an exponential increase in the number of day surgeries. Despite advances, inadequate pain control and postoperative nausea vomiting (PONV) affects the recovery, discharge and overall satisfaction of day surgery patients. For moderate to severe pain, opioids remain the primary modality of analgesia. Considering opioid related side effects, health providers must carefully select an opioid which maximises analgesia and minimizes side effects. This chapter highlights the challenges of choosing the appropriate opioid in the context of acute surgical pain that is associated with day surgeries. It also describes the protocol and methods that were used in the randomized controlled trial comparing morphine (M) and hydromorphone (HM), with the primary objective of achieving satisfactory analgesia with minimal emesis.

Citation: Shanthanna H, Paul J, Lovrics P, Devereaux PJ, Bhandari M, Thabane L. Satisfactory Analgesia with Minimal Emesis in Day Surgeries (SAME DayS): a protocol for a randomised controlled trial of morphine versus hydromorphone. BMJ Open. 2018 Jun 22;8(6):e022504.

Open access Protocol

BMJ Open

Satisfactory Analgesia with Minimal Emesis in Day Surgeries (SAME DayS): a protocol for a randomised controlled trial of morphine versus hydromorphone

Harsha Shanthanna,[1] James Paul,[2] Peter Lovrics,[3] P J Devereaux,[4] Mohit Bhandari,[5] Lehana Thabane[6]

To cite: Shanthanna H, Paul J, Lovrics P, *et al*. Satisfactory Analgesia with Minimal Emesis in Day Surgeries (SAME DayS): a protocol for a randomised controlled trial of morphine versus hydromorphone. *BMJ Open* 2018;**8**:e022504. doi:10.1136/bmjopen-2018-022504

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-022504).

Received 22 February 2018
Revised 6 May 2018
Accepted 24 May 2018

[1]Department of Anesthesia, St Joseph's Health Care, McMaster University, Hamilton, Ontario, Canada
[2]Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada
[3]Department of Surgery, Joseph's Healthcare, McMaster University, Hamilton, Ontario, Canada
[4]Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[5]Department of Surgery, McMaster University, Hamilton, Ontario, Canada
[6]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

Correspondence to
Dr Harsha Shanthanna; shanthh@mcmaster.ca

ABSTRACT

Introduction There has been an exponential increase in the number of ambulatory surgeries (AS). Pain and postoperative nausea vomiting (PONV) affects the recovery, discharge and overall satisfaction of patients having AS. Opioids remain the primary modality for moderate to severe pain. Since there is no perfect opioid, physicians should ideally use the opioid that optimally balances benefits and risks. Present decisions on the choice between morphine (M) and hydromorphone (HM) are based on individual experience and observation. Our primary objective is to compare the proportion of patients having AS achieving satisfactory analgesia without significant PONV when using M compared with HM. Secondarily we will compare the proportion of patients with adverse events, analgesic used, patient satisfaction, time to discharge and postdischarge symptoms.

Methods and analysis This is a two-arm, multicentre, parallel group, randomised controlled trial of 400 patients having AS. Eligible patients undergoing AS of the abdominal and pelvic regions with a potential to cause moderate to severe pain will be recruited in the preoperative clinic. Using a computer-generated randomization, with a 1:1 allocation ratio, patients will be randomised to M or HM. Patients, healthcare providers and research personnel will be blinded. Study interventions will be administered in the recovery using equianalgesic doses of M or HM in concealed syringes. Patients will be followed in hospital and up to 3 months. Intention-to-treat approach will be used for analysis.

Ethics and dissemination This study has been approved by the Hamilton integrated research ethics board. We plan to publish our trial findings and present our findings at scientific meetings.

Trail registration number NCT02223377; Pre-results.

Strengths and limitations of this study

- This trial will inform the relative benefits and risks of morphine versus hydromorphone in patients having ambulatory surgeries.
- Our pragmatic design mirrors everyday practice, and this will facilitate knowledge translation and clinical applicability.
- This trial will also evaluate postdischarge symptoms, including persistent pain.
- The outcomes of pain and nausea, although measured using validated scales, suffer from their inherent subjective limitations.
- For equianalgesic dose ratio between morphine:hydromorphone, we have considered the most commonly used ratio of 1: 5, although other ratios have been reported in literature.

INTRODUCTION

The burden of pain and postoperative nausea vomiting (PONV) in ambulatory surgeries (AS)

It is estimated that currently around 70% of surgeries are being done as AS.[1] Pain and PONV are recognised as the leading factors affecting its quality of AS,[2 3] affecting the recovery, discharge and overall satisfaction of patients.[4 5] Postsurgical pain is inadequately treated in 30%–40% of patients, and 20%–30% of patients having AS suffer from significant PONV.[3 6 7] The time to discharge increases by 25% in patients having AS who develop PONV,[8] and a single episode of PONV can prolong the postanaesthetic care unit (PACU) stay by 25 min.[9] Studies also show that patients rate PONV to be the most undesirable outcome associated with anaesthesia[4] and are willing to spend up to US$100 for an effective antiemetic treatment.[10]

Opioids and the challenge of pain relief without side effects

For the management of postoperative pain, multimodal analgesia is frequently employed. Despite efforts to increase the use of other options, opioids have remained the primary modality to manage moderate to severe pain.[7] Opioids are potent analgesics. They also cause several side effects such as drowsiness, sedation, PONV, itching and respiratory depression. Morphine (M) has been

considered the gold standard long-acting opioid, used widely for postoperative analgesia; however, hydromorphone (HM) is increasingly used in many centres and settings. Both M and HM are mu agonists and exert no ceiling effect for their analgesia; frequently, incomplete or inadequate analgesia is related to the appearance of side effects. HM is approximately five times more potent, and its distribution to cerebral tissues allows for easier titration.[11] Presently, many believe that HM has a more favourable side effect profile compared with M,[12 13] and at many centres, including ours, the use of HM is preferred as the first option for patient-controlled analgesia (PCA). It is also observed that healthcare providers may be willing to provide higher doses of HM compared with M in emergency departments as the actual quantity of drug is much smaller and therefore may cause less concern.[14 15]

Literature review and limitations within the existing evidence

Our comprehensive search (up to 2016 September) involving PubMed, Embase and Cochrane databases did not identify any randomised controlled trial (RCT) comparing M and HM in patients having AS. However, we identified four studies that compared the use of intravenous M and HM in acute pain settings,[16–19] and two among them were conducted in perioperative settings.[18 19] Hong *et al* studied the difference in nausea between the two medications in 50 patients using PCA and found no difference.[19] The long-acting study drugs were administered intraoperatively, without any standardisation of anaesthetic techniques. The study was also not blinded. Rapp *et al* compared the analgesia and side effects between the two medications in 61 surgical patients using PCA. They did not include any sample size calculation and also did not specify the primary outcome; however, they found the effects to be similar.[18] Felden *et al* attempted to summarise the evidence in a systematic review and meta-analysis, published in 2013.[11] Notably, they considered the use of M versus HM in both acute and chronic pain scenarios and also as any route of administration. For acute pain, they identified seven studies out of which four used intravenous administration. For meta-analysis, using a random-effects model, they reported effect sizes as standardised difference in means using Cohen's d. They pooled acute and chronic pain studies separately. For acute pain they observed that the analgesia was better with HM than M, demonstrated by a small difference in effect size (d=−0.228, p=0.012), without any such difference in chronic pain. Based on the above literature, we feel that there is uncertainty and limited data to make reasonable conclusions for clinical practice.

Patients symptoms after discharge

It is increasingly appreciated that research and healthcare delivery have not focused enough on the postdischarge symptoms after AS. In this direction, two crucial aspects are to be considered. Compared with inpatients, patients having AS have less efficient access to health services, and it could be wrong to assume that the burden of pain, nausea and other symptoms, after patients having AS, is not substantial.[20] A significant number of patients suffer from continuing pain even at 24 hours,[21] and studies have shown that differences in anaesthetic management and choice of medications have made a difference in patients' perception of pain in AS in the first 24 hours and beyond.[22] The review by Wu *et al* has noted that only 30%–42% of studies on patients having AS assessed for pain or PONV after discharge.[20] Most were not randomised trials and many had methodological limitations. It has been observed that up to 10%–50% patients and 2%–11% patients suffer from moderate and severe level of chronic postsurgical pain (CPSP), respectively.[23] Not many studies have assessed the incidence of CPSP in AS trials. Our study will allow us to estimate the overall burden on CPSP at 3 months in patients having AS.

Clinical hypothesis

In patients who undergo AS causing at least moderate pain, HM increases the proportion of patients demonstrating '*satisfactory analgesia with minimal or no postoperative nausea-vomiting (PONV)*' (satisfactory analgesia with minimal PONV: pain=<4/10 in numerical analogue scale, with minimal or no PONV <2/5 in verbal descriptive scale) compared with M, when both are administered intravenously, in equianalgesic doses, and are compared at 2 hours or earlier after surgery, in PACU.

OBJECTIVES

The primary objective is to compare the proportion of patients with Satisfactory Analgesia and Minimal Emesis (SAME) after AS, when M is compared with HM during their stabilisation in PACU.

Secondary objectives include comparison of patients with severe itching, significant sedation and respiratory depression in PACU; comparison of time to discharge from PACU and hospital; comparison of analgesic doses used as equivalent morphine units (EMU); comparison of postdischarge symptoms of pain, nausea and vomiting within the first 24 hours; and incidence and type of CPSP at 3 months after discharge.

METHODS

Sites

The study will be conducted at three hospitals affiliated with McMaster University, Canada: St Joseph's Hospital, McMaster University Medical Centre and Juravinski Hospital.

Design

This will be a multicentre RCT with a two-arm parallel design (figure 1).

Patient selection

Patients will be screened during their 'pre-anaesthetic visit' by a trained research assistant (RA) using the following

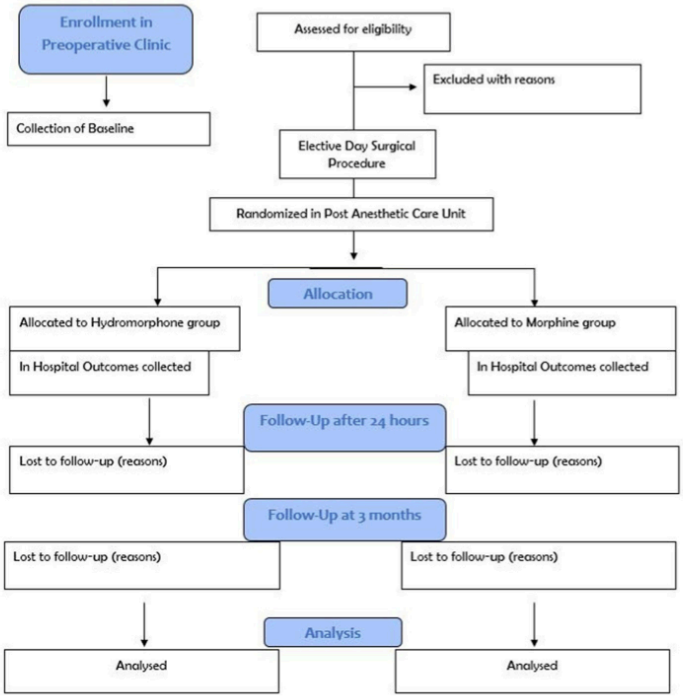


Figure 1 Satisfactory Analgesia with Minimal Emesis in Day Surgeries study Consolidated Standards of Reporting Trials flow diagram.

selection criteria. Informed consent of willing patients will be obtained along with their baseline parameters.

Inclusion criteria

Age 18–70 years; patients of elective day surgeries within the scope of general surgical, gastrointestinal and gynaecological specialties; surgeries with a potential to cause moderate to severe pain (cholecystectomy, appendectomy, ovarian cystectomy, hernia repair) and ability to communicate in English.

Exclusion criteria

Not consenting; allergy to M or HM; patients for surgeries with potential to cause minimal pain (tubectomy, diagnostic laparoscopy, dilation and curettage); surgeries with planned surgical time <1 hour; patients for orthopaedic, urological, plastic or other surgeries planned for a nerve block; patient on regular opioid medication (intake >3 days/week); severe obesity (body mass index (BMI) >35); history of schizophrenia or bipolar disease; current history of opioid drug addiction; and patients with confirmed sleep apnoea. The baseline parameters will include recording of the following variables. (1) Apfel Score (for PONV prediction) collected on four items[24]; (2) Hospital Anxiety Depression Scale score collected on 14 items[25]; (3) Pain Catastrophizing Scale collected on 13 items[26]; (4) presence of preoperative pain in the surgical area—yes/no; (5) if present: is it mild/moderate/severe; and (6) presence of chronic pain (>4 months) in other parts of the body.

Control of bias

Randomisation and allocation

Treatment allocation will be done using a random, computer-generated table, with an allocation ratio of 1:1, using random permuted block sizes, with stratification based on each centre (three sites).

Allocation concealment

Study allocation will be handled by the respective pharmacy at each hospital site and concealed by providing sequentially coded and numbered syringe packets of study medications, labelled with serial numbers and no identifiers for the medication. The study packets (containing prepared study medication syringes) will be made available in a safe drug locker within a fridge at the respective PACU.

Achievement of randomisation

The randomisation for each patient would happen on the day of surgery, inside the PACU, by allotting the next available medication packet. To ensure that the respective

patient and medication is matched for subsequent analysis, the PACU nurse will attach the medication sequence number on the patient study records and also note down the patient hospital ID on the medication record log.

Achievement of blinding

Since the medication syringes contain clear solutions of study medications in EMU units, physicians, patients, the PACU nurses and RA are effectively blinded.

Application of interventions

The operating room (OR)

Patients included in the study would be managed according to the OR protocol. Patients will have preoperative dexamethasone as an intravenous infusion. As the nature of the included surgeries demands, patients will only have a general anaesthetic, without the use of study medications. The protocol would allow for the appropriate use of sedation, intravenous or inhalational anaesthetics, and intraoperative analgesia using any short-acting opioids. The use of study medications during surgery will not be allowed. All patients will have local anaesthetic infiltration as 20–30 mL using 0.25% bupivacaine with or without epinephrine, at the end of surgery.

PACU protocol

The PACU nurse will administer the medications to provide postoperative analgesia with equianalgesic doses of M or HM, administered in titrated doses. Syringes will be pre-prepared from the pharmacy in EMU; 1 mL=1 mg of M or 0.2 mg of HM. We have considered a potency ratio of 1:5 (M:HM), considered equivalent in literature.[11] Analgesia will be provided according to the following guideline. A similar method has been advised to be safe and effective for titrated analgesia in PACU.[27]

PACU protocol (titrate the opioid medication to achieve the desired pain score)

- Patient to be asked for their pain score, and if it is >4 out of 10 (NAS): to receive the first dose within 5 min after coming to PACU: 0.04 mg/kg morphine units (rounding off to the nearest 1 mL or 0.5 mL); with a maximum of 3 mg of morphine equivalents.
- Repeat doses: 0.02 mg/kg morphine units every 5–10 min to titrate for analgesia and side effects (rounding off to the nearest 1 mL or 0.5 mL).
- If no side effects observed, titrate to have analgesia: NAS<4/10.
- PONV observed: record it and treat it with antiemetics (ondansetron 1–4 mg intravenous, dimenhydrinate 25–50 mg).
- Sedation observed (<3 Ramsay Sedation Scale)—withhold the next dose and restart the bolus if the score is >3.
- Respiratory depression: withhold the next dose, treat with naloxone if necessary.
- Use ketorolac intravenous 15–30 mg as the rescue medication if the patient does not tolerate the study opioid or if the patient does not satisfy the success of satisfactory analgesia even at 1 hour.

Day surgery unit (DSU) protocol

The DSU nurse will follow patient and collect the relevant outcomes before hospital discharge. In DSU, patients shall be offered oral analgesia (oxycocet (oxycodone+acetaminophen), or tylenol #3 (codeine+acetaminophen)) and antiemetics as necessary. Relevant secondary outcomes are noted before the discharge of patients.

Follow-up

Patients will be followed up by a phone call and a mailed letter at 24 hours post surgery and at 3 months, respectively. Participant flow through the study is shown in figure 1 (Consolidated Standards of Reporting Trials (CONSORT) flow chart).

Outcomes

Primary outcome and measurement

Proportion of patients achieving SAME, compared between the two groups, at or before 2 hours after surgery. Patient should satisfy a pain score≤4/10 in numerical rating scale (NRS) (0–10) with minimal nausea vomiting <2/4 in verbal descriptive scale (VDS). These observations will be made by the PACU nurse with clear guidance on deciding whether a patient satisfied the outcome or not.

Secondary outcomes and measurement

The following secondary outcomes will be captured during the in-hospital follow-up of study patients:

- Proportion of patients with severe itching: measured as visual analogue scale (VAS)>5/10.
- Proportion of patients with severe sedation: measured as Ramsay sedation score >3/6[28].
- Proportion of patients with respiratory depression: patients needing naloxone treatment.
- Differences in total analgesic used in PACU: mean differences in EMU.
- Differences in time to discharge (or readiness) from PACU: time in hours.
- Differences in time to discharge (or readiness) from hospital: time in hours.
- Differences in patient satisfaction scores: mean differences in 0–10 VAS.

Tertiary outcomes and measurement

All outcomes after hospital discharge will be considered as tertiary outcomes and collected at two different time points: 24 hours after surgery and at 3 months.

Outcomes at 24 hours

Patients will be approached by 1–2 phone calls done the next day; if unanswered, a repeat call will be made on the subsequent day (second day after discharge) to ask the following questions.

1. What was your average pain score over the last 24 hours in 0–10 NRS scale after you were discharged home?

Table 1 Sample size estimation

Power (beta) %	Risk of PONV with morphine (%)	Risk of PONV with hydromorphone (%)	Sample size per group
80	20	14	615
80	25	17	406
80	25	12	139
80	20	10	199
90	20	10	266

PONV, postoperative nausea vomiting.

2. After discharge, did you have nausea—severe enough to require medications at home?
3. After discharge, did you have vomiting—severe enough to require medications at home?
4. After discharged, did you require a visit to ER, or readmission?

Outcomes at 3 months

Patients will be contacted by a mailed package at 3 months after surgery to collect the following outcomes. If the mailed packages are not received after 3 months, patients will be contacted by phone to collect the outcomes of PPSP.

1. Do you have persistent pain (which started with or after surgery) at or near the surgical area? Yes/no?
2. Intensity of pain: 0–10 NRS.
3. Brief pain inventory—interference items[29]: seven items each scored between 0 and 10.
4. Global impression of change[29]: Likert scale options of 1–7.
5. Analgesic use: Did you have to use any pain medications beyond 1 month to help with pain that started with or after surgery?

ANALYSIS

Sample size estimation (table 1)

This was estimated based on the primary binary outcome of proportion of patients with SAME compared using a χ^2 test. According to literature, approximately 30%–40% of patients suffer from inadequate analgesia after their AS, with a similar number also known to suffer from PONV.[3 7] Our chart review at our hospital suggested that approximately 20% of patients suffer from inadequate analgesia with PONV using M. For a two-sided test, a sample size of 199 per group will have 80% power to detect a statistically significant difference of 10% or more using a χ^2 test, with an alpha of 0.05 (table 1). For the primary outcome analysis, we expect minimal loss through attrition as randomisation would happen after surgery (confirming that patients fit the criteria) and the study involves a follow-up within the hospital. By rounding off we set a target of 200 per group for a total of 400 patients. This was estimated using power and sample size software program by Vanderbilt University (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize#PS:_Power_and_Sample_Size_Calculation), V.3.0.43.

Statistical analysis

The trial will be reported as per the CONSORT standards for reporting randomised trials.[30] The study will be analysed using an intention-to-treat (ITT) approach. For ITT, we will analyse patients within their randomised groups. We will use multiple imputation strategy to account for missing outcomes in ITT. Since we used a randomisation stratified on the basis of site, binary outcomes will be compared using Mantel-Haenszel χ^2 test and continuous outcomes using analysis of variance (ANOVA).[31] Among the baseline variables, higher BMI, higher Apfel score, anxiety, depression, catastrophising, presence of moderate to severe preoperative pain in the surgical area and presence of chronic pain in other parts of the body are known to be associated with higher pain or increased chances of PONV.[32] Similarly, intraoperative factors such as dose of dexamethasone, total intraoperative opioid used (morphine equivalents), duration and type of surgery (laparoscopic vs open) are known to influence postoperative outcomes of analgesia and PONV. Sensitivity analysis will be conducted to explore the influence of these factors on the outcomes with multivariable logistic analysis using logistic regression for binary outcomes and linear regression continuous outcomes. For the regression model, we will use appropriate interaction terms between the subgroup variable and the treatment group. We will check for the residual to assess model assumptions and goodness of fit. Up-to-date versions of SAS and SPSS will be used to conduct all analyses. For all analyses, we will use a two-sided test with alpha=0.05 for significance. Dichotomous outcomes will be reported as relative risk and relative risk reductions and continuous outcomes as difference in means with SD. Precision will be reported using 95% CI. List of outcomes and their analysis is provided in table 2.

Project coordination and reporting

This trial will be coordinated from the research office, Department of Anesthesia, and conducted at three hospital sites affiliated with McMaster University, Hamilton: St Joseph's Hospital, McMaster University Medical Centre and Juravinski Hospital.

Data management and quality control

All study data including case record forms (CRFs) of each patient shall be securely stored at the central office. A summary table indicating study timeline from enrolment to final follow-up (http://www.spirit-statement.org/title/) shall be included for each patient. CRFs will be collected as paper forms. They shall be periodically cross-checked for completeness and entered into a suitable electronic master file. All reports of incorrect randomisations, protocol violations or incomplete data shall be noted.

Table 2 List of outcomes, measurement and analysis

Outcome measure	Measurement	Time of measurement	Analysis method
Primary outcome			
Satisfactory analgesia with minimal PONV	Number of patients with NRS<4/10 and VDS<2/5	At 2 hours or at the time of discharge from PACU	M-H χ^2
Secondary outcomes			
Severe itching	Number of patients with VAS>5/10	At 2 hours or at the time of discharge from PACU	M-H χ^2 or Fisher's test
Severe sedation	Number of patients with Ramsay score>3/6	At 2 hours or at the time of discharge from PACU	M-H χ^2 or Fisher's test
Severe respiratory depression	Number of patients needing treatment	At 2 hours or at the time of discharge from PACU	M-H χ^2 or Fisher's test
Use of rescue analgesia	Total dose used per patients as a rescue therapy	At 2 hours or at the time of discharge from PACU	ANOVA
Mean dose of opioid analgesic used in PACU	Dose of analgesic used per patient in EMU	At the time of hospital discharge	ANOVA
Patient satisfaction—mean score (0–10)	VAS 0–10 0=completely unsatisfied; 10=extremely satisfied	At the time of hospital discharge	ANOVA
Time to discharge from PACU (discharge readiness)	Mean time in hours	At 2 hours or at the time of discharge from PACU	ANOVA
Time to discharge from the hospital (discharge readiness)	Mean time in hours	At the time of hospital discharge	ANOVA
Tertiary outcomes			
Average pain score over the last 24 hours	Comparison of mean pain scores NRS 0–10	24 hours after surgery	ANOVA
Nausea severe enough to need treatment after discharge	Number of patients	24 hours after surgery	M-H χ^2 or Fisher's test
Vomiting severe enough to need treatment after discharge	Number of patients	24 hours after surgery	M-H χ^2 or Fisher's test
Requiring a ER visit or readmission	Number of patients	24 hours after surgery	M-H χ^2 or Fisher's test
Persistent pain in the surgical area	Number of patients	3 months after surgery	M-H χ^2 or Fisher's test
Intensity of pain	NRS 0–10	3 months after surgery	M-H χ^2 or Fisher's test
Interference in daily activities	Comparison of mean BPI seven items with 0–10 scale	3 months after surgery	ANOVA
Global impression of change	0–7 Likert scale	3 months after surgery	M-H χ^2 or Fisher's test
Analgesic use for>1 month	Number of patients	3 months after surgery	M-H χ^2 or Fisher's test
Sensitivity analysis			
Adjusting for baseline and surgical covariates			Multivariable regression

ANOVA, analysis of variance; EMU, equivalent morphine units; ER, emergency room; M-H, Mantel-Haenszel; NRS, numerical rating scale; PACU, postanaesthetic care unit; PONV, postoperative nausea vomiting; VAS, visual analogue scale; VDS, verbal descriptive scale.

Risk assessment and protocol adherence

This trial does not entail any higher risk than the standard of care to the patients. This is a pragmatic trial and involves the use of medications of known benefit and in clinically acceptable doses. It also involves use of intraoperative short-acting opioids in the form of fentanyl or sufentanil or remifentanil in small boluses or infusion. Although this may be a slight departure from the normal practice for some, we do not anticipate this to be a major issue as the surgeries would be of 1–2 hours duration. Patients can be effectively and safely managed with short-acting opioids until patients are shifted to PACU. The protocol also involves the use of study medications in PACU at an initial dose of 0.05 mg/kg, followed by 0.03/mg/kg EMU boluses. Studies have shown that intravenous morphine titration in PACU after moderately painful surgeries requires a mean morphine dose of 0.17±0.10 mg/kg.[33] Only doses as high as 0.15 mg/kg were found to be associated with significant adverse effects.

Patient and public involvement

Patients and public were not directly involved in the development of this study protocol. However, our study outcomes were guided by patient preferences expressed in previous studies, especially as it concerns AS. We will disseminate results to the study participants through the journal publication, as well as from our research website.

DISCUSSION

This RCT looks at the use of M and HM in patients having AS and compares the clinical effectiveness in achieving effective analgesia with minimal PONV. It allows for physicians to make a choice based on evidence rather than individual observations. The perceived advantages of the study include better analgesia, fewer side effects, early discharge, reduced use of medications, less overall cost and better patient satisfaction. These are noted to be reflective of the most ideal outcomes for a AS setting. The study will also provide an estimate of incidence of pain, nausea and vomiting after discharge, within the first 24 hours after surgery, and PPSP at 3 months.

Potential pitfalls

The primary outcome of SAME is being measured using subjective pain scale of NRS and VDS for nausea vomiting. Although there are inherent limitations of such scales, they are widely used in practice and are well validated. For equianalgesic dose ratio between M:HM, we have considered the most commonly used ration of 1:5, although other ratios have been reported in literature.

ETHICS AND DISSEMINATION

The study has been approved by the Hamilton integrated research ethics board. We plan to report and publish our study findings in a high-impact medical journal, with online access. We also to plan to present it in select conferences and scientific meetings.

Acknowledgements The authors thank Toni Tidy, Geoff Travis, Diane Buckley, Raffy Gutman, Anne Clark and Helen Akinboule for their contributions as research coordinators working for this project. They sincerely thank their research pharmacists Christine Wallace and Gita Sobhi for their assistance. They also thank the dedicated team of nurses working in the postanaesthetic recovery units and the day surgery units for their involvement and support in this study.

Contributors HS: primary investigator involved in the study design, protocol writing and study conduct. JP: co-primary investigator involved in the study design, protocol writing and study conduct. PL: co-investigator involved in protocol writing and study conduct. PJD, MB and LT: co-investigators involved in assisting with study methodology, protocol writing, supervision and interpretation of the trial.

Funding The study was supported by AbbVie New Investigator Award in Anesthesia (2014), Canadian Anesthesiologists' Society; and the Department of Anesthesia, McMaster University, Canada. The primary investigator, Harsha Shanthanna, was supported by the Canadian Institute of Health Research (CIHR) RCT mentoring stipend grant award between March 2017 and February 2018.

Competing interests None declared.

Patient consent Not required.

Ethics approval Hamilton Integrated Research Ethics Board, McMaster University, Canada.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Sarin P, Philip BK, Mitani A, *et al*. Specialized ambulatory anesthesia teams contribute to decreased ambulatory surgery recovery room length of stay. *Ochsner J* 2012;12:94–100.
2. Troy AM, Cunningham AJ. Ambulatory surgery: an overview. *Curr Opin Anaesthesiol* 2002;15:647–57.
3. Shnaider I, Chung F. Outcomes in day surgery. *Curr Opin Anaesthesiol* 2006;19:622–9.
4. Macario A, Weinger M, Carney S, *et al*. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg* 1999;89:652–8.
5. Chatterjee S, Rudra A, Sengupta S. Current concepts in the management of postoperative nausea and vomiting. *Anesthesiol Res Pract* 2011;2011:1–10.
6. Lovatsis D, José JB, Tufman A, *et al*. Assessment of patient satisfaction with postoperative pain management after ambulatory gynaecologic laparoscopy. *J Obstet Gynaecol Can* 2007;29:664–7.
7. White PF. Pain management after ambulatory surgery - where is the disconnect? *Can J Anaesth* 2008;55:201–7.
8. Chung F, Mezei G. Factors contributing to a prolonged stay after ambulatory surgery. *Anesth Analg* 1999;89:1352–9.
9. Habib AS, Chen YT, Taguchi A, *et al*. Postoperative nausea and vomiting following inpatient surgeries in a teaching hospital: a retrospective database analysis. *Curr Med Res Opin* 2006;22:1093–9.
10. Gan T, Sloan F, Dear GL, *et al*. How much are patients willing to pay to avoid postoperative nausea and vomiting? *Anesth Analg* 2001;92:393–400.
11. Felden L, Walter C, Harder S, *et al*. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. *Br J Anaesth* 2011;107:319–28.
12. Maxwell LG, Kaufmann SC, Bitzer S, *et al*. The effects of a small-dose naloxone infusion on opioid-induced side effects and analgesia in children and adolescents treated with intravenous patient-

controlled analgesia: a double-blind, prospective, randomized, controlled study. *Anesth Analg* 2005;100:953–8.
13. Karl HW, Tyler DC, Miser AW. Controlled trial of morphine vs hydromorphone for patient-controlled analgesia in children with postoperative pain. *Pain Med* 2012;13:1658–9.
14. Aubrun F, Mazoit JX, Riou B. Postoperative intravenous morphine titration. *Br J Anaesth* 2012;108:193–201.
15. Patanwala AE, Keim SM, Erstad BL. Intravenous opioids for severe acute pain in the emergency department. *Ann Pharmacother* 2010;44:1800–9.
16. Chang AK, Bijur PE, Meyer RH, *et al*. Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial. *Ann Emerg Med* 2006;48:164–72.
17. Chang AK, Bijur PE, Baccelieri A, *et al*. Efficacy and safety profile of a single dose of hydromorphone compared with morphine in older adults with acute, severe pain: a prospective, randomized, double-blind clinical trial. *Am J Geriatr Pharmacother* 2009;7:1–10.
18. Rapp SE, Egan KJ, Ross BK, *et al*. A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* 1996;82:1043–8.
19. Hong D, Flood P, Diaz G. The side effects of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* 2008;107:1384–9.
20. Wu CL, Berenholtz SM, Pronovost PJ, *et al*. Systematic review and analysis of postdischarge symptoms after outpatient surgery. *Anesthesiology* 2002;96:994–1003.
21. Odom-Forren J, Rayens MK, Gokun Y, *et al*. The relationship of pain and nausea in postoperative patients for 1 week after ambulatory surgery. *Clin J Pain* 2015;31:845-51.
22. Ogurlu M, Sari S, Küçük M, *et al*. Comparison of the effect of propofol and sevoflurane anaesthesia on acute and chronic postoperative pain after hysterectomy. *Anaesth Intensive Care* 2014;42:365–70.
23. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006;367:1618–25.
24. Apfel CC, Philip BK, Cakmakkaya OS, *et al*. Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? *Anesthesiology* 2012;117:475–86.
25. McIntosh S, Adams J. Anxiety and quality of recovery in day surgery: A questionnaire study using Hospital Anxiety and Depression Scale and Quality of Recovery Score. *Int J Nurs Pract* 2011;17:85–92.
26. Gramke HF, de Rijke JM, van Kleef M, *et al*. Predictive factors of postoperative pain after day-case surgery. *Clin J Pain* 2009;25:455–60.
27. Schug SA, Chong C. Pain management after ambulatory surgery. *Curr Opin Anaesthesiol* 2009;22:738–43.
28. Ding L, Zhang H, Mi W, *et al*. Effects of dexmedetomidine on anesthesia recovery period and postoperative cognitive function of patients after robot-assisted laparoscopic radical cystectomy. *Int J Clin Exp Med* 2015;8:11388–95.
29. Dworkin RH, Turk DC, Farrar JT, *et al*. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;113(1-2):9–19.
30. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010;152:726–32.
31. Kahan BC, Morris TP. Adjusting for multiple prognostic factors in the analysis of randomised trials. *BMC Med Res Methodol* 2013;13:99.
32. Ip HY, Abrishami A, Peng PW, *et al*. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology* 2009;111:657–77.
33. Aubrun F, Amour J, Rosenthal D, *et al*. Effects of a loading dose of morphine before i.v. morphine titration for postoperative pain relief: a randomized, double-blind, placebo-control study. *Br J Anaesth* 2007;98:124–30.

Chapter 3: Comparison of Morphine and Hydromorphone in Same Day Surgeries

Introduction

Opioids remain the mainstay therapy for post-surgical pain. Although both morphine and hydromorphone are potent analgesics, it has been suggested that hydromorphone is clinically better. We performed a multicentre RCT in 402 patients having ambulatory surgery. Our primary objective was to compare morphine with hydromorphone for achieving satisfactory analgesia with minimal emesis (SAME). A random computer-generated allocation, stratified by site, was developed by our pharmacy. Concealment was achieved by allocating patients to study groups by nurses using sequentially coded study medication syringes having equi-analgesic doses, made available in the postoperative recovery room. Patients, health providers, and research personnel were blinded. The operating-room protocol allowed for routine anaesthetic management, excluding the use of study medications. Study medications were administered by recovery nurses as per an algorithm. Analyses utilised the intention-to-treat principle, and regression analyses were used for outcomes as appropriate and using multiple imputation. Of 751 patients, 402 were randomised between morphine (n=199) and hydromorphone (n=203). Baseline and intraoperative variables were comparable across the groups. The odds of achieving SAME were similar between the groups (odds ratio: 1.01; 95% confidence interval: 0.57–1.80). There were no differences in the side-effects of severe itching, respiratory depression, or sedation. Patient satisfaction, discharge times, and post-discharge outcomes, including pain and nausea/vomiting over 24 h, were also comparable. We conclude that there is no difference between morphine and hydromorphone regarding analgesia and common side-effects. The appearance of dose-limiting side-effects is idiosyncratic; the clinical decision must be based on individual responses.

Citation: Shanthanna H, Paul J, Lovrics P, Vanniyasingam T, Devereaux PJ, Bhandari M, Thabane L. Satisfactory analgesia with minimal emesis in day surgeries: a randomised controlled trial of morphine versus hydromorphone. Br J Anaesth. 2019 Jun;122(6):e107-e113.

BJA

British Journal of Anaesthesia, 122 (6): e107–e113 (2019)

doi: 10.1016/j.bja.2019.03.036
Advance Access Publication Date: 23 April 2019
Clinical Trials

Satisfactory analgesia with minimal emesis in day surgeries: a randomised controlled trial of morphine versus hydromorphone

H. Shanthanna[1,*], J. Paul[2], P. Lovrics[3], T. Vanniyasingam[2], P. J. Devereaux[4], M. Bhandari[5] and L. Thabane[4]

[1]Department of Anesthesia, St Joseph's Healthcare, McMaster University, Canada, [2]Department of Anesthesia, McMaster University, Canada, [3]Department of Surgery, St Joseph's Healthcare, McMaster University, Canada, [4]Departments of Health Research Methods, Evidence, and Impact and Medicine, McMaster University, Canada and [5]Department of Surgery, McMaster University, Hamilton, ON, Canada

*Corresponding author. E-mail: shanthh@mcmaster.ca

Background: Opioids remain the mainstay therapy for post-surgical pain. Although both morphine and hydromorphone are potent analgesics, it has been suggested that hydromorphone is clinically better. Our primary objective was to compare morphine with hydromorphone for achieving satisfactory analgesia with minimal emesis (SAME).
Methods: We performed a multicentre RCT in 402 patients having ambulatory surgery. A random computer-generated allocation, stratified by site, was developed by our pharmacy. Concealment was achieved by allocating patients to study groups by nurses using sequentially coded study medication syringes having equi-analgesic doses, made available in the postoperative recovery room. Patients, health providers, and research personnel were blinded. The operating-room protocol allowed for routine anaesthetic management, excluding the use of study medications. Study medications were administered by recovery nurses as per an algorithm. Analyses utilised the intention-to-treat principle, and regression analyses were used for outcomes as appropriate and using multiple imputation.
Results: Of 751 patients, 402 were randomised between morphine (n=199) and hydromorphone (n=203). Baseline and intraoperative variables were comparable across the groups. The odds of achieving SAME were similar between the groups (odds ratio: 1.01; 95% confidence interval: 0.57–1.80). There were no differences in the side-effects of severe itching, respiratory depression, or sedation. Patient satisfaction, discharge times, and post-discharge outcomes, including pain and nausea/vomiting over 24 h, were also comparable.
Conclusions: There was no difference between morphine and hydromorphone regarding analgesia and common side-effects. The appearance of dose-limiting side-effects is idiosyncratic; the clinical decision must be based on individual responses.
Clinical trial registration: NCT02223377.

Keywords: ambulatory surgery; analgesics; opioid; hydromorphone; morphine; postoperative nausea and vomiting; side-effects

Editorial decision: 24 March 2019; **Accepted:** 24 March 2019

Editor's key points

- Both morphine and hydromorphone are potent opioid analgesics used to treat postoperative pain, but it has been suggested that hydromorphone is clinically better.
- These two opioids were compared in a multicentre RCT in ambulatory surgery patients for their ability to achieve satisfactory analgesia with minimal emesis.
- There was no difference between morphine and hydromorphone in their analgesic and common side-effects.
- The relative analgesic potency of hydromorphone appears more than five-fold higher than that of morphine.

In most centres, greater than 70% of surgeries are performed as ambulatory surgeries.[1] Uncontrolled pain and postoperative nausea and vomiting (PONV) continue to affect the recovery, discharge, and overall satisfaction of patients having ambulatory surgeries.[2,3] Post-surgical pain is inadequately treated in 30–40% of patients,[3–5] and patients report PONV to be the most undesirable outcome associated with anaesthesia.[6] Despite being potent analgesics, opioids have several side-effects, including drowsiness, sedation, PONV, itching, and respiratory depression. Both morphine (M) and hydromorphone (HM) are potent long-acting analgesics. HM is approximately five times more potent, and many believe that HM has a more favourable side-effect profile compared with M.[7] It has been observed that health providers could administer higher doses of HM compared with M, as the actual quantity of drug is much smaller, and it may cause fewer side-effects.[8,9]

A 2013 systematic review and meta-analysis summarised the existing evidence comparing M with HM for acute and chronic pain via any route of administration.[10] Only four of the seven acute pain studies involved i.v. administration. They observed that analgesia was better with HM than M, with a small difference in effect size (Cohen's d=−0.228; P=0.012), and without any difference in chronic pain. Existing studies are small and limited, and have considered analgesic effectiveness as an average group effect rather than an individual patient-level effect.[11] Hence, they do not allow for confident conclusions for clinical practice, leading to treatment choices based on individual perceptions rather than on evidence.

We did not identify any RCT comparing M and HM in ambulatory surgery patients in a comprehensive search (up to September 2016) involving PubMed, Embase, and Cochrane databases. Our hypothesis was, in patients having ambulatory surgeries causing moderate-to-severe pain, analgesic therapy with HM increases the proportion of patients achieving a state of 'satisfactory analgesia with minimal emesis' (SAME) compared with M. To test our hypothesis, we administered study medications intravenously in equi-analgesic doses in the PACU. SAME was defined as pain ≤4/10 in a numerical rating scale (NRS) with PONV <2/4 in a verbal descriptive scale (VDS). The primary objective of the trial was to compare the proportion of patients achieving SAME during their stabilisation in the PACU. The secondary objectives included incidence of severe itching, significant sedation, and respiratory depression in the PACU; analgesic doses used as equivalent M units (EMUs); time to discharge from PACU and hospital; and patient satisfaction at discharge. As tertiary objectives, we compared the post-discharge symptoms of pain, nausea/vomiting, and need for emergency room visit or readmission within 24 h.

Methods

Complete details of the study rationale and methods are provided in our published protocol.[11] The trial is registered in clinicaltrials.gov as NCT02223377, and was approved by the Hamilton Integrated Research Ethics Board. This multicentre trial utilised a two-arm parallel design to randomise patients at three hospitals affiliated with McMaster University, Hamilton, ON, Canada.

For each day, the pre-anaesthetic clinic list was screened for potential patients based on available surgical information. Potential subjects were screened in person based on our selection criteria during their pre-anaesthetic visit, and informed consent was obtained from willing patients along with their baseline parameters. Patients who were 18–70 yr old with an ability to communicate in English and having elective day surgeries with a potential to cause moderate-to-severe pain were included. Patients were excluded if they had an allergy to either study medication, were undergoing a surgery with a planned surgical time <1 h, a planned anaesthetic of a nerve block or neuraxial technique (such as orthopaedic, urological, and plastic), a history of regular opioid usage (intake >3 days $week^{-1}$ for the past 3 months), severe obesity (BMI >35), history of schizophrenia or bipolar disease, current history of opioid drug addiction, and confirmed sleep apnoea. At the preoperative visit, we recorded the (i) Apfel score (for PONV prediction)[12]; (ii) Hospital Anxiety and Depression Scale score[13]; (iii) Pain Catastrophizing Scale[14]; (iv) presence of preoperative pain in the surgical area; (v) if present, is it mild/moderate/severe; and (vi) presence of chronic pain (>3 months) in other parts of the body.

Measures to minimise potential bias

Treatment allocation was done using a random, computer-generated table, with an allocation ratio of 1:1, using random permuted block sizes, with stratification based on each centre (three sites). The final study enrolment and allocation were performed at PACU, determined by their sequence of entry. Sequentially numbered syringe packets of study medications, matched to their randomised allocation, were prepared by the pharmacy, without other identifiers. Based on the number of study subjects for a day, these packets (containing prepared study medication syringes) were made available in a safe drug locker within a refrigerator at the respective PACU. Randomisation was achieved by PACU nurses picking the next available study packet and allocating it to the next subject in sequence. The nurses were not aware of the allocation sequence, and were also blinded to study medications.

To ensure that the respective subject and medication were matched for subsequent analysis, the PACU nurse attached the medication sequence number on the subject study records, and also noted the hospital identification on the medication record log. Randomisation after surgery allowed for excluding patients whose surgical plan changed during the course of the operation (admission), or in case the anaesthetist did not follow the operating room study protocol. As the medication syringes contained clear solutions of study medications in EMUs, the physicians, patients, PACU nurses, and

research assistant were effectively blinded. Details of the operating-room protocol are shown in our published protocol.[11] All subjects had a general anaesthetic, without the use of study medications. The protocol allowed for the appropriate use of sedation, i.v. or inhalational anaesthetics, and intraoperative analgesia using small boluses of short-acting opioids (remifentanil, sufentanil, or fentanyl) or remifentanil infusion. All patients had local anaesthetic infiltration of bupivacaine 0.25%, 20–30 ml with or without epinephrine at the end of surgery.

Interventions

The PACU nurse administered study medications as equi-analgesic doses of either M or HM titrated according to clinical needs (Supplementary Appendix S1). Syringes were pre-prepared by the pharmacy with EMU considered as 1 ml=M 1 mg or HM 0.2 mg.[10] Analgesia was based on the literature that has been reported as safe and effective in the PACU.[15] The day surgery unit (DSU) nurse caring for the subject subsequently offered oral analgesia (oxycodone+paracetamol [Oxycocet®, Teva, Canada], or codeine+paracetamol [Tylenol No. 3®, Janssen. Inc, ON, Canada]) as necessary. Relevant study outcomes were collected in the PACU and DSU.

Outcomes

The primary outcome of SAME was defined as the proportion of subjects achieving SAME (pain score ≤4/10 in NRS [0–10] with minimal nausea/vomiting <2/4 in VDS [0–4]), at or before 2 h after surgery. The VDS represents five categories and is scored as 0=no nausea, 1=mild nausea (no treatment needed), 2=moderate nausea or retching (may need treatment), 3=frequent vomiting (controlled with anti-emetics), and 4=severe vomiting (uncontrolled with anti-emetics).[16] PACU nurses would continuously observe the subject for achieving a stable state of SAME for 30 min or more within the first 2 h, before they were transferred out of PACU. If the patient could not be transferred, despite being stable and ready, the time for readiness to PACU discharge was noted. The secondary outcomes included the proportion of subjects with severe itching, severe sedation, and respiratory depression; differences in total analgesic used in PACU; differences in time to discharge (or readiness) from PACU and hospital; and differences in patient satisfaction scores. Post-discharge outcomes of average pain over the past 24 h (0–10 NRS), nausea and vomiting severe enough needing treatment, and any need for emergency room visit or readmission after discharge were collected by a telephone call 24 h after the start of surgery (next day).

Statistical analysis

The sample size was estimated based on the primary outcome of proportion of patients with SAME. Approximately 30–40% of patients suffer from inadequate analgesia and PONV after their ambulatory surgeries.[3 5] Our chart review suggested that ~20% of patients suffer from inadequate analgesia with PONV using M. We estimated that, for a two-sided test, a sample size of 199 subjects per treatment group would have 80% power to detect a statistically significant difference of 10% or more using a χ^2 test, with an alpha of 0.05. This was estimated using power and sample size software program by Vanderbilt University (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize#PS:_Power_and_Sample_Size_Calculation), version 3.0.43. We expected a minimal loss through attrition, as randomisation would happen after surgery and the study involved a follow-up within the hospital. By rounding off, we set a target of 200 per group for a total of 400 patients.

We followed the Consolidated Standards of Reporting Trials standards for reporting randomised trials,[17] and analysed using an intention-to-treat approach. Baseline and intraoperative characteristics are presented according to treatment group using descriptive statistics: counts and percentages for categorical variables, mean and standard deviation (SD) for normal continuous variables, and median and quartiles for non-normal continuous variables. Multiple imputation was applied for missing values in the primary and secondary outcomes, with a total of five imputed data sets created and assuming that the data were missing at random. Regression analyses was conducted to determine the association between treatment groups (reference level: M group) and each outcome. Centre was adjusted for in each regression model to account for the stratified randomisation approach. Logistic regression was conducted for binary outcomes and linear regression for the continuous outcomes. For all analyses, we used a two-sided test with α=0.05 designated as significant. Dichotomous outcomes were reported as counts and percentages for each treatment group, and odds ratio (OR) to compare between groups; continuous outcomes as means or medians with SD or inter-quartile range (Q1, Q3) for each group; and difference in means or medians to compare between groups. Precision was reported using 95% confidence intervals (CIs). Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA) and SPSS (IBM SPSS Statistics for Windows, version 25.0; IBM Corp., Armonk, NY, USA).

Results

Of 751 potentially eligible patients, 455 patients were enrolled and 402 patients were randomised into the study (Fig. 1). Recruitment was from February 4, 2015 to May 10, 2018. Although we avoided randomising patients in which the intraoperative protocol was not followed (when the study drug was mistakenly given in the OR), one such patient was randomised and was subsequently missed to follow-up for study outcomes. The baseline subject characteristics and relevant intraoperative variables are shown in Tables 1 and 2. The comparison of surgical types is shown in Supplementary Appendix S2. The mean anxiety scores were relatively higher compared with the depression scores, but were very similar between groups. A substantial proportion of subjects (83%) had preoperative pain at the operative site, and nearly one-third reported chronic pain in other parts of the body in both groups. A dose of dexamethasone 4 mg i.v. was considered in the first draft of the protocol to potentiate the anti-emetic effect whilst avoiding potential analgesic effects. However, the available supply of dexamethasone for use was 8 mg as an 0.8 ml solution in a 2 ml syringe. As this results in some variation in administration, we amended the protocol to allow for 8 mg i.v. (entire syringe), and to control for its effect on the primary outcome in regression analysis.

Primary outcome

The odds of achieving SAME were similar between the groups with an OR of 1.00 (95% CI: 0.56, 1.78). In both groups, 14% of

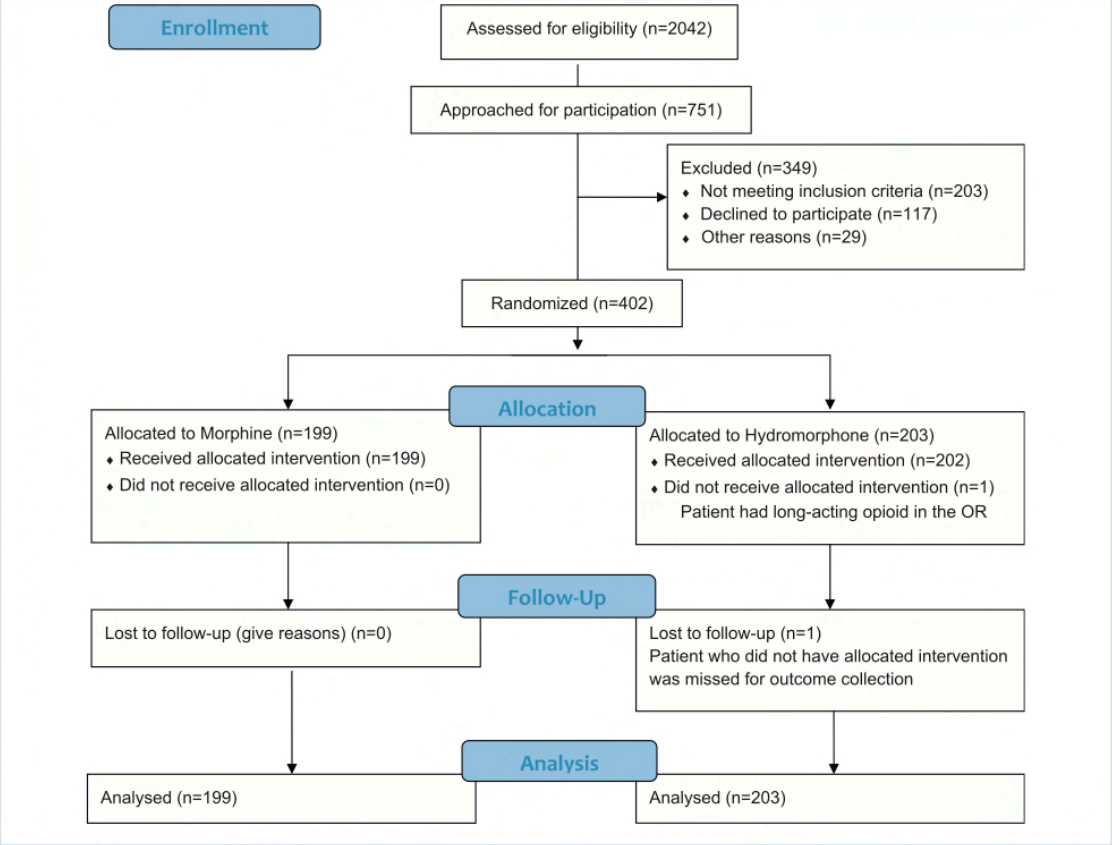


Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) 2010 flow chart.

Table 1 Baseline characteristics of study subjects. Q1, Q3, inter-quartile range; SD, standard deviation.

Variable	Hydromorphone (*n*=203)	Morphine (*n*=199)
Age (yr); mean (SD)	47.1 (14.0)	46.1 (13.8)
Female, *n* (%)	126 (62)	132 (66)
BMI, mean (SD)	27.06 (4.27)	27.55 (4.00)
Apfel score, mean (SD)	2.5 (1.0)	2.6 (0.9)
Depression score, median (Q1, Q3)	2 (1, 4)	2 (1, 5)
Anxiety score, median (Q1, Q3)	6 (3, 8)	6 (4, 9)
Catastrophising score, median (Q1, Q3)	10 (4, 17)	9 (2, 17)
Preoperative pain in the operative area, *n* (%)	83 (41)	83 (42)
Chronic pain in other areas, *n* (%)	33 (16)	35 (18)

Table 2 Intraoperative variables of study subjects. *All opioids used during surgery were converted into equivalent morphine units. Q1, Q3, inter-quartile range; SD, standard deviation.

Variable	Hydromorphone (*n*=203)	Morphine (*n*=199)
Type of surgery, *n* (%)		
Laparoscopic	185 (91)	194 (97)
Open	18 (9)	5 (2.5)
Duration of surgery (min); median (Q1, Q3)	52 (34, 74)	51 (36, 68)
Dose of dexamethasone (mg), *n* (%)		
4	77 (38)	87 (44)
8	126 (62)	112 (56)
Dose of intraoperative opioid in morphine equivalents; * median (Q1, Q3)	30 (22, 35)	30 (22, 35)

Table 3 Comparison of outcomes from surgery to discharge from hospital*Estimate has been calculated using imputed analysis. †Natural log transformation for regression analysis. ‡P-value reported based on unadjusted non-parametric Mann–Whitney U-test. . CI, confidence interval; EMU, equivalent morphine unit; SAME, satisfactory analgesia with minimal emesis; SD, standard deviation.

Outcome	Hydromorphone	Morphine	Estimate* (95% CI); P-value
SAME, n (%)	175 (87); n=202	172 (86); n=199	1.00 (0.56, 1.78); 0.997
Severe itching, n (%)	5 (2.4); n=202	2 (1.0); n=199	Not enough events to estimate
Severe sedation, n (%)	8 (4.0); n=202	5 (2.5); n=199	Not enough events to estimate
Respiratory depression, n (%)	10 (5.0); n=202	11 (5.5); n=199	Not enough events to estimate
Opioid analgesia used in PACU as EMU; mean (SD)	4.9 (3.3); n=202	5.7 (3.9); n=199	−0.73 (−1.43, −0.03); 0.040
Patients requesting oral analgesic in day surgery unit, n (%)	135 (68); n=199	128 (66); n=194	1.11 (0.73,1.70); 0.630
Discharge time from PACU (min);† mean (SD)	92.8 (50.6); n=201	91.2 (58.6); n=198	0.01 (−0.07, 0.09); 0.870
Discharge time from hospital (h); mean (SD)	3.3 (1.1); n=197	3.2 (1.1); n=199	0.03 (−0.03, 0.09); 0.267
Patient satisfaction score at discharge; mean (SD)	9.3 (1.2); n=177	9.1 (1.8); n=184	0.842‡

patients failed to achieve the primary objective of satisfactory analgesia, or suffered from significant PONV or both (Table 3).

Secondary outcomes

Only seven and 13 subjects had severe itching and severe sedation, respectively, and they were comparable between the groups. The proportion of subjects having respiratory depression needing treatment was also comparable between the groups. However, the total opioid analgesia used when considered in an EMU ratio of 5:1 (HM:M) was significantly less in the HM group: −0.73 (95% CI: −1.43, −0.03). The proportion of subjects requesting oral analgesia in each group was nearly equal. There were 41 subjects in whom patient satisfaction scores were not collected and the distribution was heavily skewed. Hence, a Mann–Whitney U-test for non-parametric distribution was conducted to report a P-value. Subjects in both groups achieved a very good satisfaction score, and had similar times of discharge from PACU and from the hospital. There were no other major side-effects or adverse outcomes relevant to the study.

Outcomes after discharge

We were able to collect these outcomes in 81% subjects in the HM group and 84% in the M group. As these were tertiary outcomes and we had larger missed outcomes, we performed a complete case analysis. As shown in Table 4, the average pain scores were similar and the proportion of subjects needing treatment for nausea was similar. Although more subjects in the HM group had vomiting requiring treatment, the events were not adequate for an adjusted logistic regression analysis. Only nine of 332 subjects required readmission or visits back to the hospital within 24 h.

Discussion

Despite the differences in pharmacokinetic properties between M and HM, a similar proportion of subjects achieved a state of SAME in our trial involving patients having ambulatory surgeries causing moderate-to-severe pain. The differences in other opioid-related side-effects in hospital and after discharge up to 24 h were comparable. As the existing literature is unclear about the choice of long-acting opioid to be used in the PACU, our trial provides clear evidence that HM is not superior to M for providing analgesia or in relation to the appearance of side-effects. The significant difference in total opioid needed in PACU suggests that the potency of HM is more than five times that of M.

Morphine continues to be the most widely available opioid across the world, and is the only long-acting opioid that gets mentioned in the latest WHO list of essential medicines for perioperative analgesia.[18] However, pharmacokinetic characteristics suggest that HM is not only more potent than M, but its composition leads to greater distribution within the brain leading to easier titration and better tolerance.[19] Our finding is in contrast to the review and meta-analysis reporting that HM is more advantageous than M for acute pain when compared for pain scores.[10] The existing studies that have compared the use of M and HM in surgical patients for i.v. administration are small and have methodological limitations.[20,21] Two studies have compared the epidural use of M and HM for acute pain. Although analgesia was comparable, the adverse effects of itching and respiratory depression were significantly more

Table 4 Comparison of outcomes 24 h after surgery. *Estimate has been calculated using a complete case analysis. CI, confidence interval; SD, standard deviation.

Outcomes	Hydromorphone (n=164)	Morphine (n=168)	Estimate* (95% CI); P-value
Average pain score over the last 24 h; mean (SD)	4.3 (2.2)	4.1 (2.2)	0.23 (−0.24, 0.71); 0.340
Vomiting (severe enough needing treatment), n (%)	11 (6.7)	5 (3.0)	Not enough events
Nausea (severe enough needing treatment), n (%)	19 (12)	16 (9.5)	1.20 (0.59, 2.44); 0.613
Emergency-room visit or readmission after discharge, n (%)	5 (3.1)	4 (2.4)	Not enough events

common with M.[22,23] A more recent review and network meta-analysis looked at ranking opioids used for acute pain as patient-controlled analgesia based on side-effects. There were only two studies comparing M and HM, and no differences in side-effects were observed. However, they observed larger differences in sedation and patient satisfaction scores when M was compared with other opioids.[24] Our reported incidence of severe sedation was less than that reported.[25] However, it is important to note that, as an outcome, we captured only sedation that interfered with achieving a state of SAME after operation, as sedation can be temporary and may still allow safe achievement of analgesic target.

In our trial, the only significant difference observed was in the actual quantity of opioid used. We considered a ratio of 5:1 (HM:M), as it is widely quoted and used, although the reported range of potency is variable, from 5:1 to 10:1.[19,26] Mahler and Forrest[27] looked at the relative potencies of HM and M in two double-blinded bioassays in postoperative patients. They observed that HM 0.9–1.2 mg could be equi-analgesic to M 10 mg, which is not a common belief.[27] It is possible that, because of this perception, and also the subjective assessment that one is administering a much smaller dose of opioid, health providers consider HM to be more effective for analgesia.[9]

Wu and colleagues[28] noted that only 30–42% of studies on patients having ambulatory surgeries assessed for pain or PONV after discharge. Patients with more pain may have a higher chance of PONV.[29] In our trial, the average pain scores over 24 h were close to 4 (considered the upper end of mild pain category) in both groups, with a relatively lower incidence of nausea/vomiting in both groups compared with the published literature.[30] This is possibly because of differences in measurement.

Our trial has several strengths. It was a moderate-size, randomised, and blinded trial with a clinically relevant outcome. Our reporting of outcomes as binary, unlike studies that report average outcomes in the form of pain scores, facilitates the interpretation of treatment effects by clinicians and improves the external validity of the study, especially when opioid effects are idiosyncratic and patient dependent. This is the largest randomised trial finding that the clinical potency of HM is six to seven times that of M. Our comparison of post-discharge outcomes also adds strength and consistency to our primary outcomes observed in a hospital.

The limitations of our trial are several. The study involved patients having ambulatory surgeries, and there is the possibility that similar observations may not be valid for patient-controlled analgesia therapy, as the effects of M could be cumulative because of an active metabolite. Similarly, our results do not apply for patients with chronic pain. We chose the cut-offs for SAME to measure a clinically meaningful state that is routinely targeted. Although it is possible to have some differences in outcome with other thresholds, we feel it is unlikely to be clinically significant, based on the observed results.

In conclusion, we found no difference in analgesia and side-effects comparing M with HM in ambulatory surgeries, both in a hospital and over the first 24 h after. Our results also suggest that the analgesic potency of HM is more than five times that of M. As it is very unlikely that there are real differences between the study medications, we do not think there would be any benefit in comparing these medications in future studies, and clinical decisions should be based on individual patient responses.

Authors' contributions

Study design: HS, JP.
Study methodology: HS, PJD, MB, LT.
Writing protocol: HS, JP, PL, PJD, MB, LT.
Study conduct: HS, JP, PL.
Study supervision: HS, PJD, MB, LT.
Data analysis: LT, TV.
Trial interpretation: HS, PJD, MB, LT.
All authors contributed to the writing of the manuscript and approved the final submitted version.

Declaration of interest

The authors declare that they have no conflicts of interest.

Funding

AbbVie New Investigator Award in Anesthesia, CAS-2014-038; Canadian Anesthesiologists' Society (2014); Department of Anesthesia, McMaster University. Canadian Institutes of Health Research RCT mentoring stipend grant award (between March 2017 and February 2018), Career Scientist Award, CAS-2018-062, Canadian Anesthesia Research Foundation (2018) (to HS).

Acknowledgements

The authors are thankful to their research team, including Toni Tidy, Geoff Travis, Diane Buckley, Raffy Gutman, Anne Clark, and Helen Akinboule for their contributions towards this project. The authors also thank their research pharmacists, Christine Wallace and Gita Sobhi, for their assistance, and the dedicated team of nurses working in the post-anaesthetic recovery units and day surgery units for their involvement and support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijhydene.2019.03.202.

References

1. Sarin P, Philip BK, Mitani A, Eappen S, Urman RD. Specialized ambulatory anesthesia teams contribute to decreased ambulatory surgery recovery room length of stay. *Ochsner J* 2012; **12**: 94–100
2. Troy AM, Cunningham AJ. Ambulatory surgery: an overview. *Curr Opin Anaesthesiol* 2002; **15**: 647–57
3. Shnaider I, Chung F. Outcomes in day surgery. *Curr Opin Anaesthesiol* 2006; **19**: 622–9
4. Lovatsis D, Jose JB, Tufman A, Drutz HP, Murphy K. Assessment of patient satisfaction with postoperative pain management after ambulatory gynaecologic laparoscopy. *J Obstet Gynaecol Can* 2007; **29**: 664–7
5. White PF. Pain management after ambulatory surgery—-where is the disconnect? *Can J Anesth* 2008; **55**: 201–7
6. Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg* 1999; **89**: 652–8
7. Karl HW, Tyler DC, Miser AW. Controlled trial of morphine vs hydromorphone for patient-controlled analgesia in children with postoperative pain. *Pain Med* 2012; **13**: 1658–9

8. Aubrun F, Mazoit JX, Riou B. Postoperative intravenous morphine titration. *Br J Anaesth* 2012; **108**: 193–201
9. Patanwala AE, Keim SM, Erstad BL. Intravenous opioids for severe acute pain in the emergency department. *Ann Pharmacother* 2010; **44**: 1800–9
10. Felden L, Walter C, Harder S, et al. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. *Br J Anaesth* 2011; **107**: 319–28
11. Shanthanna H, Paul J, Lovrics P, Devereaux PJ, Bhandari M, Thabane L. Satisfactory analgesia with minimal emesis in day surgeries (SAME DayS): a protocol for a randomised controlled trial of morphine versus hydromorphone. *BMJ Open* 2018; **8**, e022504
12. Apfel CC, Philip BK, Cakmakkaya OS, et al. Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? *Anesthesiology* 2012; **117**: 475–86
13. McIntosh S, Adams J. Anxiety and quality of recovery in day surgery: a questionnaire study using Hospital Anxiety and Depression Scale and quality of recovery score. *Int J Nurs Pract* 2011; **17**: 85–92
14. Gramke HF, de Rijke JM, van Kleef M, et al. Predictive factors of postoperative pain after day-case surgery. *Clin J Pain* 2009; **25**: 455–60
15. Schug SA, Chong C. Pain management after ambulatory surgery. *Curr Opin Anaesthesiol* 2009; **22**: 738–43
16. Arslan M, Demir ME. Prevention of postoperative nausea and vomiting with a small dose of propofol combined with dexamethasone 4 mg or dexamethasone 8 mg in patients undergoing middle ear surgery: a prospective, randomized, double-blind study. *Bratisl Lek Listy* 2011; **112**: 332–6
17. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med* 2010; **152**: 726–32
18. World Health Organization. WHO model lists of essential medicines March 2017 [updated August 2017, 20th Edn.]. https://www.who.int/medicines/publications/essentialmedicines/en/(accessed 18 January 2019).
19. Inturrisi CE. Clinical pharmacology of opioids for pain. *Clin J Pain* 2002; **18**: S3–13
20. Hong D, Flood P, Diaz G. The side effects of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* 2008; **107**: 1384–9
21. Rapp SE, Egan KJ, Ross BK, Wild LM, Terman GW, Ching JM. A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg* 1996; **82**: 1043–8
22. Chaplan SR, Duncan SR, Brodsky JB, Brose WG. Morphine and hydromorphone epidural analgesia. A prospective, randomized comparison. *Anesthesiology* 1992; **77**: 1090–4
23. Goodarzi M. Comparison of epidural morphine, hydromorphone and fentanyl for postoperative pain control in children undergoing orthopaedic surgery. *Paediatr Anaesth* 1999; **9**: 419–22
24. Dinges HC, Otto S, Stay DK, et al. Side effect rates of opioids in equianalgesic doses via intravenous patient-controlled analgesia: a systematic review and network meta-analysis. *Anesth Analg Adv* 2018; **9**. https://doi.org/10.1213/ANE.0000000000003887. Access published on November
25. Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. *Br J Anaesth* 2005; **94**: 505–13
26. Twycross R, Wilcock A, editors. *Palliative care formulary*. 3rd Edn. Oxford: Palliative Books; 2007
27. Mahler DL, Forrest Jr WH. Relative analgesic potencies of morphine and hydromorphone in postoperative pain. *Anesthesiology* 1975; **42**: 602–7
28. Wu CL, Berenholtz SM, Pronovost PJ, Fleisher LA. Systematic review and analysis of postdischarge symptoms after outpatient surgery. *Anesthesiology* 2002; **96**: 994–1003
29. Odom-Forren J, Rayens MK, Gokun Y, et al. The relationship of pain and nausea in postoperative patients for 1 week after ambulatory surgery. *Clin J Pain* 2015; **31**: 845–51
30. Le TP, Gan TJ. Update on the management of postoperative nausea and vomiting and postdischarge nausea and vomiting in ambulatory surgery. *Anesthesiol Clin* 2010; **28**: 225–49

Handling editor: H.C. Hemmings Jr

Supplementary Appendix 1: Post Anaesthetic Care Unit Protocol (titrate the opioid medication to achieve the desired pain score)

- Patient to be asked for their pain score upon entry, and if it is more than 4 out of 10 (NAS): to receive the 1st dose within 5 minutes after coming to PACU: 0.04 $mg \cdot kg^{-1}$ morphine units (rounding off to the nearest 1 mL or 0.5 mL); with a maximum of 3 mg of morphine equivalents.
- Repeat doses: 0.02 $mg \cdot kg^{-1}$ morphine unit every 5–10 minutes to titrate for analgesia and side effects (rounding off to the nearest 1 mL or 0.5 mL).
- If no side effects observed-titrate to have analgesia: NAS ≤4/10.
- PONV observed: record it and treat it with antiemetics (ondansetron 1–4 mg IV, dimenhydrinate 25–50 mg).
- Sedation observed (<3-Ramsey Sedation Scale)-withhold the next dose and restart the bolus if the score is >3.
- Respiratory depression: withhold the next dose, treat with naloxone if necessary.
- Use ketorolac IV 15–30 mg as the rescue medication if the patient does not tolerate the study opioid or if the patient does not satisfy the success of satisfactory analgesia even at 1 hour.

Supplementary Appendix 2: Types of surgery within the study groups

	Hydromorphone (n=203)	**Morphine (n=199)**
Excision of ovarian cyst or resection of endometriosis	12	21
Appendectomy	5	2
Cholecystectomy	64	68
Ventral/Umbilical/Incisional Hernia	78	65
Laparoscopic Salpingo-oophorectomy	36	32
Diagnostic laparoscopy and lysis of adhesions	2	6
Tubal ligation	6	5

PART 2: Analgesic Intervention to Prevent Persistent Post-Surgical Pain

Chapter 4: Preventing persisting post-surgical pain after thoracoscopic lobectomy surgeries, a pilot randomized factorial design randomized control trial

Introduction

Persistent post-surgical pain (PPSP) is considered as pain that develops or increases after a surgical procedure and affects 10–50% of surgical population. The consequences of PPSP include physical and emotional suffering, leading to chronic pain, disability, poor quality of life, and increased health costs. Presently, there is no established effective method of preventing PPSP after thoracic surgery. We conducted a feasibility 2×2 factorial trial comparing N-methyl-D-aspartate (NMDA) antagonists versus placebo and intravenous steroids versus placebo, in patients having elective video-assisted thoracic surgery lobectomies, at St. Joseph's Hamilton, Canada (site 1) and Cleveland Clinic, Cleveland, USA (site 2). Our feasibility objectives were: 1) recruitment rate per week; 2) recruitment of ≥90% of eligible patients; and 3) >90% follow-up. Secondary objectives were incidence and intensity of persistent post-surgical pain (PPSP) using 0–10 numerical rating scale (NRS), and other clinical outcomes. Using a computerized randomization system, patients were allocated to one of the four study groups: NMDA active with steroid placebo; NMDA placebo with steroid active; both NMDA and steroid active; both NMDA and steroid placebo. Patients, health providers, and data analysts were blinded to allocation. Patients were followed for three months after randomization. Out of 41 eligible patients, 27 (66%) were randomized. The trial was stopped after one-month recruitment at site 2, because the study medication expired. At site 1 and 2, the recruitment rate per week was 0.63; 95% confidence interval (CI) (0.47–0.79); and 1 (0.83–1.17); and the follow-up was complete for 100% and 66.7% of patients, respectively. In total, only 4 patients (15%), and 2 patients (7%) had PPSP at rest, and with movement, respectively. There were no significant differences between groups in clinical outcomes. Based on these outcomes we conclude that considerations for protocol changes are necessary if a larger trial is to go forward.

Status: This chapter is being prepared for a journal submission.

N-methyl-D-aspartate antagonists and steroids for the prevention of persisting post-surgical pain after thoracoscopic surgeries: a randomized controlled, factorial design, international, multicentre pilot trial

Harsha Shanthanna[a]*; Alparslan Turan[b]; Jessica Vincent[c]; Remie Saab[b]; Yaron Shargall[d]; Turlough O'Hare[a]; Kimberly Davis[e]; Sylvanus Fonguh[c]; Balasubramaniam Kumar[c]; James Paul[a]; Ian Gilron[f]; Henrik Kehlet[g]; Daniel I. Sessler[b]; Mohit Bhandari[h]; Lehana Thabane[i]; PJ Devereaux[i]

[a]Department of Anesthesia, McMaster University, Hamilton, ON, Canada;
[b]Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA;
[c]Population Health Research Institute, Hamilton, ON, Canada;
[d]Department of Surgery, St Joseph's Healthcare Hamilton, Hamilton, ON, Canada;
[e]Acute Pain Service, St. Joseph Healthcare Hamilton, Hamilton, ON, Canada;
[f]Departments of Anesthesiology and Perioperative Medicine, Biomedical and Molecular Sciences, Centre for Neuroscience Studies and School of Policy Studies, Queen's University, Kingston, ON, Canada;
[g]Section of Surgical Pathophysiology, Rigshospitalet, Copenhagen, Denmark;
[h]Department of Surgery, McMaster University, Hamilton, ON, Canada;
[i]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada

*Harsha Shanthanna MD
Department of Anesthesia, McMaster University
1280 Main St. W.,
Hamilton, Ontario, L8S 4K1
Canada
Telephone: 905-525-9140 ext. 21737
Fax: 905-523-1224
e-mail: shanthh@mcmaster.ca

ABSTRACT

Objective: We conducted a feasibility 2×2 factorial trial comparing N-methyl-D-aspartate (NMDA) antagonists versus placebo and intravenous steroids versus placebo, in patients having elective video-assisted thoracic surgery lobectomies, at St. Joseph's Hamilton, Canada (site 1) and Cleveland Clinic, Cleveland, USA (site 2). Our feasibility objectives were: 1) recruitment rate per week; 2) recruitment of ≥90% of eligible patients; and 3) >90% follow-up. Secondary objectives were incidence and intensity of persistent post-surgical pain (PPSP) using 0–10 numerical rating scale (NRS), and other clinical outcomes.

Methods: Using a computerized randomization system, patients were allocated to one of the four study groups: NMDA active with steroid placebo; NMDA placebo with steroid active; both NMDA and steroid active; both NMDA and steroid placebo. Patients, health providers, and data analysts were blinded to allocation. Patients were followed for three months after randomization.

Results: Out of 41 eligible patients, 27 (66%) were randomized. The trial was stopped after one-month recruitment at site 2, because the study medication expired and there was no supply from our source. At site 1 and 2, the recruitment rate per week was 0.63; 95% confidence interval (CI) (0.47–0.79); and 1 (0.83–1.17); and the follow-up was complete for 100% and 66.7% of patients, respectively. In total, only 4 patients (15%), and 2 patients (7%) had PPSP at rest, and with movement, respectively. There were no significant differences between groups in clinical outcomes.

Conclusion: Our trial feasibility objectives were not met and considerations for protocol changes are necessary if a larger trial is to go forward.

Trial Registration: NCT02950233

Funding: 2016, Michael G DeGroote Institute of Pain Research and Care grant, $ 30,000 (CAD) and 2016 Carl Koller Memorial Research Grant award, American Society of Regional Anesthesia and Pain Medicine, $50,624 (USD)

Ethical committee approvals: An ethical approval was obtained from Hamilton Integrated Research Ethics Board, # 2305, on March 23, 2017; and IRB of Cleveland Clinic #17-1608, on March 1, 2018.

Introduction

Burden of the problem and etiological considerations

Persistent post-surgical pain (PPSP) is defined as pain that develops or increases after a surgical procedure. It is known to affect 10–50% of the surgical population (1, 2). The incidence of PPSP after thoracic surgeries is as high as 25–60% (3). Video-assisted thoracic surgeries (VATS) are assumed to have a lower incidence of PPSP compared to open thoracic surgeries; however, the existing literature is limited (4, 5). The consequences of PPSP include physical and emotional suffering, leading to chronic pain, disability, poor quality of life, and increased health costs (6). Presently, there is no established effective method of preventing PPSP after thoracic surgery. The factors contributing to the high incidence of PPSP after thoracic surgeries are not entirely clear. It is likely that several surgical and patient factors independently influence the development of PPSP. Surgical injury leads to changes of peripheral and central sensitization. The changes involved in these sensitization processes have the potential to cause pathological, persistent pain due to neuroplasticity (7). The underlying nature of PPSP after thoracic surgeries is not fully understood. Based on the available evidence, it is considered to be predominantly neuropathic. The neuropathic component may not be due to direct nerve injury (8), as nerve-sparing surgeries do not seem to prevent or predict the development of PPSP (9, 10); however, subclinical changes of neuro-inflammation (8, 11) may result in neuropathic pain, which is associated with more severe persistent pain and has substantial impact on patients' lives (12) (13)**.**

Study Interventions

Ketamine is a potent anesthetic and analgesic agent (14) and acts by blocking N-methyl-D-aspartate (NMDA) receptors via a non-competitive mechanism (15). Low-dose ketamine has been effectively used to improve perioperative analgesia and to decrease opioid requirements (16). At subanesthetic doses (1–6 mcg/kg/min), ketamine can have anti-hyperalgesic effects, without significant cardiovascular and respiratory adverse effects (17, 18). The Cochrane review noted 14 randomized control trials (RCTs) on the use of ketamine for preventing PPSP (19). Although they did not find any significant evidence supporting ketamine for outcomes at three months (5 studies), a sub-analysis of studies using >24 hours infusion showed results favoring ketamine, odds ratio (OR), 0.37; 95% confidence interval (CI), 0.14 to 0.98. At six months (8 studies), the results favored the use of ketamine, irrespective of the duration of infusion, OR, 0.50; 95% CI, 0.33 to 0.76. Memantine is an oral NMDA receptor antagonist that blocks the sustained activation of the receptor, such as that occurring under pathological conditions. It is 100% bioavailable after an oral dose, undergoes minimal metabolism, and exhibits a terminal elimination half-life of 60 to 80 hours. (20). A recent review looking at the use of memantine for preventing PPSP observed that there is potential for decreasing the intensity of PPSP based on two RCTs, a mean difference in the end score of 1.02 units in a 0–10 numerical rating scale (NRS), where 0=no pain and 10=maximum pain (95% CI, 1.38 to 0.66) (21). Use of oral memantine after ketamine infusion may facilitate sustained NMDA blockade after surgery (22).

Steroids are potent anti-inflammatory agents affecting both inflammatory and immune pathways (23, 24). Among the commonly used agents, dexamethasone is nearly

five times as potent as methylprednisolone and has a biological half-life of 36–72 hours (23). The benefits of using steroids in surgical population include decreased postoperative nausea-vomiting (PONV), improved analgesia, earlier discharge, and better satisfaction (25) (26). Steroids have been safely used to improve perioperative outcomes in abdominal (27), orthopedic (28), and other surgeries (29). Although the potential for steroids to modify PPSP exists (1, 28, 30), it has not been well studied (19). No study has attempted to evaluate the effect of two doses of a long-acting steroid in moderate doses.

Summary

PPSP after VATS lobectomy is an important health problem for which there is no established method of prevention. NMDA antagonists and steroids can modify pain signaling-sensitization pathways, and inflammatory-immune pathways, and hence may prevent the development of PPSP. Since these agents act through different biological mechanisms, and we are unaware of any biological reason for any negative interaction, it is appropriate to study their effects in a factorial design to increase efficiency. This pilot trial was proposed to establish the feasibility of a large multicentre trial.

Objectives

Our feasibility objectives included determining the feasibility of recruiting eligible patients and patients completing the three months follow-up. Our clinical objectives included determining the effect of NMDA antagonists and intravenous (IV) steroids in patients having VATS lobectomies on the: 1) incidence of PPSP with movement three months after randomization; 2) intensity of PPSP at rest and with movement at three months after randomization; 3) rate of change of postoperative pain intensity over time; 4) use of narcotic analgesic medication >3 days/weeks beyond 4 weeks after randomization; 5) presence of neuropathic pain; 6) incidence of pain interfering with the activities of daily living; 7) thoracic surgery-specific activity limitations; 8) change in global health status; 9) quality of life; and 10) incidence of adverse effects.

Methods

The PAIN-STOP pilot trial was a multicentre RCT using a 2 × 2 factorial design to evaluate NMDA antagonists versus placebo, and dexamethasone versus placebo. Randomization was stratified by site. Patients, health care providers, data collectors, outcome adjudicators, and investigators were blinded to treatment allocation. The trial was conducted in two centres: St Joseph's Hospital, Hamilton, Canada (site 1), and Cleveland Clinic, Cleveland, USA (site 2).

Patient Selection

Inclusion and exclusion criteria: Patients were eligible if they were between 18–75 years of age, were scheduled for elective VATS pulmonary lobectomy, and provided informed consent to participate. Patients were excluded if they met one or more of the following criteria: not willing to participate; existing pain on the same side of the chest of moderate to severe intensity (>3/10 in 0–10 NRS, where 0=no pain and 10=maximum pain); current history of intracranial mass or cerebral aneurysm or raised intraocular pressure; glomerular filtration rate <30 mL/min based on creatinine clearance; known allergies to one or more of the study medications; history of steroid treatment >10 mg/day

of prednisolone or its equivalent for >3weeks within the 3 months before randomization; history of schizophrenia or bipolar disorder; current history of drug addiction (prescription or non-prescription drug addiction diagnosed by a physician, excluding alcohol); pregnancy; and previous participation in the PAIN-STOP trial.

Patient recruitment: Eligible patients were identified from the thoracic surgery operating room booking list and approached by the research personnel during their pre-surgical consult. To provide study information and to enhance patient participation, patients were provided with an information brochure (Appendix 1) about postoperative pain and its treatment. They were also informed about the risk of PPSP after VATS procedures and its burden. Patients fulfilling the selection criteria were consented. Study personnel collected baseline information including patient demographics, smoking history, diagnosis, and history of radiation or chemotherapy. The following additional baseline information was collected from each consenting patient: 1) Hospital Anxiety and Depression Score (31); 2) Pain Catastrophizing Score (32); 3) pain elsewhere in the body and its severity; and 4) the use of any ongoing analgesic medications.

Assignment of Interventions

Randomization was performed before surgery via an Interactive Web Randomization System (IWRS). The IWRS is a 24-hour computerized internet randomization system maintained by the coordinating centre at the Population Health Research Institute, McMaster University in Hamilton, Ontario, Canada. Patients were randomized using block randomization stratified by centre, in a 1:1:1:1 fashion to receive, 1) NMDA active and dexamethasone placebo; 2) dexamethasone active and NMDA placebo; 3) NMDA active and dexamethasone active; 4) NMDA placebo and dexamethasone placebo. Patients, health care providers, data collectors, data analysts, and outcome adjudicators were masked to treatment allocation. The research personnel obtained the masked study medication kit from the hospital pharmacy, and delivered it to the anesthesiologist, and the nursing staff who provided these drugs to the patients in hospital.

Study Interventions

NMDA antagonist treatment included active ketamine administered at 0.5 mg/kg as an IV bolus during induction, and 0.1 mg/kg/hr IV infusion starting in the post-anesthetic care unit, and continuing up to 24 hours or until discharge from a monitored bed. Placebo ketamine (0.9% normal saline solution) was administered by infusion at the same rate and duration as above. Starting on the 1st postoperative day, oral memantine (or matching placebo) was self-administered at 5 mg BID for the 1st week and increased to 10 mg BID starting in week 2, and continued until the end of 4 weeks after surgery. The steroid intervention involved 25 mg of IV dexamethasone administered in a 50 mL normal saline bag, post-induction before incision, and on the morning of post-operative day 2. For patients allocated to placebo, 50 mL of saline was administered at the same time points.

Monitoring and safety of ketamine administration

As necessitated by the hospital policy and as suggested by the existing guidelines, study patients were observed in a high dependency bed (step down unit) and monitored for respiratory rate, continuous electrocardiogram, blood pressure, sedation level, oxygen

saturation, and pain scores (33). Infusion of ketamine or placebo was titrated to side effects such as disorientation, dystonia, sedation, hallucination, nightmares, and delirium. Observation of one or more of the above side effects required stopping the infusion until the side effect resolved and restarting at half the dose rate. If the same side effect occurred again the infusion was discontinued. The reason for decreasing the concentration or stopping the infusion was noted.

Surgical Protocol

All study patients were planned to have elective VATS lobectomy under general anesthesia using appropriate IV induction and inhalational medications. Intraoperative analgesia was provided using IV opioids, with or without IV ketorolac 15–30 mg, as decided appropriate by the treating anesthesiologist. All patients had continuous electrocardiogram, oxygen saturation, intra-arterial blood pressure, and urinary catheter monitoring, as required by local standard practices. At the end of surgical procedure, all patients had local anesthetic infiltration to sites of trochar insertion, and intercostal block above and below the site of chest tube insertions with 0.25% bupivacaine with or without adrenaline. The anesthesiologist administered the study medications. In the event of conversion of VATS to open procedure, the study drug administration continued. For these patients, decision on the intraoperative placement of paravertebral catheter or postoperative placement of thoracic epidural catheter was done on a case-by-case basis, as per the decision of the involved surgeon and the anesthesiologist. Analgesia was provided with opioid-based patient controlled analgesia (PCA) along with non-steroidal anti-inflammatory drugs (NSAIDs).

Post-discharge Care

Patients continued with their regular prescription medications that they had before surgery along with study medications continued up to one month. For the first two weeks, post-discharge analgesia included around-the-clock NSAIDs plus moderate-strength opioid, such as codeine plus acetaminophen or oxycodone plus acetaminophen, for regular and breakthrough pain. Following this, analgesic prescriptions were made based on individual patient's need. Use of opioid analgesia was recorded in a pain diary and follow-up phone calls. Patients were not allowed the use of other atypical analgesics such as antidepressants or gabapentinoids, unless patients had been on these medications before surgery. For patients with PPSP at three months, referral arrangements for the assessment and management of persistent pain at the respective hospital's chronic pain clinic were made.

Patient Follow-up

Study personnel followed patients daily in hospital and ensured compliance with study medications and recorded outcomes. Patients were contacted by phone on day 8 and two months post-randomization. Patients completed a diary with daily recording of drug intake, pain scores, and analgesic use for the first 30 days; and one to thrice-weekly recording of pain scores at rest and with movement, and analgesic use from 30 days to three months post-randomization. Patients were encouraged to visit the hospital at the end of one month and three months post-randomization (final follow-up). Research personnel coordinated these visits with the surgeon's office to facilitate patient attending a surgical

and study follow-up on the same day. For patients unable to make a visit, a phone follow-up was arranged.

Study Outcomes

The primary (feasibility) outcomes included the ability to: 1) recruit at least four patients per month per site; 2) recruitment of ≥90% of eligible patients; and 3) obtain a follow-up in >90% of enrolled patients at three months.

Secondary outcomes included the primary and secondary outcomes for the main clinical trial as summarized in Table 1, collected at three months after randomization, unless stated otherwise. Adverse outcomes were noted as tertiary outcomes from the time of randomization up to three months (Table 1).

Blinded outcome adjudicators (expert physicians) adjudicated the outcomes of pneumonia and persistent air leak, which were used for analyses of these events.

Table 1: Secondary and tertiary outcomes

Secondary Outcomes: The following were collected at three months after randomization, unless otherwise specified.	
1	Incidence of PPSP (>3/10 on a 0–10 NRS) with movement (34).
2	Intensity of PPSP, (i.e., average NRS score during the last week).
3	The rate of change of postoperative pain intensity from surgery up to three months after randomization (pain trajectory) (35).
4	Use of narcotic analgesic medication >3 days/week beyond four weeks after randomization.
5	Presence of neuropathic pain (i.e., >3 out of 7 items using DN4 scale) (36).
6	Difference in interference with activities of daily living measured using BPI interference score (34).
7	Difference in thoracic surgery-specific activity limitations (37).
8	Global health status measured using GIC (34).
9	Difference in quality of life using EORTC QoL-30 (38).
Tertiary Outcomes: The incidences of adverse outcomes were noted from randomization up to three months.	
1	Myocardial infarction
2	Myocardial injury after non-cardiac surgery (39).
3	Postoperative pneumonia
4	Prolonged air-leak
5	New intubation and positive pressure ventilation
6	Surgical site infection
PPSP: persistent post-surgical pain; NRS: numerical rating scale; DN: Douleur Neuropathique; BPI: Brief Pain Inventory; GIC: global impression of change; QoL: quality of life; EORTC: European Organization for Research and Treatment of Cancer	

Statistical Analyses and Sample Size

The analysis and reporting of results was performed according to CONSORT guidelines extension to pilot and feasibility RCTs (40). We analyzed patients in the

treatment group to which they were allocated, according to the intention-to-treat principle, and patients lost to follow-up were censored at the time they were lost to follow-up. As a feasibility study, analysis of all clinical outcomes was exploratory. Feasibility outcomes were assessed as proportions and rates with 95% CI. For the analysis of clinical outcomes, we compared patients allocated to 'NMDA antagonists' to 'NMDA placebo' and patients allocated to 'steroids' to 'steroid placebo'. Analysis of continuous outcomes was based on independent *t* test, and binary outcomes on logistic regression. The results on the estimates of effect are reported as mean difference for continuous outcomes and OR for binary outcomes, with corresponding 95% CI. No interim analyses were planned. For pain trajectory-representing the change in postoperative pain over time, repeated pain measures were analyzed using a mixed effects model to obtain slope and curve for treatment and placebo groups (41). All analyses were performed using SAS 9.2 (Cary, NC). Sample size was based on feasibility considerations (42, 43) with a total sample of 48 patients, with 12 in each group. This is considered appropriate for a pilot feasibility trial.

Results

The study was initiated at site 1 on May 3, 2017 and at site 2 on April 5, 2018. Out of 98 patients screened for eligibility, 27 were randomized, and all except one patient completed the final three-month follow-up. We had to stop recruitment on April 20, 2018 because the packaged study medications were expiring and there was no available supply of 5 mg memantine tablets from our source. The CONSORT flow chart (Figure 1) shows the patient flow and reasons for non-inclusion. The baseline characteristics of included patients are shown in Table 2. No patients had a prior history of PPSP and scores for both anxiety and depression were high (indicative of severe rating) in all four groups. The mean dose of opioids (morphine equivalent dose per day) before surgery was similar. The intraoperative and postoperative characteristics of patients are summarized in Table 3.

Table 2: Baseline Characteristics of Patients

	NMDA active (n=13) Mean (SD) or Number (%)	NMDA Placebo (n=14) Mean (SD) or Number (%)	Steroid Active (n=14) Mean (SD) or Number (%)	Steroid Placebo (n=13) Mean (SD) or Number (%)
Age	65.9±6.4	63.9±8.4	66.4±6.4	63.2±8.4
Male	6 (46.2)	7 (50.0)	5 (35.7)	8 (61.5)
BMI	27.1±5.0	30.0±5.9	27.1±6.2	30.2±4.7
History of chemo or radiotherapy for cancer in the last 12 months	2 (15.4)	1 (7.1)	2 (14.3)	1 (7.7)

History of previous chest surgery on the same side	1 (7.7)	1 (7.1)	1 (7.1)	1 (7.7)
History of chronic pain in other parts of the body	2 (15.4)	4 (28.6)	3 (21.4)	3 (23.1)
Prior history of PPSP	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HADS-Anxiety score	18.2±3.4	18.9±1.1	18.6±2.5	18.6±2.5
HADS-Depression score	15.5±1.0	15.2±1.5	15.2±0.9	15.5±1.6
Summary PCS score	11.5±12.0	12.9±13.2	15.6±13.5	8.9±10.8
Total dose of opioids as MED per day	5.7±2.5	4.5±0.8	5.7±2.5	4.5±0.8
NMDA: N-methyl-D-aspartate; SD: Standard deviation; BMI: Body mass index; HADS: Hospital anxiety and depression scale; PCS: Patient catastrophizing scale; MED: Morphine dose equivalent				

The most common diagnosis was primary lung cancer. Four patients needed conversion to open in the NMDA placebo, and steroid placebo groups, and had postoperative epidural or paravertebral catheters for analgesia. A majority of patients had only one chest drain of 28 French size. The utility incision performed to extract the resected lung tissue was less than 4 cm in most patients. The amount of PCA opioid used was higher in placebo groups compared to their respective active groups. Number of days with chest tube and total duration of hospital stay were similar across groups. One patient who had both active interventions had myocardial injury after noncardiac surgery (MINS).

Figure 1: CONSORT 2010 Flow Diagram

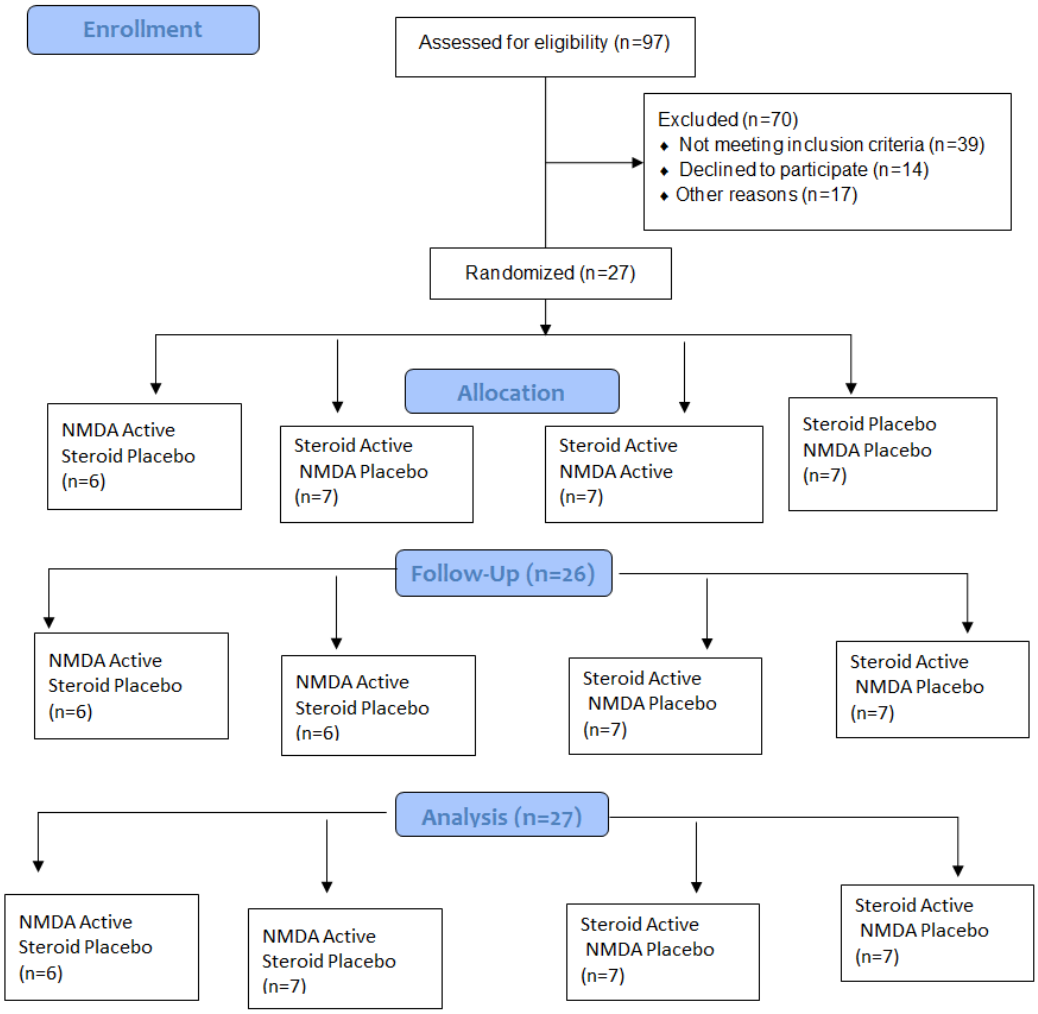


Table 3: Intraoperative and postoperative characteristics of study patients

	Steroid active (n=14)	Steroid placebo (n=13)	NMDA active (n=13)	NMDA placebo (n=14)
Operative Characteristics				
Diagnosis - N (%)				
Primary Lung Cancer	11 (78.6)	12 (92.3)	12 (92.3)	11 (78.6)
Metastasis	3 (21.4)	0 (0.0)	1 (7.7)	2 (14.3)
Infection	0 (0.0)	1 (7.7)	0 (0.0)	1 (7.1)
Lobe Resected - N (%)				

Upper	8 (57.1)	9 (69.2)	10 (76.9)	7 (50.0)
Middle	2 (14.3)	2 (15.4)	0 (0.0)	4 (28.6)
Lower	7 (50.0)	4 (30.8)	5 (38.5)	6 (42.9)
Conversion to Open-N(%)	2 (14.3)	4 (30.8)	2 (15.4)	4 (28.6)
Number of ports - N (%)				
1	1 (7.1)	1 (7.7)	1 (7.7)	1 (7.1)
2	1 (7.1)	0 (0.0)	1 (7.7)	0 (0.0)
3	8 (57.1)	7 (53.8)	6 (46.2)	9 (64.3)
4	4 (28.6)	3 (23.1)	4 (30.8)	3 (21.4)
Number of ports with rib spreader - N (%)	0 (0.0)	2 (15.4)	1 (7.7)	1 (7.1)
Number of chest drains - N (%)				
1	12 (85.7)	9 (69.2)	11 (84.6)	10 (71.4)
2	2 (14.3)	3 (23.1)	1 (7.7)	4 (28.6)
Largest chest tube size used - N (%)				
24	1 (7.1)	0 (0.0)	1 (7.7)	0 (0.0)
28	12 (85.7)	11 (84.6)	10 (76.9)	13 (92.9)
Other (9)	1 (7.1)	1 (7.7)	1 (7.7)	1 (7.1)
Length of utility incision - N (%)				
< 4 cm	9 (64.3)	5 (38.5)	8 (61.5)	6 (42.9)
4-8 cm	5 (35.7)	3 (23.1)	3 (23.1)	5 (35.7)
> 8 cm	0 (0.0)	2 (15.4)	1 (7.7)	1 (7.1)
Postoperative Characteristics				
ICU admissions after surgery N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Need for continuous epidural or PVB for >6 hours N (%)	1 (7.1)	3 (23.1)	1 (7.7)	3 (21.4)
Total Opioid used with PCA as MED - Median (IQR)*	15.0 (10.0-45.0)	40.0 (15.0-80.0)	15.0 (10.0-95.0)	30.0 (10.0-60.0)
Number of days with chest tube - Median (IQR)	2.0 (1.0-2.0)	2.5 (2.0-4.0)	2.0 (2.0-5.5)	2.0 (1.0-3.0)
Peak value of troponin measured during hospital stay - Median (IQR)	17.5 (2.0-32.0)	3.0 (3.0-7.0)	17.5 (3.0-32.0)	3.0 (2.5-5.0)

Total duration of hospital stay (days) - Median (IQR)	4.0 (3.0-5.0)	5.0 (4.0-10.0)	5.0 (4.0-6.0)	4.0 (4.0-7.0)
NMDA: N-methyl-D-aspartate; IQR: interquartile range; SD: standard deviation; NRS: numerical rating scale; N: number; MED: Morphine dose equivalent; PCA: patient-controlled analgesia				

Outcomes

Feasibility Outcomes: At site 1, the percentage of eligible patients recruited was 65% (24/37). Out of 88 patients screened, 24 consented, and 13 refused; 30 were above the upper age limit; 15 patients were participating in a competing trial; and six were excluded (three due to known history of intracranial mass, two due to prior history of schizophrenia or bipolar disease, and one due to current pain on the same side of the chest). We only had two weeks of recruitment at site 2. Among nine patients screened, four were eligible, and three provided consent. The recruitment rate per week (95% CI) were 0.63 (0.47–0.79); and 1 (0.83–1.17), respectively, at sites 1 and 2. With only one patient lost to follow-up in site 2, the percentage of randomized patients with follow-up at three months after randomization was 100% and 66.7% at site 1 and 2, respectively.

Treatment Compliance and Follow-up: We were able administer study medications as per the protocol in all except one patient, as the anesthesiologist refused to administer the study medication. Only one other patient did not receive his second dose of steroid intervention. All other patients continued with their study medications.

Clinical Outcomes: At three months post randomization, the number of patients who had any PPSP (resting score >0 in 0–10 NRS), and PPSP on movements (>3 in 0–10 NRS) were four, and two patients respectively. The secondary outcomes are shown in Table 4 and Figure 2 (rate of change in postoperative pain intensity), and Appendix 2 and 3 (global change and quality of life). There were no important differences in any outcomes.

Table 4: Summary of clinical outcomes

Outcomes (all observed at 3 months after randomization except[#])	Steroid Active	Steroid Placebo	NMDA Active	NMDA Placebo
Intensity of PPSP (resting pain) on a scale of 0-10 NRS; Median (IQR)	3.0 (2.0-5.0)	1.0 (1.0-1.0)	2.0 (1.0-3.0)	5.0 (5.0-5.0)
Incidence of PPSP with movement (> 3/10 in 0-10 NRS); N (%)	2 (14.3)	0 (0.0)	1 (8.3)	1 (7.1)
Use of narcotic analgesic medication >3 days/week beyond 4 weeks[#]; N (%)	5 (35.7)	3 (25.0)	4 (33.3)	4 (28.6)
Presence of neuropathic pain as >3 out 7 items using DN4 scale; N (%)	1 (16.7)	0 (0.0)	1 (33.3)	0 (0.0)

Interference in activities of daily living using BPI in patients with PPSP; Mean (SD)	2.5±2.0	1.1±1.0	3.7±2.4	1.3±0.4
Thoracic surgery-specific activity limitations; Mean (SD)	0.6±0.7	0.2±0.2	1.0±0.8	0.2±0.2
PPSP: persistent post-surgical pain; NMDA: N-methyl-D-aspartate; IQR: interquartile range; DN: Douleur Neuropathique; BPI: Brief Pain Inventory; SD: standard deviation; NRS: numerical rating scale; N: number				

We did not observe any influence of the study interventions on the resolution of postoperative pain intensity over time. The adjusted difference in mean intensity between treatment and placebo groups, and test for interaction effect for different time points were not significant (Figure 2). The tertiary outcomes are summarized in Table 5. There were no deaths or major adverse effects due to treatment.

Figure 2: Rate of change in postoperative pain intensity since surgery up to three months after randomization

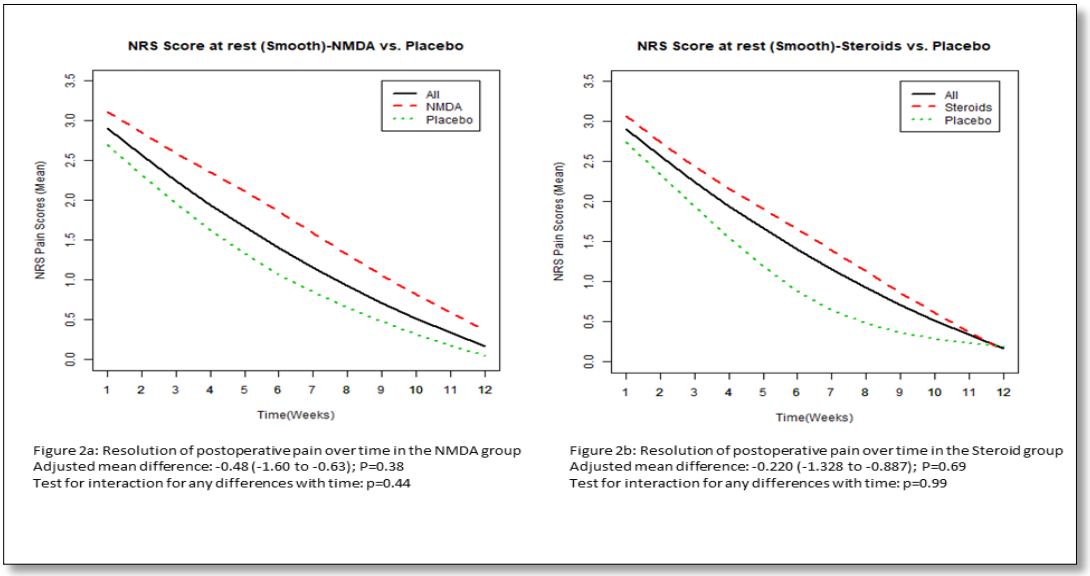


Figure 2a: Resolution of postoperative pain over time in the NMDA group
Adjusted mean difference: -0.48 (-1.60 to -0.63); P=0.38
Test for interaction for any differences with time: p=0.44

Figure 2b: Resolution of postoperative pain over time in the Steroid group
Adjusted mean difference: -0.220 (-1.328 to -0.887); P=0.69
Test for interaction for any differences with time: p=0.99

Table 5: Summary of tertiary outcomes

Outcomes	Steroid Active N (%)	Steroid Placebo N (%)	NMDA Active N (%)	NMDA Placebo N (%)
Myocardial infarction(MI)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction after non-cardiac surgery (MINS)	1 (7.7)	0 (0.0)	1 (7.1)	0 (0.0)
Postoperative pneumonia	0 (0.0)	1 (7.1)	0 (0.0)	1 (7.7)
Prolonged air-Leak	1 (7.7)	0 (0.0)	0 (0.0)	1 (7.7)
New intubation and positive pressure ventilation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical site infection	1 (7.7)	1 (7.1)	1 (7.1)	1 (7.7)

NMDA: N-methyl-D-aspartate; N: number

Discussion

In this factorial design pilot trial comparing NMDA antagonists with placebo and steroids with placebo in VATS lobectomy patients, we were unable to demonstrate feasibility based on lower than expected recruitment rate, and other logistical challenges that did not allow us to complete the full study recruitment. We also observed that our estimate of patients suffering from PPSP at three months was lower than previously reported; only 2 of 27 patients (7%) fulfilled the criteria of PPSP with movement at three months after randomization. We also did not observe any particular effect of study interventions on postoperative pain resolution, either in direction or magnitude, except for differences in PCA opioid used during the postoperative stay in hospital (Table 2).

This feasibility trial involved significant challenges. It was planned as an international trial as we appreciated the need to involve other centres beyond Canada to recruit a relatively larger sample size for the main trial. The study interventions were not approved by the health regulatory agencies for preventing PPSP. This necessitated that we seek approval from Health Canada and Food and Drug Agency (FDA), apart from obtaining individual site ethics approval, which needed to be coordinated with the regulatory approvals as well. The trial involved the use of memantine, a drug that is approved for use in patients with Alzheimer's disease. Its dosing recommendations include starting at 5 mg and titrated upwards to 10 mg twice a day over 2–4 weeks (44). However, most available preparations come as 10 mg tablets and patients are informed to take half of the tablet for the initial 5 mg dose, which is not appropriate for research (45).

Only some companies satisfy regulatory approvals for clinical use in both Canada and the USA (46). Furthermore, acquisition, preparation, and packaging of study medications (including over-encapsulation of placebo capsules) from an appropriate company, and submission of batch certificate number are needed for regulatory approvals. Although we were able to work in parallel towards overcoming the above challenges, some procedures needed to happen in sequence, and thereby delaying trial initiation at site 2. Although we initiated our process of ethics approval in September 2017 at site 2, for reasons beyond our control, we were unable get approval until March 2018. Finally, we were limited by the expiration of prepared study medications on April 20, 2018. Moreover, the source supplying our study medications was out of their supply of memantine 5 mg at that time.

Besides the above-mentioned challenges, we also faced recruitment challenges in site 1. Increased use of advanced technology provides minimally invasive options including robotic surgeries for lung resection (47). At both centres robotic lung resection surgery was an option, and at site 1, there was an active study comparing robotic versus VATS lobectomies that blinded patients for their procedures [https://clinicaltrials.gov/ct2/show/NCT02617186]. Since our trial involved selecting patients having VATS lobectomy, we were unable to approach 15 other eligible patients as it risked unblinding for this competing trial.

Patient recruitment for clinical trials can be challenging (48, 49). In particular, recruitment for surgical trials is more unpredictable, sometimes with less than 50% recruitment rate (50). It is potentially possible that a certain degree of complexity in our trial and the need to be on study treatment for one month after surgery could have been a reason some patients declining participation. In our study, appreciating the need to better inform patients about the burden of PPSP, and the importance of our study, we prepared an information brochure (Appendix 1) using layman language. Since patient consent was planned to coincide with their preoperative visit, we prioritized to identify appropriate patients before this visit, and distribute this brochure. However, we faced challenges in identifying such patients ahead of time, due to clinical demands.

Although the burden of PPSP is high with thoracic surgery, its incidence after VATS lobectomies is not consistent across studies and can vary from 22 to 63% (4, 5, 51). Based on the available literature, we estimated a lower limit of 20% incidence with movement. In our study, 28 patients were excluded based on the age limit. Younger age is considered an important risk factor for PPSP (1, 52). Although, we had initially considered to limit the upper age at 65 years, we expanded our upper limit to 75 years with an amendment to improve recruitment. Our consideration for limiting the age was to focus on a more susceptible population with a higher incidence of PPSP. Despite this, we observed a PPSP rate of 15% at rest and 7% with movement (clinically important PPSP). Since this is a pilot study, it is not appropriate to infer about potential treatment effects of study interventions. We have highlighted that there is sound rationale to test these interventions to influence the course of persisting postoperative pain.

We need to acknowledge that there are limited data on the optimal dosing and timing of our study interventions to prevent PPSP. We used IV ketamine up to 24 hours after surgery, based on the need for monitored bed, and logistical considerations as many VATS lobectomy patients are moved to a non-monitored bed before 24 hours. In

comparison, a recent smaller study reported a significant risk reduction using a combination of pregabalin and ketamine, with an infusion of ketamine (0.1 mg/kg/hr) for 48 hours after surgery in cardiac surgery patients (53). Another review and meta-analysis looking at memantine for treating or preventing pain observed considerable variation in the dose and duration of its treatment (21). Studying pain trajectories in the postoperative period can provide significant information about resolution of postoperative pain and PPSP (54, 55). The existing knowledge about the transition from a state of physiologically acceptable postoperative pain into a state of PPSP is unclear (22). In our study the adjusted mean pain intensity decreased over time and by 8–9 weeks, it was <1 in all patients' groups (Figure 2).

Despite these challenges, our trial has several merits. Firstly, it further demonstrates the need for a pilot trial before embarking on a larger surgical trial. An empirical study looking at completion and publication rates of RCTs in surgery found that nearly half (43%) were discontinued, in comparison to 27% in medicine trials (56). Our study also highlights the limitations of assuming a relatively higher PPSP risk in VATS lobectomy population.

Conclusion: Based on our results, we believe appropriate changes to study population, such as including other populations at higher risk of PPSP along with VATS lobectomy patients, with stratification based on surgical type, should be considered to make a larger trial feasible. This could also allow participation of other study centres.

Appendix 1: Study patient information brochure

PAIN STOP STUDY

All persistent pain was once new!

Persistent pain after surgery is a condition in which pain due to surgery, can continue beyond the period of healing.

The risk of persistent pain exists with many surgeries such as amputations, chest and breast surgeries.

The risk of persistent pain after thoracic surgery is estimated between 40-60%

Preventing Pain After Thoracic Lobectomy Procedures

PERSISTENT PAIN

"One of the most underestimated health care problems in the present world"

STUDY INFORMATION

You will be given study medications during and after your hospital stay, for up to 30 days.

You will be needed to maintain a pain and medication diary for 30 days.

You will have a telephone follow up on day 8 and at 2 months after surgery.

You will be encouraged to visit hospital after 30 days, and at 3 months after surgery.

If you are interested in participating, please contact our research coordinator by email or phone.

Lung operations can involve a lot of trauma and inflammation. This leads to increased pain signals.

Ketamine and Memantine can decrease amplification of pain signals.
Use of steroids decreases inflammation.

You will have 50% chances of receiving the above study medications.

We will study their effects to decrease persistent pain.

Approval: This study has been approved by the ocal ethics Committee

Funding: American Society of Regional Anesthesia and Pain and Medicine (ASRA); and Michael DeGroote Institute of Pain Research and Care (IPRC).

Clinical Trial Registration Number:

Sponsor and Study Coordinating Group

PAIN-STOP Project Office
Population Health Research Institute
Hamilton General Hospital
Campus, DBCVSRI
237 Barton Street East
Hamilton, Ontario, Canada L8L 2X2

What are the benefits of participating in the study?

You will be followed by the research team with regards to study or other outcomes up to 3 months after surgery.

Your regular follow up will allow us to monitor you for pain, and refer you to chronic pain clinic if you develop persisting pain.

You will be advancing the scientific knowledge around managing persistent pain.

What are the risks of participating in the study?

The study medications are presently safely used in humans, but for other indications.

Even if you belong to inactive medication group (placebo), you will receive all the necessary care and medications required for your surgery as a regular patient.

Whom do I contact for study information?

Primary Investigator: Harsha Shanthanna
Assistant Professor Anesthesiology
St Joseph's Hospital
Email: shanthh@mcmaster.ca

Research Coordinator:
St Joseph's Hospital
Email:
Phone:

Appendix 2: Change in global health status measured using global impression of change questionnaire

Outcome category	Steroid Active (n=13)	Steroid Placebo (n=12)	NMDA Active (n=11)	NMDA Placebo (n=13)
Very much improved	3 (21.4)	5 (41.7)	5 (41.7)	3 (21.4)
Much improved	1 (7.1)	1 (8.3)	1 (8.3)	1 (7.1)
Minimally improved	1 (7.1)	0 (0.0)	1 (8.3)	0 (0.0)
No change	7 (50.0)	3 (25.0)	4 (33.3)	6 (42.9)
Minimally worse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Much worse	1 (7.1)	1 (8.3)	0 (0.0)	2 (14.3)
Very much worse	0 (0.0)	1 (8.3)	0 (0.0)	1 (7.1)

Appendix 3: Difference in Quality of Life measured using European Organization for Research and Treatment of Cancer (EORTC) QoL-30

Outcome category	Steroids Active (n=13)	Steroids Placebo (n=11)	NMDA active (n=11)	NMDA Placebo (n=13)
*Functioning Scales (Mean SD)**				
Physical (Items 1 - 5)	69.7±16.7	76.4±33.0	78.8±22.5	67.7±26.9
Role (Items 6 , 7)	73.1±35.1	68.2±44.4	74.2±38.3	67.9±40.5
Cognitive (Items 20,25)	85.9±13.3	89.4±17.1	89.4±15.4	85.9±15.0
Emotional (Items 21 - 24)	78.2±16.5	81.8±33.1	77.3±27.7	82.1±23.3
Social (Items 26 , 27)	76.9±33.7	74.2±39.0	80.3±26.7	71.8±42.2
Global Quality of life (Items 29 , 30)	80.8±33.2	84.8±36.9	95.5±25.6	71.8±37.7
*Symptom Scale and/items (Mean SD)***				
Fatigue (Items 10 , 12 , 18)	31.6±30.4	27.3±35.3	25.3±29.9	33.3±34.5
Nausea and vomiting (Items 14 , 15)	7.7±16.1	4.5±15.1	4.5±10.8	7.7±18.8
Pain (Items 9 , 19)	24.4±32.4	22.7±31.9	13.6±16.4	32.1±38.8
Dyspnea (Item 8)	15.4±22.0	45.5±37.3	21.2±22.5	35.9±39.6
Sleep disturbance (Item 11)	30.8±44.0	24.2±39.7	33.3±44.7	23.1±39.4
Appetite loss (Item 13)	23.1±39.4	9.1±30.2	9.1±21.6	23.1±43.9
Constipation (Item 16)	10.3±28.5	9.1±30.2	12.1±30.8	7.7±27.7
Diarrhea (Item 17)	10.3±21.0	12.1±22.5	6.1±13.5	15.4±25.9
Financial Impact (Item 28)	7.7±14.6	27.3±41.7	15.2±22.9	17.9±37.6

SD: standard deviation; NMDA: N methyl D Aspartate
*Scores range from 0 to 100, with a higher score representing a higher level of functioning.
**Scores range from 0 to 100, with a higher score representing a greater degree of symptoms.

Supplementary Appendix: CONSORT 2010 checklist of information to include when reporting a pilot or feasibility randomized trial in a journal or conference abstract

Item	Description	Reported on line number
Title	Identification of study as randomised pilot or feasibility trial	Title page
Authors *	Contact details for the corresponding author	Title page
Trial design	Description of pilot trial design (eg, parallel, cluster)	1
Methods		
Participants	Eligibility criteria for participants and the settings where the pilot trial was conducted	2
Interventions	Interventions intended for each group	8-9
Objective	Specific objectives of the pilot trial	4-5
Outcome	Prespecified assessment or measurement to address the pilot trial objectives**	4-5
Randomization	How participants were allocated to interventions	7
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	9
Results		
Numbers randomized	Number of participants screened and randomised to each group for the pilot trial objectives**	11
Recruitment	Trial status†	11
Numbers analysed	Number of participants analysed in each group for the pilot objectives**	12
Outcome	Results for the pilot objectives, including any expressions of uncertainty**	12-13
Harms	Important adverse events or side effects	15
Conclusions	General interpretation of the results of pilot trial and their implications for the future definitive trial	17-18
Trial registration	Registration number for pilot trial and name of trial register	Abstract page
Funding	Source of funding for pilot trial	Abstract page

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

Supplementary Appendix: CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	Title page (29)
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	30
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	31
	2b	Specific objectives or research questions for pilot trial	32
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	32
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	32
	4b	Settings and locations where the data were collected	33
	4c	How participants were identified and consented	33
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	33
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	35
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	NA
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	35

Sample size	7a	Rationale for numbers in the pilot trial	35-36
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	33
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	33
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	33
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	33
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	33-34
	11b	If relevant, description of the similarity of interventions	34
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	35-36
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	38
	13b	For each group, losses and exclusions after randomisation, together with reasons	36, 38
Recruitment	14a	Dates defining the periods of recruitment and follow-up	36
	14b	Why the pilot trial ended or was stopped	36
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	36
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	38
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any	40-41

		estimates. If relevant, these results should be by randomised group	
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	42
	19a	If relevant, other important unintended consequences	
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	43
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	42-44
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	42-44
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	44
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	30
Protocol	24	Where the pilot trial protocol can be accessed, if available	30
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	30
	26	Ethical approval or approval by research review committee, confirmed with reference number	30

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

References

1. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367(9522):1618-25.
2. Werner MU, Kongsgaard UE. I. Defining persistent post-surgical pain: is an update required? British journal of anaesthesia. 2014;113(1):1-4.
3. Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2009;36(1):170-80.
4. Gottschalk A, Cohen SP, Yang S, Ochroch EA. Preventing and treating pain after thoracic surgery. Anesthesiology. 2006;104(3):594-600.
5. Pluijms WA, Steegers MA, Verhagen AF, Scheffer GJ, Wilder-Smith OH. Chronic post-thoracotomy pain: a retrospective study. Acta Anaesthesiol Scand. 2006;50(7):804-8.
6. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. JAMA. 1998;280(2):147-51.
7. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-15.
8. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008;70(18):1630-5.
9. Macrae WA. Chronic post-surgical pain: 10 years on. British journal of anaesthesia. 2008;101(1):77-86.
10. Carpenter JS, Sloan P, Andrykowski MA, McGrath P, Sloan D, Rexford T, et al. Risk factors for pain after mastectomy/lumpectomy. Cancer Pract. 1999;7(2):66-70.
11. Ellis A, Bennett DL. Neuroinflammation and the generation of neuropathic pain. British journal of anaesthesia. 2013;111(1):26-37.
12. Katz N. The impact of pain management on quality of life. J Pain Symptom Manage. 2002;24(1 Suppl):S38-47.
13. Diagnostic Methods for Neuropathic Pain: A Review of Diagnostic Accuracy. Ottawa ON: 2015 Canadian Agency for Drugs and Technologies in Health.; 2015 Apr 07.
14. Okon T. Ketamine: an introduction for the pain and palliative medicine physician. Pain physician. 2007;10(3):493-500.
15. Orser BA, Pennefather PS, MacDonald JF. Multiple mechanisms of ketamine blockade of N-methyl-D-aspartate receptors. Anesthesiology. 1997;86(4):903-17.
16. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain. 1999;82(2):111-25.
17. Mathews TJ, Churchhouse AM, Housden T, Dunning J. Does adding ketamine to morphine patient-controlled analgesia safely improve post-thoracotomy pain? Interact Cardiovasc Thorac Surg. 2012;14(2):194-9.
18. Wang L, Johnston B, Kaushal A, Cheng D, Zhu F, Martin J. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in

adults: a systematic review and meta-analysis of randomized trials. Can J Anaesth. 2016;63(3):311-25.
19. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database Syst Rev. 2013;7:CD008307.
20. Kumar S. Memantine: pharmacological properties and clinical uses. Neurol India. 2004;52(3):307-9.
21. Kurian R, Raza K, Shanthanna H. A systematic review and meta-analysis of memantine for the prevention or treatment of chronic pain. Eur J Pain. 2019.
22. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert review of neurotherapeutics. 2009;9(5):723-44.
23. Becker DE. Basic and clinical pharmacology of glucocorticosteroids. Anesth Prog. 2013;60(1):25-31; quiz 2.
24. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. The New England journal of medicine. 2005;353(16):1711-23.
25. Turan A, Sessler DI. Steroids to ameliorate postoperative pain. Anesthesiology. 2011;115(3):457-9.
26. Weis F, Kilger E, Roozendaal B, de Quervain DJ, Lamm P, Schmidt M, et al. Stress doses of hydrocortisone reduce chronic stress symptoms and improve health-related quality of life in high-risk patients after cardiac surgery: a randomized study. The Journal of thoracic and cardiovascular surgery. 2006;131(2):277-82.
27. Srinivasa S, Kahokehr AA, Yu TC, Hill AG. Preoperative glucocorticoid use in major abdominal surgery: systematic review and meta-analysis of randomized trials. Annals of surgery. 2011;254(2):183-91.
28. Lunn TH, Kehlet H. Perioperative glucocorticoids in hip and knee surgery - benefit vs. harm? A review of randomized clinical trials. Acta Anaesthesiol Scand. 2013;57(7):823-34.
29. Stewart R, Bill R, Ullah R, McConaghy P, Hall SJ. Dexamethasone reduces pain after tonsillectomy in adults. Clin Otolaryngol Allied Sci. 2002;27(5):321-6.
30. Lunn TH, Kristensen BB, Andersen LO, Husted H, Otte KS, Gaarn-Larsen L, et al. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial. British journal of anaesthesia. 2011;106(2):230-8.
31. Kazemi H, Ghassemi S, Fereshtehnejad SM, Amini A, Kolivand PH, Doroudi T. Anxiety and depression in patients with amputated limbs suffering from phantom pain: a comparative study with non-phantom chronic pain. Int J Prev Med. 2013;4(2):218-25.
32. Carriere JS, Thibault P, Milioto M, Sullivan MJ. Expectancies Mediate the Relations Among Pain Catastrophizing, Fear of Movement, and Return to Work Outcomes After Whiplash Injury. J Pain. 2015;16(12):1280-7.
33. Authority NSH. Ketamine for Adjunct Analgesia, Medication Manual 2015 [Available from: http://policy.nshealth.ca/Site_Published/dha9/document_render.aspx?documentRenderIdType=6&documentRender.GenericField=&documentRender.Id=57824.

34. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1-2):9-19.
35. Chapman CR, Donaldson GW, Davis JJ, Bradshaw DH. Improving individual measurement of postoperative pain: the pain trajectory. J Pain. 2011;12(2):257-62.
36. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114(1-2):29-36.
37. Ringsted TK, Wildgaard K, Kreiner S, Kehlet H. Pain-related impairment of daily activities after thoracic surgery: a questionnaire validation. Clin J Pain. 2013;29(9):791-9.
38. Balduyck B, Hendriks J, Lauwers P, Van Schil P. Quality of life after lung cancer surgery: a prospective pilot study comparing bronchial sleeve lobectomy with pneumonectomy. J Thorac Oncol. 2008;3(6):604-8.
39. Devereaux PJ, Szczeklik W. Myocardial injury after non-cardiac surgery: diagnosis and management. Eur Heart J. 2019.
40. Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ (Clinical research ed). 2016;355:i5239.
41. Chapman CR, Zaslansky R, Donaldson GW, Shinfeld A. Postoperative pain trajectories in cardiac surgery patients. Pain Res Treat. 2012;2012:608359.
42. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, et al. A tutorial on pilot studies: the what, why and how. BMC medical research methodology. 2010;10:1.
43. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharmaceutical Statistics. 2005;4(4):287-91.
44. Gauthier S, Herrmann N, Ferreri F, Agbokou C. Use of memantine to treat Alzheimer's disease. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2006;175(5):501-2.
45. Ebixa. Ebixa produc monograph: Lundbeck; [Available from: https://www.lundbeck.com/au/products/our-products/ebixa.
46. Inc P. pms-Memantine product monograph 2016 [Available from: https://pdf.hres.ca/dpd_pm/00034930.PDF.
47. Onugha O, Ivey R, McKenna R. Novel Techniques and Approaches to Minimally Invasive Thoracic Surgery. Surg Technol Int. 2017;30:231-5.
48. Kadam RA, Borde SU, Madas SA, Salvi SS, Limaye SS. Challenges in recruitment and retention of clinical trial subjects. Perspect Clin Res. 2016;7(3):137-43.
49. Gul RB, Ali PA. Clinical trials: the challenge of recruitment and retention of participants. J Clin Nurs. 2010;19(1-2):227-33.
50. Thoma A, Farrokhyar F, McKnight L, Bhandari M. Practical tips for surgical research: how to optimize patient recruitment. Can J Surg. 2010;53(3):205-10.
51. Freixinet JL, Canalis E, Julia G, Rodriguez P, Santana N, Rodriguez de Castro F. Axillary thoracotomy versus videothoracoscopy for the treatment of primary spontaneous pneumothorax. The Annals of thoracic surgery. 2004;78(2):417-20.

52. Gerbershagen HJ, Pogatzki-Zahn E, Aduckathil S, Peelen LM, Kappen TH, van Wijck AJ, et al. Procedure-specific risk factor analysis for the development of severe postoperative pain. Anesthesiology. 2014;120(5):1237-45.
53. Anwar S, Cooper J, Rahman J, Sharma C, Langford R. Prolonged Perioperative Use of Pregabalin and Ketamine to Prevent Persistent Pain after Cardiac Surgery. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2019.
54. Tighe PJ, Le-Wendling LT, Patel A, Zou B, Fillingim RB. Clinically derived early postoperative pain trajectories differ by age, sex, and type of surgery. Pain. 2015;156(4):609-17.
55. Okamoto A, Yamasaki M, Yokota I, Mori M, Matsuda M, Yamaguchi Y, et al. Classification of acute pain trajectory after breast cancer surgery identifies patients at risk for persistent pain: a prospective observational study. J Pain Res. 2018;11:2197-206.
56. Rosenthal R, Kasenda B, Dell-Kuster S, von Elm E, You J, Blumle A, et al. Completion and Publication Rates of Randomized Controlled Trials in Surgery: An Empirical Study. Annals of surgery. 2015;262(1):68-73.

PART 3: Analgesic Intervention in Chronic Low Back Pain

Chapter 5: The need to evaluate the use of gabapentinoids in the treatment of chronic low back pain

Introduction

Chronic low back pain (CLBP) is a common condition and causes significant pain, distress and disability across the world. It is multifactorial in aetiology and is challenging to manage. In most cases the underlying mechanism of pain is predominantly non-specific, although there could be an element of neuropathic pain in some patients. Neuropathic pain is more severe, with significant disability. Gabapentinoids, including gabapentin and pregabalin, have proven efficacy in some neuropathic pain conditions. However, a substantial population of patients with CLBP are treated with gabapentinoids despite no clear evidence. In this chapter, we describe the etiological and treatment considerations in CLBP, apart from limitations within the existing evidence to treat this condition. It also describes the protocol of our systematic review and meta-analysis of randomised control trials using gabapentinoids in the treatment of CLBP.

Citation: Shanthanna H, Gilron I, Thabane L, Devereaux PJ, Bhandari M, AlAmri R, Rajarathinam M, Kamath S. Gabapentinoids for chronic low back pain: a protocol for systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2016 Nov 10;6(11):e013200.

Open Access Protocol

BMJ Open

Gabapentinoids for chronic low back pain: a protocol for systematic review and meta-analysis of randomised controlled trials

Harsha Shanthanna,[1] Ian Gilron,[2] Lehana Thabane,[1,3] Philip J Devereaux,[3,4] Mohit Bhandari,[3,5] Rizq AlAmri,[1] Manikandan Rajarathinam,[1] Sriganesh Kamath[1,6]

To cite: Shanthanna H, Gilron I, Thabane L, *et al*. Gabapentinoids for chronic low back pain: a protocol for systematic review and meta-analysis of randomised controlled trials. *BMJ Open* 2016;**6**:e013200. doi:10.1136/bmjopen-2016-013200

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-013200).

Received 28 June 2016
Revised 29 September 2016
Accepted 21 October 2016

For numbered affiliations see end of article.

Correspondence to
Dr Harsha Shanthanna; harshamd@gmail.com

ABSTRACT

Introduction: Chronic low back pain (CLBP) is a common condition and causes significant pain, distress and disability across the world. It is multifactorial in aetiology and is challenging to manage. Although the underlying mechanism of pain is predominantly non-specific, many argue that there is a substantial neuropathic pain element. Neuropathic pain is more severe, with significant disability. Gabapentinoids, including gabapentin and pregabalin, have proven efficacy in some neuropathic pain conditions. Despite no clear evidence, a substantial population of patients with CLBP are treated with gabapentinoids.

Objectives: We aim to assess whether the use of gabapentinoids is effective and safe in the treatment of predominant CLBP, by conducting a systematic review and meta-analysis of randomised control trials (RCTs).

Methodology: We will search the databases of MEDLINE, EMBASE and Cochrane for RCTs published in English language and have used gabapentinoids for the treatment of CLBP. Study selection and data extraction will be performed independently by paired reviewers using structured electronic forms, piloted between pairs of reviewers. The review outcomes will be guided by Initiative on Methods, Measurement and Pain Assessment in Clinical Trials guidelines, with pain relief as the primary outcome. We propose to carry out meta-analysis if there are three or more studies in a particular outcome domain, using a random effects model. Pooled outcomes will be reported as weighted mean differences or standardised mean differences and risk ratios with their corresponding 95% CIs, for continuous outcomes and dichotomous outcomes, respectively. Rating of quality of evidence will be reported using GRADE summary of findings table.

Discussion: The proposed systematic review will be able to provide valuable evidence to help decision-making in the use of gabapentinoids for the treatment of CLBP. This will help advance patient care and potentially highlight limitations in existing evidence to direct future research.

Ethics and dissemination: Being a systematic review, this study would not necessitate ethical review and approval. We plan to report and publish our study findings in a high impact medical journal, with online access.

Trial registration number: CRD42016034040.

Strengths and limitations of this study

- There are no existing reviews on the use of gabapentinoids for predominant, chronic low back pain (CLBP).
- Our review methodology incorporates a detailed risk of bias assessment, including elements that have been proposed specifically for chronic pain trials by well-known Cochrane pain researchers.
- Our review team consists of experts in the field of analgesia drug trials and also experienced research methodologists.
- Our review involves select population of predominant CLBP and hence may limit its applicability to patients with leg and back pain or predominant leg pain.
- Our review, and hence its results, would be limited by the number and quality of randomised controlled studies in this area.
- Owing to the variability involved in the study population, and also in the way of outcome measurements, our results may carry substantial heterogeneity.

BACKGROUND

Burden of chronic low back pain

Chronic low back pain (CLBP) is very common. It is typically considered to be pain felt in the area of the low back and lasting at least 12 weeks or more in duration.[1 2] Exact estimates of the prevalence of CLBP are difficult to establish because of the variability in the questions and criteria used in epidemiological studies.[3] Many studies looking at the burden of CLBP have included population with acute (<12 weeks) low back pain

(LBP).[3] The life time prevalence of LBP—not necessarily chronic, varies between 51% and 80%.[1] A majority of these episodes are self-limiting. When CLBP alone is considered, it is estimated to be around 5.9–18.1%.[1 4] CLBP causes significant pain, suffering, impairment of daily activities, and decreased quality of life.[4] Among chronic conditions CLBP has been noted to be the leading cause of years lived with disability.[5]

Aetiological considerations of CLBP

Axial CLBP is multifactorial and in many patients diffuse and non-specific.[6] There are several musculoskeletal structures within and around the neuroaxial canal capable of structural damage leading to physiological pain.[1 7] On an aetiological and therapeutic perspective, CLBP with sciatica or neurogenic claudication needs to be separated from predominant or isolated CLBP.[8] Nearly 85% of isolated CLBP lacks a clear pathoanatomical diagnosis.[9] On the basis of the underlying nature of pain mechanism, chronic pain conditions could be considered to be either 'neuropathic pain' (NP), or 'non-neuropathic pain' (NNP),[10 11] also referred to as nociceptive.[11] Central sensitisation (CS) is another category that is supposed to be distinct, but can have overlapping features, within the mechanism-based classification.[12 13] It is proposed that CS type of pain may be involved in a large number of CLBP patients.[14–16] In general, identifying a condition as NP in nature carries important implications for diagnosis and management. It has been suggested that NP conditions are more painful, are associated with greater levels of physical and psychological dysfunction and are challenging to treat.[17 18] Within the CLBP patients, the diagnosis of NP is a challenge. Most epidemiological studies depend on the screening questionnaires presently available in patients of predominant CLBP.[19 20] On the basis of studies using screening questionnaires, a recent review suggested a median rate of 41% with a range of 17–55% of primary NP.[1 10] Others have reported a much lower rate of 4%.[21] Data from a US health insurance database showed that the claims for back and neck pain with neuropathic involvement is the most frequent neuropathic disorder.[22]

Treatment considerations in CLBP

CLBP requires a multidisciplinary approach,[3 7] and in practice, medications remain an important modality of treatment.[23] Up to 80% of patients in the US are prescribed one or more drugs for LBP in their first visit.[3] Among the antiepileptics, pregabalin (PG) and gabapentin (GP) are commonly used for many NP conditions.[24–26] These two medications, grouped together as gabapentinoids, act by α-2 delta2 subunit of presynaptic voltage-dependent calcium channels, there by modulating pathologically enhanced neurotransmission in the primary afferent neurons.[27 28] The use of both medications necessitates slow initiation and titration of dosage and a significant increase in overall treatment costs.[29] The treatment with gabepentinoids can also be associated with side effects. The side effects common to these medications commonly include sedation, dizziness, peripheral oedema, dry mouth, drowsiness, fatigue, nausea and weight gain.[30 31]

Limitations of existing evidence for the treatment of CLBP

Analgesic effectiveness of most treatments on non-specific CLBP is considered to be small.[6] Although there have been several systematic reviews on the effectiveness of medications for the treatment of CLBP, none of the reviews have specifically reviewed the evidence for the effectiveness and safety of the use of gabapentinoids. White *et al*[23] were able to assess the effects of non-steroidal anti-inflammatory drugs (NSAIDs), opioids and antidepressants on CLBP. They observed that NSAIDs were helpful, but antidepressants were no more helpful than placebo with respect to pain, functional status or depression,[23] although a previous meta-analysis by Salerno *et al*[32] had observed that antidepressants were better than placebo. In a recent review, Chou and Huffman reviewed medications for acute and chronic LBP conditions in a review of the evidence for American Pain Society/American College of Physicians Clinical Practice Guideline development. Among medications for CLBP, they found small to moderate benefit with tricyclic antidepressants, and GP in patients with radiculopathy associated with CLBP.[33] This was based on three small trials of GP. They did not identify trials with predominant axial CLBP. The review by Morlion identified two studies for PG and one study for GP. They did not perform a meta-analysis and observed that PG is only effective in a combination therapy.[27] More recently, Romano *et al*[34] performed a systematic review of antineuropathic and antinociceptive drugs in patients with CLBP. They also observed that PG combined with celecoxib or opioids was more effective than either monotherapy, based on two small studies. Overall the benefits of treating patients with predominant CLBP by either GP or PG are not clear. We aim to perform a systematic review and meta-analysis to look at the evidence to support the use of gabapentinoids in the treatment of CLBP.

OBJECTIVES

Primary objectives of this systematic review are: (1) to assess the effectiveness of PG and gabapentin (GB) for pain relief in patients with predominant CLBP; and (2) to assess the safety of using PG and GB in patients with predominant CLBP.

The secondary objectives of this review are as follows: (1) assessing the effects of PG and GB on the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) outcomes;[35] these outcomes include physical functioning, emotional functioning, participant ratings of global improvement and satisfaction with treatment, and participant disposition and (2)

to assess whether PG and GB selectively improve pain relief in patients with predominant neuropathic CLBP.

METHODS AND ANALYSIS

Our review protocol has been registered with PROSPERO with the registration number CRD42016034040. This protocol has been prepared for publication according to PRISMA-P guidelines.[36]

Eligibility criteria

Participants

We will include studies with adult (≥18 years of age) patients with CLBP of 3 months or more, with or without lower limb pain. Studies with patients of back and leg/radicular pain will only be included if the population consisted of predominant CLBP, rather than leg/radicular pain. If a trial involves a mix of CLBP and other chronic pain patients, we will include the study only if they report outcomes separately for our study population of interest, or if at least 90% of the trial patients are >18 years with predominant CLBP.

Studies

Randomised controlled trials (RCTs) published in English will be eligible for our review.

Interventions

Eligible studies must randomise patients to receive 'PG' or 'GB', either 'alone' or 'in combination with other treatment', and compare it with any active or inactive treatments. We will separately consider the comparisons of active and inactive treatments for pooling.

Information sources

We will search the electronic databases of EMBASE, MEDLINE and the Cochrane Central Registry of Controlled Trials (CENTRAL), from their inception until 26 January 2016. Our search will be limited to reports published in English. Further, we will search the WHO clinical trial registry (http://apps.who.int/trialsearch/Default.aspx), and clinical trial registry (https://clinicaltrials.gov/), to look for any registered studies, which fulfil our eligibility criteria and crosscheck for their published results. Unpublished, but completed study results will be requested from the authors or investigators. To further ensure comprehensiveness, we will review the bibliographies of recent reviews and selected studies.

Search strategy

The search will be performed using a sensitive strategy, in consultation with an experienced librarian, for each specific database. The search terms will include terms referring to study population of low back pain, and terms referring to study interventions—GB, PG and anticonvulsants (see online supplementary appendix 1). We will limit our search to English language. Non-randomised trials would be excluded during the study selection process.

Study screening and selection

Study selection will be performed in two stages, with paired reviewers screening studies independently and in duplicate. The first level will be performed on titles and available abstracts, and full text screening will be performed on citations felt potentially eligible by either reviewer. To ensure consistency, reviewers will perform a calibration exercise, before beginning with screening. Reviewers will be asked to resolve disagreement by consensus or, if a discrepancy remains, through discussion with an arbitrator (HS). A quadratic kappa statistic on the full article final decisions will be calculated as a measure of interobserver agreement, independent of chance regarding study eligibility and interpreted as almost perfect agreement (0.81–0.99); substantial agreement (0.61–0.80); moderate agreement (0.41–0.60); fair agreement (0.21–0.40); slight agreement (0.01–0.20); <0 as less than chance agreement.[37]

Data management

Data collection process

Paired reviewers will extract the data independently and in duplicate, using electronic data extraction forms. The forms will be specifically adapted to the present review and will be piloted between the paired reviewers for consistency and accuracy. To assist with the data extraction, an instruction manual will be provided along with each relevant form.

Data items

Extracted data will include study characteristics, risk of bias items, demographic information, participant flow through the study and outcomes on continuous and binary measures captured on six core domains as recommended by the IMMPACT statement guidelines.[35]

Outcomes and prioritisation

We will consider pain relief and safety as our primary outcomes and other outcomes (as guided by IMMPACT) as secondary outcomes. We will also prioritise the use of intention to treat analysis (ITT). We will only pool data across trials if there are three or more studies contributing to an outcome domain. Since PG or GB can be used alone or in combination, we will consider pooling studies using PG or GB, either alone or in combination separately. For the primary outcome of pain relief, we will extract continuous outcomes and dichotomous outcomes (success/failure) reported in each study, at various time points. For pooling across studies, we will use the most common outcome type reported. If we consider pooling using the continuous outcomes, we will convert all into a common 0–10 Numerical Rating Scale (NRS), as it is commonly used, and easy to interpret.[35] We will capture baseline and end scores and change scores. We will prioritise change scores, if reported, for

the analysis. We will consider the pain relief outcomes reported at the most common time point or the longest follow-up time point for pooling. Safety will be assessed by comparing the risk of serious adverse events causing death, hospitalisation or treatment or study withdrawal. Secondary outcomes will include the comparisons of improvement in physical functioning, emotional functioning and participant ratings of global improvement and satisfaction.

Data synthesis and analysis of outcomes

Extracted data will be compiled in Microsoft EXCEL for analysis. Risk of bias will be assessed using Cochrane modified risk of bias tool. Included study characteristics will be noted in a table. For the primary analysis, we will use a complete case analysis with ITT. Analysis and synthesis will be carried out using Review Manager (RevMan) (Computer program), V.5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014; and Microsoft Excel 2011 (Mac version). Using random effects model for pooling, we will calculate either the risk ratio (to be interpreted as the risk of having success) for dichotomous outcomes and weighted mean difference (WMD) or standardised mean differences (SMD) for continuous outcomes, as appropriate. We will consider the inclusion of crossover studies for analysis if the study includes a reasonable washout period to deal with carryover effects, and in which the order of receiving treatments was randomised. For pooling, we will consider results reported from paired test. If not provided, we will consider results of unpaired test (similar to a parallel group trial), and noting that it is conservative, as it will receive less weight. If there is a strong possibility of carryover effect, or if the final results are poorly reported, or if there is a significant drop out rate (>20%), we will include the results from the first period only.[38]

Risk of bias assessment and identification

Risk of bias within the included studies will be assessed using the Cochrane risk of bias tool based on the components of random sequence generation; allocation concealment; blinding of participants; blinding of outcome assessment; incomplete outcome data and selective outcome reporting. For our review, the possibility of selective outcome reporting will be when the outcomes are described in the methods section but not identified or reported in the results section of the same study report.[39] Among trials of chronic pain treatment, there is a potential for bias with outcome assessment time and the threshold used to establish the success of treatment based on improvement in pain relief. We will consider outcome assessment <12 weeks, and <30% improvement in pain relief as indicators of potential bias, as suggested by Moore *et al*.[40 41] We will use a modified Cochrane risk-of-bias instrument, with response options of 'definitely yes', 'probably yes', 'probably no' and 'definitely no'" We will assign trials in the 'definitely yes' and 'probably yes' categories a high risk of bias and those in the 'probably no' and 'definitely no' categories a low risk of bias. Any disagreement on the risk of bias item scoring will be noted and arbitrated by the primary investigator (HS). For crossover trials, we will also identify the potential bias resulting from carryover effect, order of randomisation and analysis method.[38]

Assessment of heterogeneity

Statistical heterogeneity will be calculated using Cochrane's Q test, with a threshold of p value at 0.10, and the percentage variability in individual effect estimates will be described by I^2 statistic. We will consider the I^2 threshold as 0–40%: might not be important; 30–60%: may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity and 75–100%: considerable heterogeneity, as suggested in the Cochrane handbook.[38] To explain heterogeneity of >40%, we will consider the following a priori hypotheses: differences in population, duration of CLBP, dosages of intervention, treatment duration, treatment combinations and outcome measurement standards.

Subgroup analysis

In studies that have separately reported pain relief in patients who were screened for the presence of NP, we will perform a subgroup analysis to look for the effect of our study interventions (GB or PG) on pain relief. These patients will be considered to be NP if they are screened for the presence of leg pain along with CLBP, or NP is identified by a screening questionnaire at the baseline.

Sensitivity analysis

This will be carried out for studies with loss to follow-up (LTFU) and studies with high risk of bias on a particular component across studies. We will consider patients loss to follow-up (LTFU) subsequent to randomisation as missing for data analysis and will be explored further for imputation, if it is >5%. For trials in which the authors report total missing participant data only, without specifying at what stage the participants were missing, we will consider the total sample size and the actual sample size included for final analysis and assume that missing data were equally distributed between the arms. For trials in which the authors reported imputed analysis only, we will use the imputed results for the meta-analysis. We will perform imputation strategies as described by Ebrahim *et al*,[42] and Akl *et al*,[43] for continuous measures and dichotomous measures, respectively. We will perform this analysis only for the pain relief outcome.

Addressing potential biases

If there are more than 10 studies for our meta-analysis, funnel plot will be used to assess for publication bias. Trials with low sample size can increase the chances of random error and also show erroneously large treatment effect sizes. Inclusion of such studies in a meta-analysis

increases the chances of publication bias.[44 45] As suggested by Moore *et al*,[40] we will consider a sample size threshold of <50 to identify a trial as having the potential for publication bias based on low sample size.

Interpretation and reporting

Reporting of outcomes will be performed as WMD or SMD for continuous outcomes, and relative risks (RR) for dichotomous outcomes, with their 95% CIs. For dichotomous outcomes, we will also report the findings in measures of absolute risk reduction. Rating of quality of evidence will also be performed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, by using a 'summary of findings' table.

DISCUSSION

Treatment of CLBP requires a multimodal approach. Considerations for choosing appropriate medications include a rationale based on underlying mechanism and treatment effectiveness. Since CLBP is recurrent and long standing, it may require long-term treatment involving significant costs to the patient and the payer. Although gabapentinoids are commonly used for the treatment of CLBP, their effectiveness is not clear. Our review will look for existing evidence in the form of RCTs. This will help guide treatment decisions for CLBP, advance patient care based on available evidence, and highlight limitations in existing evidence to direct future research.

Limitations and challenges

Our review does not include studies that focus primarily on patients with lumbar radicular symptoms. Although there are no existing reviews in this population for the use of gabapentinoids, we felt that addition of such studies will add to the clinical heterogeneity. Lumbar radicular pain has a much pathophysiology and elements leading to neuropathic pain. Since there is a stronger rationale to use gabapentinoids in that population, we feel that results obtained from the inclusion of such studies may potentially lessen the clarity and impact of evidence directed at isolated or predominant CLBP. Despite this exclusion, studies included in our review may still involve considerable heterogeneity. This may be as a result of variability in underlying pathology, duration of chronic pain and presence of other conditions of chronic pain, variability in the time and the method of outcome collection for pain relief or other outcomes. Inclusion of crossover trials in a meta-analysis has its limitations. We have outlined our plan to include and analyse crossover studies in the 'Methods and analysis' section.

Author affiliations
[1]Department of Anesthesiology, McMaster University, Michael DeGroote School of Medicine, Hamilton, Ontario, Canada
[2]Department of Anesthesiology and Biomedical Sciences, Queen's University, Kingston, Ontario, Canada
[3]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada
[4]Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[5]Department of Surgery, McMaster University, Hamilton, Ontario, Canada
[6]Department of Neuroanesthesia, National Institute of Mental Health and Neurosciences, Bangalore, India

Acknowledgements The authors acknowledge the assistance provided by Rachel Couban (librarian) in conducting the literature search.

Contributors HS is the primary investigator; conceived the study concept; involved in conduct of the review and analysis and drafted the protocol manuscript. IG is a coinvestigator and content expert on neuropathic pain and analgesic clinical trials and involved in conduct and interpretation of study results. LT is a coinvestigator and involved in methodological supervision and conduct and interpretation of study results. PJD and MB are coinvestigators and involved in methodological supervision and conduct and interpretation of study results. MR, SK and RA are coinvestigators and involved in conduct of the review and manuscript preparation. All authors approve the publication of the protocol.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Hooten WM, Cohen SP. Evaluation and treatment of low back pain: a clinically focused review for primary care specialists. *Mayo Clin Proc* 2015;90:1699–718.
2. Juniper M, Le TK, Mladsi D. The epidemiology, economic burden, and pharmacological treatment of chronic low back pain in France, Germany, Italy, Spain and the UK: a literature-based review. *Expert Opin Pharmacother* 2009;10:2581–92.
3. Parthan A, Evans CJ, Le K. Chronic low back pain: epidemiology, economic burden and patient-reported outcomes in the USA. *Expert Rev Pharmacoecon Outcomes Res* 2006;6:359–69.
4. Hoy D, Bain C, Williams G, *et al*. A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012;64:2028–37.
5. Murray CJ, Atkinson C, Bhalla K, *et al*. The state of US health, 1990–2010: burden of diseases, injuries, and risk factors. *JAMA* 2013;310:591–608.
6. Machado LA, Kamper SJ, Herbert RD, *et al*. Analgesic effects of treatments for non-specific low back pain: a meta-analysis of placebo-controlled randomized trials. *Rheumatology (Oxf)* 2009;48:520–7.
7. Rathmell JP. A 50-year-old man with chronic low back pain. *JAMA* 2008;299:2066–77.
8. Carragee EJ. Clinical practice. Persistent low back pain. *N Engl J Med* 2005;352:1891–8.
9. Deyo RA, Weinstein JN. Low back pain. *N Engl J Med* 2001;344:363–70.
10. Kaki AM, El-Yaski AZ, Youseif E. Identifying neuropathic pain among patients with chronic low-back pain: use of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale. *Reg Anesth Pain Med* 2005;30:422–8.
11. Nicholson B. Differential diagnosis: nociceptive and neuropathic pain. *Am J Manag Care* 2006;12(9 Suppl):S256–62.
12. Smart KM, Blake C, Staines A, *et al*. Clinical indicators of 'nociceptive', 'peripheral neuropathic' and 'central' mechanisms of musculoskeletal pain. A Delphi survey of expert clinicians. *Man Ther* 2010;15:80–7.
13. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* 2009;10:895–926.
14. Nijs J, Apeldoorn A, Hallegraeff H, *et al*. Low back pain: guidelines for the clinical classification of predominant neuropathic, nociceptive, or central sensitization pain. *Pain Physician* 2015;18:E333–46.

15. Roussel NA, Nijs J, Meeus M, *et al*. Central sensitization and altered central pain processing in chronic low back pain: fact or myth? *Clin J Pain* 2013;29:625–38.
16. Smart KM, Blake C, Staines A, *et al*. Mechanisms-based classifications of musculoskeletal pain: part 1 of 3: symptoms and signs of central sensitisation in patients with low back (+/− leg) pain. *Man Ther* 2012;17:336–44.
17. Smith BH, Torrance N, Bennett MI, *et al*. Health and quality of life associated with chronic pain of predominantly neuropathic origin in the community. *Clin J Pain* 2007;23:143–9.
18. Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol* 2010;9:807–19.
19. Haanpaa M, Attal N, Backonja M, *et al*. NeuPSIG guidelines on neuropathic pain assessment. *Pain* 2011;152:14–27.
20. La Cesa S, Tamburin S, Tugnoli V, *et al*. How to diagnose neuropathic pain? The contribution from clinical examination, pain questionnaires and diagnostic tests. *Neurol Sci* 2015;36:2169–75.
21. Morlion B. The relevance of neuropathic components in chronic back pain. *Curr Med Res Opin* 2011;27:2067–8.
22. Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. *J Pain* 2004;5:143–9.
23. White AP, Arnold PM, Norvell DC, *et al*. Pharmacologic management of chronic low back pain: synthesis of the evidence. *Spine* 2011;36(21 Suppl):S131–43.
24. Gajraj NM. Pregabalin: its pharmacology and use in pain management. *Anesth Analg* 2007;105:1805–15.
25. Bennett MI, Simpson KH. Gabapentin in the treatment of neuropathic pain. *Palliat Med* 2004;18:5–11.
26. Finnerup NB, Attal N, Haroutounian S, *et al*. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol* 2015;14:162–73.
27. Morlion B. Pharmacotherapy of low back pain: targeting nociceptive and neuropathic pain components. *Curr Med Res Opin* 2011;27:11–33.
28. Patel R, Dickenson AH. Mechanisms of the gabapentinoids and alpha 2 delta-1 calcium channel subunit in neuropathic pain. *Pharmacol Res Perspect* 2016;4:e00205.
29. Sætterstrøm B, Poulsen PB, Olsen J, *et al*. PSY9 real-life cost-analyses of chronic low-back pain patients with neuropathic pain components in Denmark. *Value Health* 2012;15:A509.
30. Malizels M, McCarberg B. Antidepressants and antiepileptic drugs for chronic non-cancer pain. *Am Fam Physician* 2005;71:483–90.
31. Toth C. Drug safety evaluation of pregabalin. *Expert Opin Drug Saf* 2012;11:487–502.
32. Salerno SM, Browning R, Jackson JL. The effect of antidepressant treatment on chronic back pain: a meta-analysis. *Arch Intern Med* 2002;162:19–24.
33. Chou R, Huffman LH. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/ American College of Physicians clinical practice guideline. *Ann Intern Med* 2007;147:505–14.
34. Romano CL, Romano D, Lacerenza M. Antineuropathic and antinociceptive drugs combination in patients with chronic low back pain: a systematic review. *Pain Res Treat* 2012;2012:154781.
35. Dworkin RH, Turk DC, Farrar JT, *et al*. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;113:9–19.
36. Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
37. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med* 2005;37:360–3.
38. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions, Version 5.1.0*. The Cochrane Collaboration, 2011. http://www.cochrane-handbook.org
39. Chan AW, Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. *BMJ* 2005;330:753.
40. Andrew Moore R, Eccleston C, Derry S, *et al*. "Evidence" in chronic pain—establishing best practice in the reporting of systematic reviews. *Pain* 2010;150:386–9.
41. Moore RA, Gavaghan D, Tramer MR, *et al*. Size is everything—large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;78:209–16.
42. Ebrahim S, Johnston BC, Akl EA, *et al*. Addressing continuous data measured with different instruments for participants excluded from trial analysis: a guide for systematic reviewers. *J Clin Epidemiol* 2014;67:560–70.
43. Akl EA, Johnston BC, Alonso-Coello P, *et al*. Addressing dichotomous data for participants excluded from trial analysis: a guide for systematic reviewers. *PLoS One* 2013;8:e57132.
44. Ioannidis JP, Cappelleri JC, Lau J. Issues in comparisons between meta-analyses and large trials. *JAMA* 1998;279:1089–93.
45. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol* 2000;53:1119–29.

APPENDIX 1: Search Strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 exp Back Pain/ (32247)
2 low back pain.mp. (26237)
3 dorsalgia.mp. (75)
4 back ache.mp. (85)
5 (lumbar adj pain).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1238)
6 exp Coccyx/ or coccydynia.mp. (970)
7 exp Spondylosis/ (6155)
8 lumbago.mp. (1226)
9 back disorder.mp. (116)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (46531)
11 exp Anticonvulsants/ or exp gamma-Aminobutyric Acid/ or gabapentin.mp. (162086)
12 gaba agents.mp. or exp GABA Agents/ (147096)
13 gabapentinoids.mp. (95)
14 pregabalin.mp. or exp Pregabalin/ (2385)
15 lyrica.mp. (88)
16 neurontin.mp. (144)
17 11 or 12 or 13 or 14 or 15 or 16 (212270)
18 10 and 17 (211)

Database: Embase <1974 to 2016 Jan 26>

Search Strategy:

1 exp backache/ (81835)
2 backache.mp. (41855)
3 exp low back pain/ (42900)
4 low back pain.mp. (48181)
5 low back pain.mp. (48181)
6 lumbago.mp. (1695)
7 spondylosis.mp. (8115)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (94182)
9 exp gabapentin/ or gabapentin.mp. (24302)
10 anticonvulsants.mp. or exp anticonvulsive agent/ (320763)
11 neurontin.mp. (1935)
12 gabapentinoids.mp. (163)
13 pregabalin/ (9498)
14 pregabalin.mp. (9777)
15 lyrica.mp. (910)
16 9 or 10 or 11 or 12 or 13 or 14 or 15 (321222)
17 8 and 16 (2606)
18 limit 17 to english language (2447)

Search Name: CENTRAL-Gabapentinoids for LBP
Last Saved: 21/01/2016 17:52:05.327
Description:
ID Search
#1 MeSH descriptor: [Low Back Pain] explode all trees
#2 low back ache
#3 lumbago
#4 low back pain
#5 MeSH descriptor: [Anticonvulsants] explode all trees
#6 gabapentin
#7 pregabalin
#8 neurontin
#9 lyrica
#10 gabapentinoids
#11 #1 or #2 or #3 or #4
#12 #5 or #6 or #7 or #8 or #9 or #10
#13 #11 and #12

Chapter 6: A systematic review and meta-analysis of gabapentinoids for chronic low back pain

Introduction

Chronic Low Back Pain (CLBP) is very common, with a lifetime prevalence between 51% and 80%. In majority, it is nonspecific in nature and multifactorial in etiology. Pregabalin (PG) and Gabapentin (GB) are gabapentinoids are increasingly used for nonspecific CLBP. Concerns have been raised about such use from guidelines. In this review we aimed to assess the effectiveness and safety of gabapentinoids in adult CLBP patients. We searched MEDLINE, EMBASE, and Cochrane databases from their inception until December 20th, 2016 for randomized control trials reporting the use of gabapentinoids for the treatment of CLBP of >3 months duration, in adult patients. Study selection and data extraction was performed independently by paired reviewers. Outcomes were guided by Initiative on Methods, Measurement and Pain Assessment in Clinical Trials guidelines, with pain relief and safety as the primary outcomes. Meta-analyses were performed for outcomes reported in 3 or more studies. Outcomes were reported as mean differences (MDs) or risk ratios (RRs) with their corresponding 95% confidence intervals (CIs), and I2 in percentage representing the percentage variability in effect estimates that could be explained by heterogeneity. GRADE (Grading of Recommendations Assessment, Development, and Evaluation) was used to assess the quality of evidence. Out of 1,385 citations, eight studies were included. Based on the interventions and comparators, studies were analyzed in 3 different groups. GB compared with placebo (3 studies, n = 185) showed minimal improvement of pain (MD = 0.22 units, 95% CI [-0.5 to 0.07] I2 = 0%; GRADE: very low). Three studies compared PG with other types of analgesic medication (n = 332) and showed greater improvement in the other analgesic group (MD = 0.42 units, 95% CI [0.20 to 0.64] I2 = 0; GRADE: very low). Studies using PG as an adjuvant (n = 423) were not pooled due to heterogeneity, but the largest of them showed no benefit of adding PG to tapentadol. There were no deaths or hospitalizations reported. Compared with placebo, adverse events were more commonly reported with GB. The number needed to harm with 95% CI for dizziness, fatigue, difficulties with mentation, and visual disturbances were 7 (4 to 30), 8 (4 to 44), 6 (4 to 15), and 6 (4 to 13) respectively. Functional and emotional improvements were reported by few studies and showed no significant improvements. We conclude that existing evidence on the use of gabapentinoids in CLBP is limited and demonstrates significant risk of adverse effects without any demonstrated benefit. There is need for large high-quality trials to more definitively inform this issue.

Citation: Shanthanna H, Gilron I, Rajarathinam M, AlAmri R, Kamath S, Thabane L, Devereaux PJ, Bhandari M. Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. PLoS Med. 2017 Aug 15;14(8):e1002369.

PLOS | MEDICINE

RESEARCH ARTICLE

Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials

Harsha Shanthanna[1,2]*, Ian Gilron[3], Manikandan Rajarathinam[1], Rizq AlAmri[1], Sriganesh Kamath[1,4], Lehana Thabane[1,2,5], Philip J. Devereaux[2,6], Mohit Bhandari[2,7]

1 Department of Anesthesiology, St Joseph's Healthcare, McMaster University, Hamilton, Ontario, Canada, **2** Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada, **3** Departments of Anesthesiology & Perioperative Medicine and Biomedical & Molecular Sciences, Queen's University, Kingston, Ontario, Canada, **4** Department of Neuroanesthesia, National Institute of Mental Health and Neuro Sciences, Bangalore, India, **5** Biostatistics Unit, St Joseph's Healthcare, Hamilton, Ontario, Canada, **6** Department of Medicine, McMaster University, Hamilton, Ontario, Canada, **7** Department of Surgery, McMaster University, Hamilton, Ontario, Canada

* shanthh@mcmaster.ca

OPEN ACCESS

Citation: Shanthanna H, Gilron I, Rajarathinam M, AlAmri R, Kamath S, Thabane L, et al. (2017) Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. PLoS Med 14(8): e1002369. https://doi.org/10.1371/journal.pmed.1002369

Academic Editor: Alexander C. Tsai, Massachusetts General Hospital, UNITED STATES

Received: March 3, 2017

Accepted: July 6, 2017

Published: August 15, 2017

Data Availability Statement: All data are available in the manuscript or the supporting information files.

Funding: The article processing charges for the article were supported through funds from a Canadian Institute of Health Research (CIHR) Randomized Controlled Trials Mentoring Program grant, awarded to Dr. Shanthanna in 2014.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Background and objective

Chronic Low Back Pain (CLBP) is very common, with a lifetime prevalence between 51% and 80%. In majority, it is nonspecific in nature and multifactorial in etiology. Pregabalin (PG) and Gabapentin (GB) are gabapentinoids that have demonstrated benefit in neuropathic pain conditions. Despite no clear rationale, they are increasingly used for nonspecific CLBP. They necessitate prolonged use and are associated with adverse effects and increased cost. Recent guidelines from the National Health Service (NHS), England, expressed concerns on their off-label use, in addition to the risk of misuse. We aimed to assess the effectiveness and safety of gabapentinoids in adult CLBP patients.

Methods

Electronic databases of MEDLINE, EMBASE, and Cochrane were searched from their inception until December 20th, 2016. We included randomized control trials reporting the use of gabapentinoids for the treatment of CLBP of >3 months duration, in adult patients. Study selection and data extraction was performed independently by paired reviewers. Outcomes were guided by Initiative on Methods, Measurement and Pain Assessment in Clinical Trials guidelines, with pain relief and safety as the primary outcomes. Meta-analyses were performed for outcomes reported in 3 or more studies. Outcomes were reported as mean differences (MDs) or risk ratios (RRs) with their corresponding 95% confidence intervals (CIs), and I^2 in percentage representing the percentage variability in effect estimates that could be explained by heterogeneity. GRADE (Grading of Recommendations Assessment, Development, and Evaluation) was used to assess the quality of evidence.

Abbreviations: ARI, absolute risk increase; BUP, buprenorphine; CENTRAL, Cochrane Central Registry of Controlled Trials; CI, confidence interval; CLBP, chronic low back pain; CX, Celebrex; EQUATOR, Enhancing the QUAlity and Transparency Of health Research; GB, gabapentin; GIC, global impression of change; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IMMPACT, Initiative on Methods, Measurement and Pain Assessment in Clinical Trials; LTFU, loss to follow-up; MD, mean difference; NHS, National Health Service; NNH, number needed to harm; NP, neuropathic pain; PG, pregabalin; QOL, quality of life; RCT, randomized controlled trial; RoB, risk of bias; RR, risk ratio; SD, standard deviation; SMD, standardized mean difference; SOF, summary of findings; TAP, tapentadol; VAS, visual analogue scale.

Results

Out of 1,385 citations, eight studies were included. Based on the interventions and comparators, studies were analyzed in 3 different groups. GB compared with placebo (3 studies, $n = 185$) showed minimal improvement of pain (MD = 0.22 units, 95% CI [−0.5 to 0.07] $I^2 = 0\%$; GRADE: very low). Three studies compared PG with other types of analgesic medication ($n = 332$) and showed greater improvement in the other analgesic group (MD = 0.42 units, 95% CI [0.20 to 0.64] $I^2 = 0$; GRADE: very low). Studies using PG as an adjuvant ($n = 423$) were not pooled due to heterogeneity, but the largest of them showed no benefit of adding PG to tapentadol. There were no deaths or hospitalizations reported. Compared with placebo, the following adverse events were more commonly reported with GB: dizziness- (RR = 1.99, 95% CI [1.17 to 3.37], $I^2 = 49$); fatigue (RR = 1.85, 95% CI [1.12 to 3.05], $I^2 = 0$); difficulties with mentation (RR = 3.34, 95% CI [1.54 to 7.25], $I^2 = 0$); and visual disturbances (RR = 5.72, 95% CI [1.94 to 16.91], $I^2 = 0$). The number needed to harm with 95% CI for dizziness, fatigue, difficulties with mentation, and visual disturbances were 7 (4 to 30), 8 (4 to 44), 6 (4 to 15), and 6 (4 to 13) respectively. The GRADE evidence quality was noted to be very low for dizziness and fatigue, low for difficulties with mentation, and moderate for visual disturbances. Functional and emotional improvements were reported by few studies and showed no significant improvements.

Conclusions and relevance

Existing evidence on the use of gabapentinoids in CLBP is limited and demonstrates significant risk of adverse effects without any demonstrated benefit. Given the lack of efficacy, risks, and costs associated, the use of gabapentinoids for CLBP merits caution. There is need for large high-quality trials to more definitively inform this issue.

Trial registration

PROSPERO CRD42016034040

Author summary

Why was this study done?

- Chronic low back pain (CLBP) is widely prevalent, and in majority it is nonspecific (no clear etiology) in nature. Among chronic conditions, CLBP is noted to be the leading cause of years lived with disability.
- Gabapentin (GB) and Pregabalin (PG) have been shown to be helpful in neuropathic pain conditions, such as diabetic neuropathy. Despite no clear rationale, their use for CLBP has significantly increased.
- We examined the existing literature and strength of evidence to determine the usefulness of either PG or GB in decreasing pain and improving functions, and the potential adverse effects of PG and GB, in patients with predominant CLBP.

What did the researchers do and find?

- We performed a systematic review and meta-analysis of randomized control studies that used either PG or GB in patients of predominant CLBP.
- We identified only 8 randomized control studies that assessed the benefits of using GB or PG in CLBP.
- While GB showed minimal improvement of pain compared to placebo, pain relief with PG was inferior compared to the active analgesic group. GB and PG were both associated with increased risk of dizziness compared with placebo or active comparator, respectively. GB was additionally associated with increased risk of fatigue, visual disturbances, and difficulties with mentation compared with placebo.

What do these findings mean?

- There is limited evidence to support the use of either PG or GB in nonspecific CLBP.
- The limited and low-quality evidence suggests increased risk of adverse effects with only minimal benefit for GB compared with placebo and no evidence for benefit with PG compared with other analgesics.
- Their continued use in CLBP merits caution.

Introduction

Chronic Low Back Pain (CLBP) is very common and is associated with significant patient burden and heath resource expenditure [1–3]. It is largely nonspecific in nature and in up to 85% of patients lacks a clear pathoanatomical diagnosis when present in isolation [1–4]. We have previously highlighted the etiological and treatment considerations for CLBP, along with the limitations within the existing evidence [5]. A large proportion of CLBP patients are treated with routine analgesic medications with unsatisfactory results leading to frequent exploration of second line options including gabapentinoids [6, 7]. In particular, the use of gabapentin (GB) and pregabalin (PG) is made on the rationale of modulating the enhanced neurotransmission at the level of presynaptic receptors of the afferent neurons. Both of these medications primarily act on the α-2 delta-2 subunit of the voltage-dependent calcium channels [8, 9] and can be considered to have very similar pharmacodynamic actions on pain and other symptoms. They are considered to be very effective for neuropathic pain (NP) conditions. Attempts at exploiting their therapeutic potential for other pain conditions have shown mixed results [10, 11]. Use of gabapentinoids for CLBP requires slow titration to therapeutic doses and establishing maintenance on a long-term basis. With prolonged treatment, the potential gain over possible adverse effects and risks could become unclear [9]. There have been concerns over the excessive off-label use of GB, despite there being a clear lack of clinical studies [12], necessitating advisory guidelines by the National Health Services (NHS), United Kingdom on the risk of the misuse of gabapentinoids [13]. Our primary objectives were to assess the benefits of GB and PG in CLBP in decreasing pain and to examine the risk of adverse effects. Secondarily, we assessed the effects of PG and GB on the Initiative on Methods, Measurement

and Pain Assessment in Clinical Trials (IMMPACT) outcomes [14]. The outcomes considered were physical and emotional functioning, participant ratings of global improvement and satisfaction with treatment, and participant disposition. Additionally, we attempted to assess whether the use of gabapentinoids selectively improve pain relief in patients with predominant neuropathic CLBP.

Methods

As this is a systematic review, ethics committee approval is not applicable.

Protocol and registration

Our review was registered with PROSPERO with the registration number CRD42016034040. This report has been prepared according to PRISMA guidelines [15], as suggested by the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network (S1 PRISMA checklist). Our detailed review protocol has been previously published [5].

Eligibility criteria

We included randomized controlled trials (RCTs) involving adult patients (>18 years of age) with predominant CLBP of 3 months or more, with or without leg pain. We did not have any language exclusions. Studies with mixed population of chronic pain were only included if they report outcomes separately for our study population of interest, or if at least 90% of the trial patients are >18 years with predominant CLBP. Studies were further screened for interventions and were included if they randomized patients to receive "PG" or "GB," either "alone" or "in combination with other treatment," and compared it with any active or inactive treatments.

Information sources

We searched the electronic databases of EMBASE, MEDLINE, and the Cochrane Central Registry of Controlled Trials (CENTRAL), from their inception until January 26th, 2016. WHO clinical trial registry (http://apps.who.int/trialsearch/Default.aspx), and clinical trial registry (https://clinicaltrials.gov/), were also searched to look for any registered studies, fulfilling our eligibility criteria, and crosschecked for their resulting publications. To be comprehensive, bibliographies of relevant reviews and selected studies were examined. Since performing the original search, we also repeated our search on December 20th, 2016 to ensure that we have not missed any recent publications.

Search strategy

The search was performed using a sensitive strategy by an experienced librarian for each specific database. We included terms referring to study population of low back pain, and terms referring to study interventions such as GB, PG, and anticonvulsants [5]. The strategy is provided as a supplementary file (S1 Text).

Study screening and selection

Using paired reviewers screening independently and in duplicate, study selection was performed in 2 stages. Titles and abstracts were screened in the first stage, followed by full text screening on citations felt potentially eligible. A calibration exercise between reviewer pairs ensured consistency in screening and disagreement were resolved by consensus or through

discussion with the principal investigator (HS). A quadratic kappa statistic on the full article final decision was estimated as a measure of interobserver agreement [16].

Data collection process

The same paired reviewers extracted the data independently and in duplicate, using electronic data extraction forms that were piloted between the reviewers for consistency and accuracy. An instruction manual was provided to assist with the data extraction process.

Data items

Data items extracted from each study included study characteristics, risk of bias (RoB) items, demographic information, participant disposition through the study, and our review outcomes on continuous and binary measures captured on 6 core domains as recommended by the IMMPACT statement guidelines [14].

RoB in individual studies

RoB was assessed using the Cochrane RoB tool modified to capture the components of random sequence generation; allocation concealment; blinding of participants; blinding of outcome assessment; and analysis of incomplete outcome data. Further, we modified the response options of domains as "definitely yes," "probably yes," "probably no," and "definitely no." For each domain, the responses of "definitely yes" and "probably yes" categories were assigned a high RoB and those in the "probably no" and "definitely no" categories a low RoB[17]. Crossover studies were assessed for reasonable washout period [18]. No attempt was made to contact authors for clarification on the RoB items. Selective outcome reporting was judged based on the outcomes described in the methods section but not reported in the results section [19].

Additional RoB items

Additionally, we considered the domains for chronic pain studies as suggested by Moore et al. [20] and added the domains of outcome assessment time (12 weeks or more as low risk), outcome assessment threshold (>30% improvement in pain relief as low risk), and potential for publication bias based on the sample size threshold (>50 as low risk) to identify a trial as having the potential for publication bias based on low sample size. Trials with low sample size can increase the chances of erroneously large treatment effect sizes and indirectly contribute to publication bias [21, 22].

Outcomes and prioritization

A priori, we specified pain relief and safety (adverse effects) as our primary outcomes and others as secondary outcomes, and prioritized the use of intent to treat analysis. Pain relief expressed as both continuous and categorical outcomes, and at various time points, was extracted for all reported time points. For pooling, we considered the most common type and the longest duration of follow-up reported. A priori, we prioritized change scores over end scores for pooling analysis. Change scores are considered more efficient and powerful than comparison of final scores, as it removes a component of between-person variability from the analysis [18]. For pain relief expressed as continuous scores, we converted all study outcomes into a common 0–10 numerical rating scale, as it is commonly used and easy to interpret [14]. The approach to conversion into a common scale is shown in S2 Text. Safety was assessed by comparing the risk of serious adverse events causing death, hospitalisation, or study withdrawal. If unclear, we considered reporting the most commonly reported adverse effects. Due

to the expected differences within measurement scales, secondary outcomes of improvement in physical and emotional functioning, and participant ratings of global improvement and satisfaction were not converted into a single common scale.

Synthesis of results and summary measures

Data were pooled only if there are 3 or more studies contributing to an outcome domain. Our selection criteria allowed for a relatively homogeneous population of CLBP who tend to be approached similarly from a clinical situation. However, we recognized the potential for heterogeneity based on study interventions and comparator interventions. In view of these obvious sources of heterogeneity, we decided a priori to pool studies using PG or GB, either alone or in combination, separately. Extracted data were compiled and checked for accuracy using Microsoft Excel. RoB was assessed using a modified Cochrane RoB tool that is described below. For the primary analysis, we used a complete case analysis, as reported in individual studies. Sensitivity analyses for incomplete outcome data were performed. Analysis and synthesis was carried out using Review Manager (RevMan) [Computer program], Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014; and Microsoft Excel 2011 (Mac version). Based on the comparator and interventions, if we did not expect much between study variance, a fixed effects model was used for pooling. However, if we suspected between study variance, or in the presence of unexplained heterogeneity, a random effects model was chosen [18]. For crossover studies, we prioritized the results from a paired test. If not provided, results of unpaired tests were considered. If there was a potential for carryover effect, or if there is a significant drop out rate (>20%), the results from the first period only were considered [18]. Statistical heterogeneity was estimated using Cochrane's Q test, with a threshold of p-value at 0.10, and the percentage variability in individual effect estimates was described by I^2 statistic [18]. Risk Ratio (RR), and mean difference (MD) or standardized mean differences (SMDs) as appropriate, were estimated along with their 95% confidence intervals (CI). We planned to report the findings in measures of absolute risk, if they were observed to be statistically significant. Rating of quality of evidence was done using GRADE approach, with a summary of findings (SOF) table.

Additional analysis

A subgroup analysis was considered in studies that screened for the presence of NP using a screening questionnaire at baseline and reported pain relief in patients of NP separately. Sensitivity analyses for the outcome of pain relief was carried out for studies reporting >5% loss to follow-up (LTFU). These were carried out using well-described imputation strategies [23, 24].

Results

Study selection

Our search identified a total of 1,385 citations after exclusion of duplicates. Among the 29 articles assessed for full text, 21 studies were excluded with reasons that are shown in Fig 1. Eight studies were included for qualitative and six for quantitative analysis (Fig 1). There was almost perfect agreement, indicated by kappa = 0.82, between reviewers at the full-text screening stage.

Study characteristics

Important characteristics of the study population and treatments are provided in Table 1. Of the 8 studies, 3 compared the use of GB to placebo treatment [25, 27], and 5 used PG [28–32].

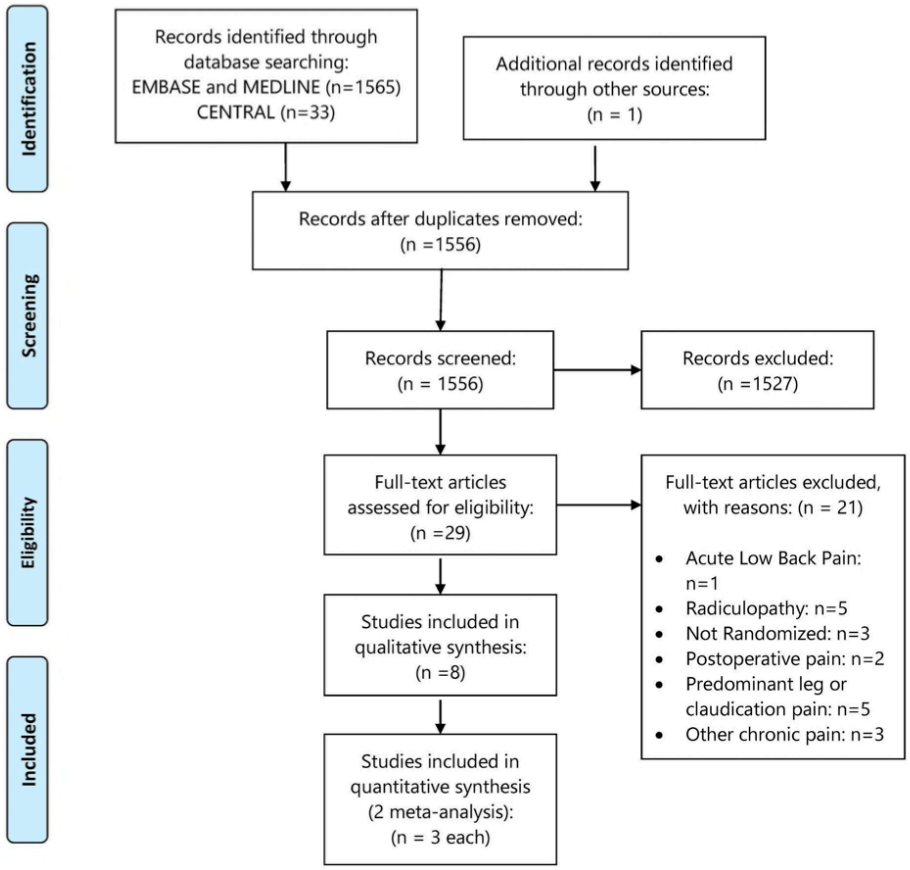


Fig 1. PRISMA flow diagram.

https://doi.org/10.1371/journal.pmed.1002369.g001

There were 2 crossover studies using GB [26] and PG [31]. Only 2 studies were multicentered and had external funding for the conduct of their trial [25, 28]. Among the PG trials, 3 trials used an active comparator (amitryptline, celebrex, tramacet) versus PG alone [29, 31, 32]. As the study by Romano et al. had 3 arms [31], they compared PG alone versus celebrex (CX) versus a combination of PG plus CX. So, there were 3 comparisons involving PG as an adjunct to an analgesic medication versus their respective analgesic medication [28, 30, 31]. The mean age ranged between 41.6 to 58.5 years, except in the study by Sakai et al. [32]. However, the duration of pre-existing CLBP had a much wider range of 13 to 213 months. The treatment doses were titrated for clinical effect in all studies, except for Sakai et al., who had a fixed dosing of PG [32]. The doses ranged from 300 to 3,600 mg/day with GB and 100 to 600 mg/day with PG, in divided doses. Only 3 studies assessed specifically for NP using a screening questionnaire [28, 31, 32].

Table 1. Characteristics of included studies: design, population, and interventions.

STUDY POPULATION DESIGN AND GROUPS	FEMALES (%)		MEAN AGE (SD)		MEAN DURATION IN MONTHS (SD)		STUDY TREATMENTS		TREATMENT DURATION	PRE-RANDOMIZATION PERIOD & REASON
Author year; population and design	**INT**	**CNT**	**INT**	**CNT**	**INT**	**CNT**	**INT**	**CNT**		
Baron 2015 CLBP >3 months 2 groups parallel design	86 (54)	95 (62)	56.3 (11.83)	58.5 (11.01)	104.4 (111.36)	112.8 (125.76)	TAP 300 mg/day + PG 100–200 mg/ day	TAP 300 mg/day + TAP 100–200 mg/ day	8 weeks	Yes Washout
Pota 2012# CLBP >12 months 2 groups parallel design	22/44 (50) in total		55.5 (8.31)		15.25 (8.69)		PG 300 mg/day + BUP 35 mcg/h	BUP 35 mcg/h	3 weeks	Yes to stabilize on BUP for 3 weeks
Sakai 2015 CLBP > 3 months 2 groups parallel design	9 (30)	11 (37)	72.03 (6.23)	72.60 (5.23)	34.77 (29.91)	34.70 (32.54)	PG 75 mg BID	TRA 2 tablets/day	4 weeks	Yes to washout and rule out acute pain
Kalita 2014 # CLBP >3 months 2 groups parallel design	91/200 (45.5) in total		42.6 (11.6)	41.6 (10.7)	35.9 (46.8)	35.2 (39.8)	PG 75 mg BID X 2 weeks; 150 mg BID X 4 weeks; 300 mg BID 6–14 weeks	AMT 12.5 mg OD X 2 weeks; 25 mg OD X 4 weeks; 50 mg OD 6–14 weeks	14 weeks	Yes to wash out and treat with NSAIDS If required
Romano 2009 CLBP> 6 months 3 groups; crossover design with 1 week washout; minimal risk of carryover effects	20 (56)		53 (16)		13 (6)		PG 1mg/kg 1st week; and 2–4 mg/ kg next 4 weeks	CX: 3–6 mg/kg PG + CX as with the 2 groups	4 weeks	Yes Washout
McCleane 2001 Chronic-duration not provided 2 groups parallel design	15 (48)	21 (62)	41.3 (13.1)	47.8 (11.7)	63.1 (45.3)	74.5 (82)	GB 300 mg OD increased weekly to 1,200 mg per day	Similar (placebo capsules)	8 weeks	Yes Not provided
McCleane 2000 CLBP >3 months (nociceptive pain); crossover design with 1 week washout; minimal risk carryover	13 (54.2)		42.4 (14.6)		105.5 (97.2)		GB 300 mg daily increasing by 300 mg weekly to a maximum dose of 15 mg/kg	Crossover placebo	6 weeks	No NA
Atkinson 2016 CLBP >6 months 2 groups parallel design with non-inferiority assumption	12 (18.9)	13 (24.5)	57.58 (8.84)	54.62 (11.38)	205.92 (181.44)	213.48 (153.6)	GB starting as 300 mg/day up to 1,200 mg TID at 4 weeks	Similar (placebo capsules)	12 weeks	No NA

AMT, Amitryptline; BID, twice a day; BUP, Buprenorphine; CLBP, chronic low back pain; CNT, control; CX, Celebrex; GB, Gabapentin; INT, intervention; NSAIDS, Nonsteroidal anti-inflammatory drugs; OD, once a day; PG, Pregabalin; PLA, Placebo; TAP, Tapentadol; TID, three times a day; TRA, Tramacet (37.5 mg Tramadol + 325 mg Acetaminophen); SD, Standard deviation

#: Study did not report separately for intervention and control groups

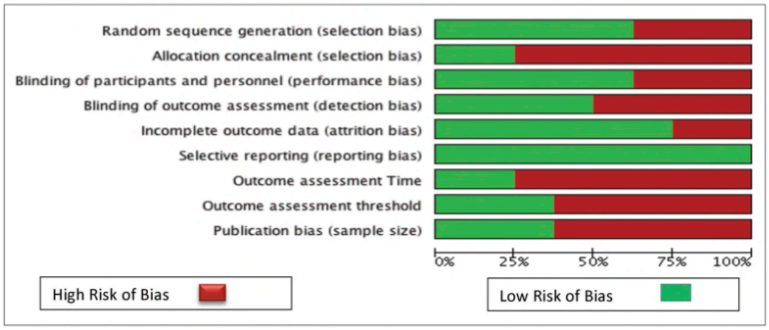
https://doi.org/10.1371/journal.pmed.1002369.t001

RoB within studies (Fig 2)

Six of the eight studies had a risk of selection bias, six for allocation concealment and three for sequence generation, and four involved a risk of detection bias. The studies by Baron et al. [28], and Atkinson et al. [25] were rated as having low RoB for most domains, and both cross-over studies had a higher risk of selection bias [26, 31].

Study outcomes and synthesis of results

Except 2 studies that reported using 0–100 scale [30, 31], all others reported their pain scores on a scale of 0–10 NRS or Visual Analogue Scale (VAS). Five studies provided a dichotomous measure of treatment success by varying thresholds [25–29, 32]. All studies reported on one or more adverse effects. Functional improvement was reported in 5 studies [25, 26, 28, 29, 32],



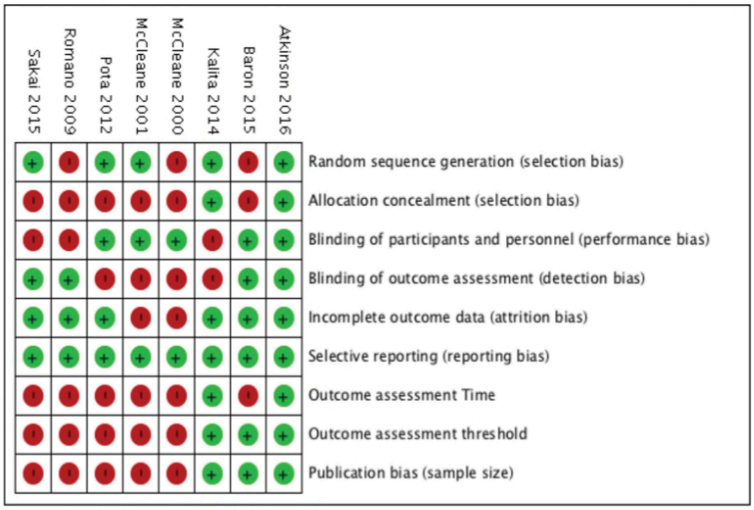


Fig 2. RoB within the included studies. RoB, risk of bias.

https://doi.org/10.1371/journal.pmed.1002369.g002

quality of life (QOL) improvement by 2 studies [28, 32], psychological improvement or improvement in depression by 3 studies [25, 28, 32], and global impression of change (GIC) only by 2 studies [25, 28].

Pain relief. Pain relief expressed in NRS or VAS scales were converted into a common scale of 0–10 NRS. Authors of 2 studies were successfully contacted to obtain final results of pain scores, as it was not clear in their reporting [25, 32]. We were unable to use the change scores as many studies did not report their change in standard deviations (SDs), and imputing them based on another study or by using a correlation coefficient of change was observed to be inappropriate and not precise [18]. So, pooling was performed using end scores. Based on the variability in the study comparisons, we decided to pool studies for the use of GB and PG. In

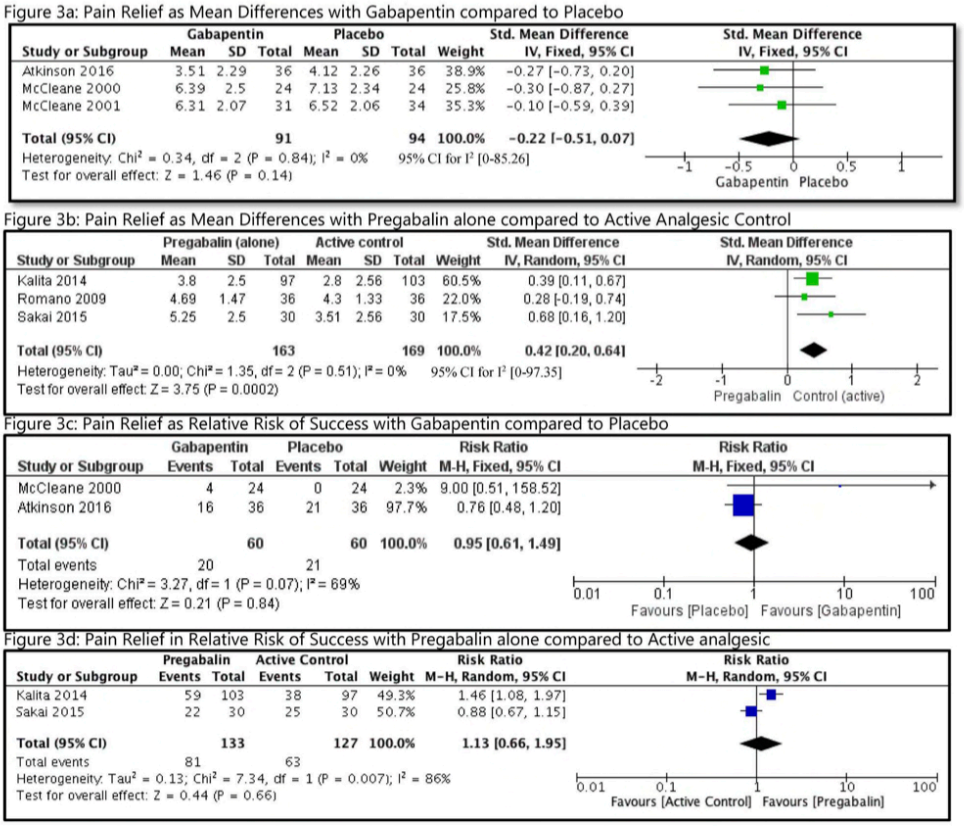


Fig 3. Analyses of pain relief with GB or PG in patients with CLBP. CLBP, chronic low back pain; GB, gabapentin; IV, intravenous; M-H, Mantel-Haenszel; PG, pregabalin.

https://doi.org/10.1371/journal.pmed.1002369.g003

the first group (Fig 3a), studies using GB ($n = 91$) versus placebo ($n = 94$) were combined using a fixed effects model. Compared with placebo, the GB group had a small reduction in pain (MD = 0.22 units, 95% CI [−0.51 to 0.07], $I^2 = 0\%$). There were no studies comparing PG with placebo. PG ($n = 163$) was compared with an active comparator ($n = 169$) in 3 studies (Fig 3b), using random effects model. This analysis showed an improvement in pain favoring the use of the active comparator group (MD = 0.42 units, 95% CI [0.20 to 0.64], $I^2 = 0$). Both the above comparisons were rated as very low quality evidence by GRADE (Table 2). The third group consisted of comparisons that used PG as an adjunct to another analgesic medication ($n = 215$), such as buprenorphine (BUP) [30], tapentadol (TAP) [28], and CX [30], and compared it with the use of analgesic medication alone ($n = 208$). We decided that it was not appropriate to pool these studies considering the clinical heterogeneity involved within the studies, on the sides of both intervention and comparator. This was supported by the substantial statistical heterogeneity observed with such an attempt using random effects model,

Table 2. GRADE summary of findings. Gabapentin or pregabalin compared to placebo or active medications for chronic low back pain: A systematic review and meta-analysis of randomized control trials.

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo or Active medications	Risk difference with Gabapentin or Pregabalin *
Gabapentin compared to Placebo (Pain Relief achieved) assessed with: Patient reported Scale from: 0 to 10 follow up: range 8 weeks to 12 weeks	185 (3 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	-	-	SMD **0.22 lower** (0.51 lower to 0.07 higher)
Pregabalin alone compared to Active control (Pain Relief achieved) assessed with: Patient reported Scale from: 0 to 10 follow up: range 4 weeks to 14 weeks	332 (3 RCTs)	⊕◯◯◯ VERY LOW [a,b,c,d]	-	-	SMD **0.42 SD higher** (0.2 higher to 0.64 higher)
Dizziness or Unsteadiness with Gabapentin compared to Placebo assessed with: Patient reported follow up: range 6 weeks to 12 weeks	221 (3 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	**RR 1.99** (1.17 to 3.37)	225 per 1,000	**223 more per 1,000** (38 more to 534 more)
Fatigue or Lethargy with Gabapentin compared to Placebo (Fatigue) assessed with: Patient reported follow up: range 6 weeks to 12 weeks	221 (3 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]	**RR 1.85** (1.12 to 3.05)	261 per 1,000	**222 more per 1,000** (31 more to 536 more)
Visual disturbances with Gabapentin compared to Placebo (Blurring of vision) assessed with: Patient reported follow up: range 6 weeks to 12 weeks	221 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,c]	**RR 5.72** (1.94 to 16.91)	180 per 1,000	**850 more per 1,000** (169 more to 2,867 more)
Dizziness or Unsteadiness with Pregabalin alone compared to Active Control assessed with: Patient reported follow up: range 4 weeks to 14 weeks	332 (3 RCTs)	⊕◯◯◯ VERY LOW [a,c,e]	**RR 2.70** (1.25 to 5.83)	130 per 1,000	**221 more per 1,000** (33 more to 629 more)
Difficulty with Mentation with Gabapentin compared to Placebo assessed with: Patient reported follow up: range 6 weeks to 12 weeks	220 (3 RCTs)	⊕⊕◯◯ LOW [a,c]	**RR 3.34** (1.54 to 7.25)	209 per 1,000	**489 more per 1,000** (113 more to 1,307 more)

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Bibliography: Shanthanna H, Gilron I, Thabane L, Devereaux PJ, Bhandari M, AlAmri R, et al. Gabapentinoids for chronic low back pain: a protocol for systematic review and meta-analysis of randomised controlled trials. BMJ open. 2016;6(11)

CI, Confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized control trial; RR, Risk ratio; SMD, Standardized mean difference

Explanations

[a.] Studies had risk of selection bias

[b.] Less than optimal information size

[c.] Based on low sample size

[d.] Variations in analgesic treatment and intervention treatment dosages

[e.] Variations within the control agents used

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

https://doi.org/10.1371/journal.pmed.1002369.t002

I^2 = 77%. The forest plot for this comparison is shown as S1 Fig. Among these 3 studies, the largest study by Baron et al. did not find any difference by adding PG to TP at their 10-week follow-up [28]. However, the smaller studies by Pota et al. [30] and Romano et al. [31] observed important differences in pain scores (difference of more than 2 points in 0–10 NRS) by using PG as an adjunct to BP and CX, respectively. There were also no significant differences when patients were assessed as success or failure with either GB versus placebo (Fig 3c) or PG versus active comparator (Fig 3d).

Adverse effects. There were no deaths or hospitalizations reported. The reasons for study withdrawal were not provided in all studies. All adverse effects reported in more than 1 study are summarized in Table 3. Compared with placebo, the following adverse events were more commonly reported with GB: dizziness-(RR = 1.99, 95% CI [1.17 to 3.37], I^2 = 49); fatigue (RR = 1.85, 95% CI [1.12 to 3.05], I^2 = 0); difficulties with mentation (RR = 3.34, 95% CI [1.54 to 7.25], I^2 = 0); and visual disturbances (RR = 5.72, 95% CI [1.94 to 16.91], I^2 = 0) (Fig 4). The GRADE quality of evidence was noted to be very low for dizziness and fatigue, low for difficulties with mentation, and moderate for visual disturbances (Table 2). The resulting absolute risk increase (ARI) percentage and necessary number needed to harm (NNH) with 95% CI for dizziness, fatigue, mental difficulties, and visual disturbances were 14% and 7 (4 to 30), 13% and 8 (4 to 44), 16% and 6 (4 to 15), and 15% and 6 (4 to 13), respectively. With PG, dizziness was more common compared to the active comparator (RR = 2.70, 95% CI [1.25 to 5.83], I^2 = 0), with very low quality of evidence. The ARI% and NNH were 9% and 11(6 to 30).

Table 3. Summary of adverse effects observed in more than one study.

Adverse Effects as Described	BARON 2015		POTA 2012		SAKAI 2015		KALITA 2014		ROMANO 2009		MCCLEANE 2001		MCCLEANE 2000		ATKINSON 2016	
	INT (154)	CNT (159)	INT (22)	CNT (22)	INT (30)	CNT (30)	INT (97)	CNT (103)	INT (36)	CNT (36)	INT (31)	CNT (34)	INT (24)	CNT (24)	INT (55)	CNT (53)
Nausea/ Vomiting	20	25	3	3	0	10			PG: 5	CX: 4 CX + PG: 7	6	5	2	2		
Drowsiness/ Somnolence/ Sedation	19	13	4	5	11	5	4	10			2	0	2	0		
Forgetfulness/ Memory disturbance													1	0	9	1
Constipation	8	11	5	3	0	6					0	1	1	0	7	9
Dizziness/Staggering/ Unsteadiness/Vertigo	28	17	0	22	11	5	6	2	PG: 5	CX: 0 CX + PG: 7	5	0			24	14
Fatigue/Loss of Energy	16	13									2	0			27	15
Difficulties with Mentation (Loss of Concentration/ Disorientation/feeling high)											1	0	1	0	21	6
Dry Mouth	8	6					1	3								
Headache	13	10									1	1	2	0		
Problems with Visual Accommodation/ Blurred Vision											1	0			19	3
Skin Rash							1	0			0	1				
Restlessness							1	0			1	0				

CNT, control; CX, Celebrex; INT, intervention; PG, Pregabalin

https://doi.org/10.1371/journal.pmed.1002369.t003

Secondary outcomes. These are summarized in Tables 4 and 5. All studies except Pota et al. had patients who were LTFU [30]. There were 5 studies that did include LTFU, even with >5% of their randomized sample, in their final analysis [25–27, 31, 32]. *Functional improvement* was observed in 5 studies using various scales [25, 26, 28, 29, 32]. The results indicate that there were improvements from the baseline in both treatment and control groups, without much difference between the groups. *Emotional functioning* was observed by 3 studies, but 2 studies reported the final scores, with no between-group differences [25, 28]. *Global improvement of change* was reported as physician-reported by Atkinson et al. [25] and patient-reported by Baron et al. [28]. There were no between-group differences in studies with GB or PG, respectively.

RoB across studies (Fig 2)

Based on our criteria, potential bias due to outcome threshold, assessment time point, and publication bias due to low sample size was observed largely by 5 studies [26, 27, 30–32].

Subgroup analysis. NP was assessed using a screening questionnaire in 3 studies. Sakai et al. observed pain scores to decrease more with tramacet compared to PG in NP patients [32]. Baron et al. observed no differences in the components of neuropathic pain symptom inventory scores using PG plus TP in comparison to TP alone [28]. Whereas, Romano et al. observed that pain scores decreased significantly in patients of NP with PG as well as in combination with CX [31].

Sensitivity analysis. The analyses for GB versus placebo, and PG versus active comparator withstood sensitivity analysis for LTFU >5% using progressively stringent imputation strategies for mean pain scores.

Discussion

Despite the widespread use, our systematic review with meta-analysis found that there are very few RCTs that have attempted to assess the benefit of using GB or PG in patients of CLBP. Use of GB and PG, compared to placebo and active analgesic comparators, respectively, were associated with significant increase in adverse effects without limited evidence for improvement in pain scores or other outcomes. We were unable to examine the pooled effect of using PG as an adjuvant analgesic medication given the limited evidence and heterogeneity of studies. It is reasonable to assume that the clinical benefit would depend upon the primary medication and its potency within each study. The differences within the results of Pota et al. [30] and Romano et al. [31], compared to Baron et al. [28] could be attributed to methodological differences. The study by Baron et al. had a larger sample size along with longer duration of follow up. Hence, the existing evidence does not support the use of gabapentinoids for predominant CLBP, and calls for larger, high quality RCTs to more definitively inform this issue.

Considering the expanding use of gabapentinoids for chronic pain and CLBP [33, 34], this review fulfils the immediate need to scrutinize and closely examine the existing evidence. Noting that there is a published Cochrane protocol [35], ours is the first review combined with meta-analysis to examine the benefits and safety of gabapentinoids in CLBP. Results of our review are in contrast with nonrandomized studies that have shown benefit with PG in patients of CLBP [36, 37]. Gabapentinoids have proven efficacy in NP conditions [38]. However, they are also widely used for conditions in which the neuropathic component is difficult to establish, most of which are off label uses [12]. This development perhaps reflects the penumbra sort of effect (clinicians generalizing the selection criteria of clinical studies into their patient population without recognizing the limitations) [39]. In England, there was a 46% and 53% rise in the prescription use of GB and PG respectively from 2011 to 2013 alone [13]. A recent Canadian study showed that the off-label use of PG is as high as 75%, and the most

Figure 4a: Dizziness observed with Gabapentin compared to Placebo

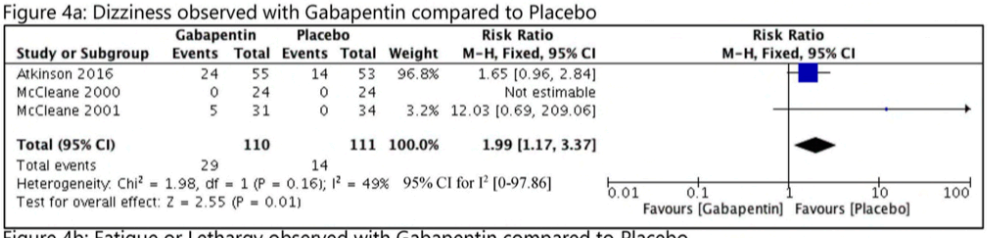


Figure 4b: Fatigue or Lethargy observed with Gabapentin compared to Placebo

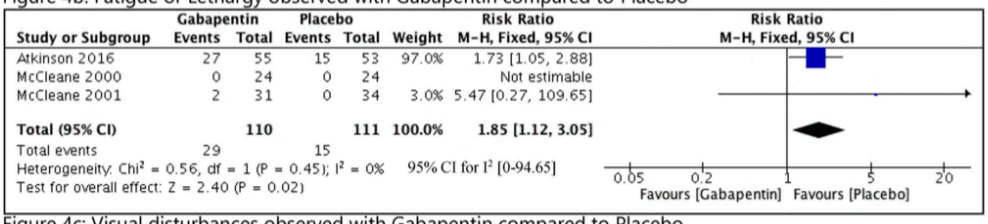


Figure 4c: Visual disturbances observed with Gabapentin compared to Placebo

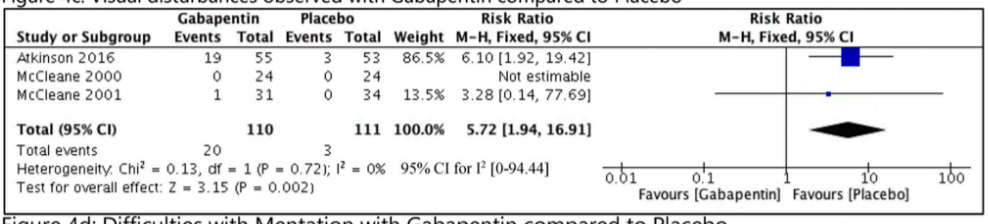


Figure 4d: Difficulties with Mentation with Gabapentin compared to Placebo

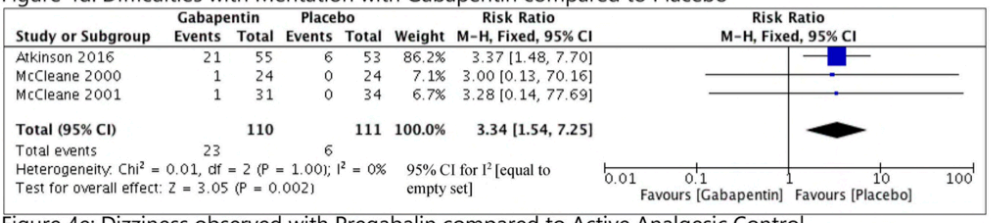


Figure 4e: Dizziness observed with Pregabalin compared to Active Analgesic Control

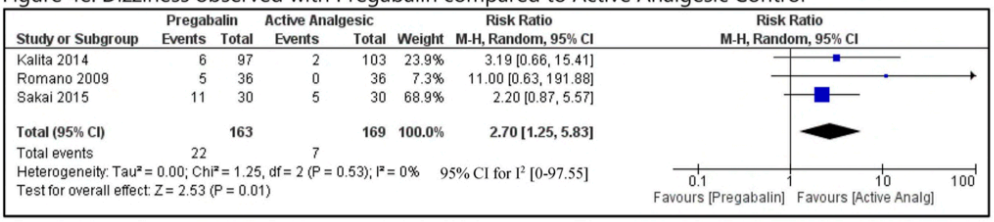


Fig 4. Analyses of adverse effects observed with GB or PG in CLBP. CLBP, chronic low back pain; GB, gabapentin; IV, intravenous; M-H, Mantel-Haenszel; PG, pregabalin.

https://doi.org/10.1371/journal.pmed.1002369.g004

Table 4. Summary of secondary outcomes-participant disposition.

PARTICIPANT DISPOSITION										
STUDY/YEAR	**RANDOMIZED**		**COMPLETED STUDY FOLLOW UP**		**TOTAL LTFU (including withdrawal due to side effects)**		**LTFU (discontinued study for side effects only)**		**ANALYZED**	
	INT	**CNT**	**INT**	**CNT**	**INT**	**CNT**	**INT**	**CNT**	**INT**	**CNT**
Baron 2015	159	154	133	126	26	28	17	16	157#	152#
Pota 2012	22	22	22	22	0	0	0	0	22	22
Sakai 2015	32	33	2	3	2	3	2	3	30	30
Kalita 2014	97	103	70	77	27	26	12	11	97#	103#
Romano 2009a	42 in each treatment period		36 in each treatment period		6 in each treatment period		4 in each treatment period		36 in each treatment period	
McCleane 2001	40	40	31	34	9	6	Not provided		31	34
McCleane 2000b	30 in each treatment period		24 in each treatment period		6 in each treatment period		1	0	24 in each treatment period	
Atkinson 2016	55	53	36	36	19	17	12	6	36	36

CNT, Control; INT, Intervention; LTFU, Loss to follow-up

[a]= triple arm crossover study;

[b]=crossover study;

[#]=performed intent to treat analysis by imputing for patients lost to follow up.

https://doi.org/10.1371/journal.pmed.1002369.t004

prevalent condition of use was CLBP [40]. The true burden of NP in CLBP is hard to establish [41]. Distribution of pain can be considered as a corollary of the pathological process, and it is important to broadly classify patients based on their predominance of axial or leg pain for diagnosis and management [2]. A common assumption is of leg pain indicating NP. However, in most cases leg pain is nonspecific and inconsistent with radicular pain, and only a painful radiculopathy with sensory signs would fulfill the diagnosis of definite NP [41]. Even if one considers that gabapentinoids are effective against NP related to CLBP, contrasting evidences are observed in literature. In patients of radicular pain or pain of spinal stenosis, observational studies of CLBP demonstrate significant improvements with PG [42, 43]. However, RCTs performed by Baron et al. in patients of lumbar radiculopathy and Markman et al. in patients of spinal stenosis did not find clinical improvements when PG was compared with placebo [44, 45]. Cohen et al. examined the benefit of GB in patients of leg pain and found no difference as compared to epidural steroid injections [46]. Even within the included study by Baron et al., the reduction of pain and NP symptoms was similar with the combination of PG with TP, compared to TP [28]. Our results are important for practitioners across several specialties who treat patients with CLBP and have to decide on the relative merits and demerits of treatment with gabapentinoids.

Our review is not without its limitations. We excluded studies in patients of predominant leg pain or spinal stenosis. This was done to limit the heterogeneity within our study population. Although the measure of heterogeneity (I^2-proportion of variability that can be explained by individual studies) was low in many comparisons, the CIs around those I^2 were very wide, reflecting that there is uncertainty in any claim of homogeneity. Heterogeneity has been shown to be an issue with meta-analyses involving a smaller number of trials or events [47]. Topiramate was not considered in this review, as it has a slightly different mechanism of action and is not commonly used, although some controlled studies have shown benefit [48]. The use of PG or GB is associated with significant adverse effects, cost [13], and potential for misuse [34, 49].

Table 5. Summary of secondary outcomes.

PHYSICIAL FUNCTIONING						
STUDY	**SCALE USED**	**DIMENSION**	**BASELINE**		**END OF STUDY**	
AUTHOR/ YEAR			INT	CNT	INT	CNT
Baron 2015c INT (159) CNT (154)	SF-12 physical function composite	0–100 (higher is better)	33.9 (8.49)	34.2 (9.26)	39.6 (9.03)	40.1 (9.64)
McCleane 2000b INT (24) CNT (24)	NRS (mobility scale)	0–10 (higher is better)	4.65 (2.03)	5.07 (2.08)	5.46 (2.41)	5.05 (2.04)
Atkinson 2016 INT (55) CNT (53)	ODI	0–100 (lower is better)	40.3 (10.4)	41.1 (9.8)	31.1 (10.6)	30.9 (13.3)
Sakai 2015 INT (30) CNT (30)	RDQ	0–24 (lower is better)	9.73 (4.44)	11.47 (4.99)	Not provided as per the treatment and control group	
Kalita 2014 INT (97) CNT (103)	ODI	0–100 (lower is better)	42.2 (15.2)	42.2 (12.5)	22 (15)	19 (12.5)
QOL						
STUDY	**SCALE USED**	**LOWEST TO HIGHEST**	**BASELINE**		**END OF STUDY**	
AUTHOR/ YEAR			INT	CNT	INT	CNT
Baron 2015c INT (159) CNT (154)	EQ-5D	0–1 (higher is better)	0.51 (0.246)	0.54 (0.262)	0.60 (0.283)	0.61 (0.305)
Sakai 2015 INT (30) CNT (30)	EQ-5D	0–1 (higher is better)	0.63 (0.10)	0.58 (0.12)	Not provided as per the treatment and control group	
EMOTIONAL FUNCTIONING						
STUDY	**SCALE USED**	**DIMESNSION**	**BASELINE**		**END OF STUDY**	
AUTHOR/ YEAR			INT	CNT	INT	CNT
Baron 2015c INT (159) CNT (154)	SF-12 mental health composite	0–100 (higher is better)	47.6 (11.85)	48.8 (11.81)	50 (11.44)	48.2 (10.71)
Atkinson 2016 INT (55) CNT (53)	Beck Depression Inventory	0–63 (lower is better)	8.38 (4.32)	8.67 (4.16)	5.79 (3.14)	7.11 (4.60)
Sakai 2015 INT (30) CNT (30)	GDI	0–15 (lower is better)	4.70 (3.44)	5.73 (4.25)	Not provided as per the treatment and control group	
GIC						
STUDY	**SCALE USED**	**CRITERIA**	**END OF TREATMENT FOLLOW UP**			
AUTHOR/ YEAR			INT	CNT		
Baron 2015c INT (159) CNT (154)	GIC-patient observed	Minimally improved to very improved	130/157	126/152		
Atkinson 2016 INT (55) CNT (53)	GIC-physician observed	Minimally improved to very improved	14/38	11/33		
NEUROPATHIC PAIN						

(*Continued*)

Table 5. (*Continued*)

STUDY/YEAR	METHOD OF SCREENING AND NEUROPATHIC PAIN TOOL USED		BASELINE		END OF TREATMENT/FOLLOW UP	
			INT	CNT	INT	CNT
Baron 2015	Pain DETECT (0–38)		Not reported	Not reported	Decreased by: −6.1 (7.42)	Decreased by: −5.8 (8.66)
Baron 2015	NPSI: all patients reported their scores for its individual domains	Overall score (0–100)	46 (18.39)	45.6 (18.52)	29.9 (22.24)	29.8 (22.18)
		Burning pain (0–10)	5 (2.38)	4.7 (2.6)	2.8 (2.69)	3 (2.67)
		Pressing pain (0–10)	4.5 (2.56)	4.6 (2.49)	3.1 (2.52)	3.2 (2.54)
		Paroxysmal pain (0–10)	4.9 (2.29)	4.9 (2.28)	3.3 (2.66)	2.9 (2.53)
		Evoked pain (0–10)	4.2 (2.22)	4.2 (2.28)	2.6 (2.37)	2.6 (2.42)
		Paresthesia/ dysthesia (0–10)	4.8 (2.46)	4.7 (2.61)	3.3 (2.66)	3.4 (2.56)
Sakai 2015	NP screening by a Japanese tool with a threshold of >6 as NP+; reported as VAS 0–10 pain scores (INT:13/30; CNT:9/30)		4.56 (3.19)	4.53 (4.46)	6.25	3.43
Romano 2009	LANSS with a threshold of >12 as NP+; 16 in each group (crossover study); After 4 weeks of treatment the pain scores in each group were reported (0–100 VAS)		PG: 47.2 (15)	CX: 46.8 (13.6)	PG: 36.3 (12.7)	CX: 45.7 (14.3)
				CX + PG: 47.9 (15.2)		CX + PG: 23.1 (14.6)

CNT, Control; CX, celebrex; EQ-5D, EuroQol 5D; GDI, geriatric depression scale; GIC, global improvement of change; INT, Intervention; LANSS, Leeds assessment of neuropathic symptoms and signs; NP, neuropathic pain; NPSI, neuropathic pain symptom inventory; NRS, numerical rating scale; ODI, Oswestry disability index; PG, Pregabalin; QOL, quality of life; RDQ, Roland Morris questionnaire; SF-12, short form health survey-12; VAS, visual analogue scale.

a=triple arm crossover study;

b=crossover study;

c=baseline scores indicate scores at randomization and not study recruitment

https://doi.org/10.1371/journal.pmed.1002369.t005

Our review demonstrates that there is limited evidence on the use of gabapentinoids in nonspecific CLBP, and the existing evidence in the form of RCTs does not support their use. It is possible that ongoing or unpublished studies [50, 51] may more definitively inform us on this issue, although one such study specific to CLBP was withdrawn prior to enrollment [52].

Supporting information

S1 Text. Search strategy for MEDLINE and EMBASE.
(DOCX)

S2 Text. Rescaling or conversion of pain scores to a common 0–10 numerical rating scale.
(DOCX)

S1 Fig. Forest plot showing comparison of studies using pregabalin as an adjunct analgesic compared to active analgesic.
(TIF)

S1 PRISMA checklist.
(DOC)

Acknowledgments

The authors acknowledge the assistance provided by Ms. Rachel Couban (librarian) and Dr. Li Wang (statistician), from the Michael DeGroote Pain Institute, McMaster University, Canada,

in conducting the literature search and statistical analysis. The authors thank Drs. Atkinson and Sakai for sharing their study results to assist with our analysis of pain relief.

Author Contributions

Conceptualization: Harsha Shanthanna, Ian Gilron, Lehana Thabane, Philip J. Devereaux, Mohit Bhandari.

Data curation: Harsha Shanthanna.

Formal analysis: Harsha Shanthanna.

Investigation: Harsha Shanthanna, Manikandan Rajarathinam, Rizq AlAmri, Sriganesh Kamath.

Methodology: Harsha Shanthanna, Ian Gilron, Lehana Thabane, Philip J. Devereaux, Mohit Bhandari.

Project administration: Manikandan Rajarathinam, Rizq AlAmri, Sriganesh Kamath.

Supervision: Lehana Thabane, Philip J. Devereaux, Mohit Bhandari.

Validation: Harsha Shanthanna.

Visualization: Harsha Shanthanna.

Writing – original draft: Harsha Shanthanna, Ian Gilron, Manikandan Rajarathinam, Rizq AlAmri, Sriganesh Kamath, Lehana Thabane, Philip J. Devereaux, Mohit Bhandari.

Writing – review & editing: Harsha Shanthanna, Ian Gilron, Manikandan Rajarathinam, Rizq AlAmri, Sriganesh Kamath, Lehana Thabane, Philip J. Devereaux, Mohit Bhandari.

References

1. Deyo RA, Weinstein JN. Low back pain. The New England journal of medicine. 2001; 344(5):363–70. https://doi.org/10.1056/NEJM200102013440508 PMID: 11172169
2. Hooten WM, Cohen SP. Evaluation and Treatment of Low Back Pain: A Clinically Focused Review for Primary Care Specialists. Mayo Clin Proc. 2015; 90(12):1699–718. https://doi.org/10.1016/j.mayocp.2015.10.009 PMID: 26653300
3. Hoy D, Bain C, Williams G, March L, Brooks P, Blyth F, et al. A systematic review of the global prevalence of low back pain. Arthritis Rheum. 2012; 64(6):2028–37. https://doi.org/10.1002/art.34347 PMID: 22231424
4. Morlion B. Chronic low back pain: pharmacological, interventional and surgical strategies. Nature reviews Neurology. 2013; 9(8):462–73. https://doi.org/10.1038/nrneurol.2013.130 PMID: 23817349
5. Shanthanna H, Gilron I, Thabane L, Devereaux PJ, Bhandari M, AlAmri R, et al. Gabapentinoids for chronic low back pain: a protocol for systematic review and meta-analysis of randomised controlled trials. BMJ open. 2016; 6(11).
6. Chou R, Huffman LH. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med. 2007; 147(7):505–14. PMID: 17909211
7. White AP, Arnold PM, Norvell DC, Ecker E, Fehlings MG. Pharmacologic management of chronic low back pain: synthesis of the evidence. Spine. 2011; 36(21 Suppl):S131–43. PMID: 21952185
8. Patel R, Dickenson AH. Mechanisms of the gabapentinoids and alpha 2 delta-1 calcium channel subunit in neuropathic pain. Pharmacol Res Perspect. 2016; 4(2):e00205. https://doi.org/10.1002/prp2.205 PMID: 27069626
9. Maizels M, McCarberg B. Antidepressants and antiepileptic drugs for chronic non-cancer pain. Am Fam Physician. 2005; 71(3):483–90. PMID: 15712623
10. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev. 2009(3):Cd007076. https://doi.org/10.1002/14651858.CD007076.pub2 PMID: 19588419

11. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database Syst Rev. 2013(7):Cd008307. https://doi.org/10.1002/14651858.CD008307.pub2 PMID: 23881791
12. Mack A. Examination of the evidence for off-label use of gabapentin. J Manag Care Pharm. 2003; 9 (6):559–68. https://doi.org/10.18553/jmcp.2003.9.6.559 PMID: 14664664
13. Public Health England and National Health Services, UK. Advice for prescribers on the risk of the misuse of pregabalin and gabapentin. https://www.gov.uk/government/publications/pregabalin-and-gabapentin-advice-for-prescribers-on-the-risk-of-misuse. First published 14 December 2014. Last accessed 22 January, 2017.
14. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005; 113(1–2):9–19. https://doi.org/10.1016/j.pain.2004.09.012 PMID: 15621359
15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International journal of surgery (London, England). 2010; 8(5):336–41.
16. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Family medicine. 2005; 37(5):360–3. PMID: 15883903
17. Schandelmaier S, Ebrahim S, Burkhardt SC, de Boer WE, Zumbrunn T, Guyatt GH, et al. Return to work coordination programmes for work disability: a meta-analysis of randomised controlled trials. PLoS ONE. 2012; 7(11):e49760. https://doi.org/10.1371/journal.pone.0049760 PMID: 23185429
18. Higgins JPT G S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 The Cochrane Collaboration: The Cochrane Collaboration; 2011. Last accessed 22 January 2017. http://handbook.cochrane.org/
19. Chan AW, Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. BMJ (Clinical research ed). 2005; 330(7494):753.
20. Andrew Moore R, Eccleston C, Derry S, Wiffen P, Bell RF, Straube S, et al. "Evidence" in chronic pain—establishing best practice in the reporting of systematic reviews. Pain. 2010; 150(3):386–9. PMID: 20627575
21. Ioannidis JP, Cappelleri JC, Lau J. Issues in comparisons between meta-analyses and large trials. Jama. 1998; 279(14):1089–93. PMID: 9546568
22. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. Journal of clinical epidemiology. 2000; 53(11):1119–29. PMID: 11106885
23. Ebrahim S, Johnston BC, Akl EA, Mustafa RA, Sun X, Walter SD, et al. Addressing continuous data measured with different instruments for participants excluded from trial analysis: a guide for systematic reviewers. J Clin Epidemiol 2014 May; 67(5):560–70. https://doi.org/10.1016/j.jclinepi.2013.11.014 PMID: 24613497
24. Akl EA, Johnston BC, Alonso-Coello P, Neumann I, Ebrahim S, Briel M, et al. Addressing dichotomous data for participants excluded from trial analysis: a guide for systematic reviewers. PLoS ONE. 2013; 8 (2):e57132. https://doi.org/10.1371/journal.pone.0057132 PMID: 23451162
25. Atkinson JH, Slater MA, Capparelli EV, Patel SM, Wolfson T, Gamst A, et al. A randomized controlled trial of gabapentin for chronic low back pain with and without a radiating component. Pain. 2016; 157 (7):1499–507. https://doi.org/10.1097/j.pain.0000000000000554 PMID: 26963844
26. McCleane GJ. Gabapentin reduces chronic benign nociceptive pain: a double-blind, placebo-controlled cross-over study. The Pain Clinic. 2000; 12(2):81–5.
27. McCleane GJ. Does gabapentin have an analgesic effect on background, movement and referred pain? A randomised, double-blind, placebo controlled study. The Pain Clinic. 2001; 13(2):103–7.
28. Baron R, Martin-Mola E, Muller M, Dubois C, Falke D, Steigerwald I. Effectiveness and Safety of Tapentadol Prolonged Release (PR) Versus a Combination of Tapentadol PR and Pregabalin for the Management of Severe, Chronic Low Back Pain With a Neuropathic Component: A Randomized, Double-blind, Phase 3b Study. Pain Pract. 2015; 15(5):455–70. https://doi.org/10.1111/papr.12200 PMID: 24738609
29. Kalita J, Kohat AK, Misra UK, Bhoi SK. An open labeled randomized controlled trial of pregabalin versus amitriptyline in chronic low backache. J Neurol Sci. 2014; 342(1–2):127–32. https://doi.org/10.1016/j.jns.2014.05.002 PMID: 24857356
30. Pota V, Barbarisi M, Sansone P, Moraci M, Pace MC, Passavanti MB, et al. Combination therapy with transdermal buprenorphine and pregabalin for chronic low back pain. Pain Manag. 2012; 2(1):23–31. https://doi.org/10.2217/pmt.11.71 PMID: 24654615

31. Romano CL, Romano D, Bonora C, Mineo G. Pregabalin, celecoxib, and their combination for treatment of chronic low-back pain. J Orthop Traumatol. 2009; 10(4):185–91. https://doi.org/10.1007/s10195-009-0077-z PMID: 19921480

32. Sakai Y, Ito K, Hida T, Ito S, Harada A. Pharmacological management of chronic low back pain in older patients: a randomized controlled trial of the effect of pregabalin and opioid administration. European spine journal: official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. 2015; 24(6):1309–17.

33. Morlion B. Pharmacotherapy of low back pain: targeting nociceptive and neuropathic pain components. Current medical research and opinion. 2011; 27(1):11–33. https://doi.org/10.1185/03007995.2010.534446 PMID: 21083513

34. Chiappini S, Schifano F. A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database. CNS drugs. 2016; 30(7):647–54. https://doi.org/10.1007/s40263-016-0359-y PMID: 27312320

35. Bezerra DM, El Dib R, Vidal EIO, De Barros GAM, Chou R, Fukushima F. Anticonvulsants for chronic low-back pain. Cochrane Database of Systematic Reviews. 2014(6). CD011171

36. Tetsunaga T, Tetsunaga T, Tanaka M, Sugimoto Y, Takigawa T, Ozaki T. Outcomes of pregabalin in lumbar-disease patients with depression. Journal of orthopaedic science: official journal of the Japanese Orthopaedic Association. 2014; 19(2):229–34.

37. Sakai Y, Ito K, Hida T, Ito S, Harada A. Neuropathic pain in elderly patients with chronic low back pai-nand effects of pregabalin: a preliminary study. Asian spine journal. 2015; 9(2):254–62. https://doi.org/10.4184/asj.2015.9.2.254 PMID: 25901238

38. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015; 14(2):162–73. https://doi.org/10.1016/S1474-4422(14)70251-0 PMID: 25575710

39. Simunovic M, Baxter NN. Knowledge translation research: a review and new concepts from a surgical case study. Surgery. 2009; 145(6):639–44. https://doi.org/10.1016/j.surg.2008.11.011 PMID: 19486766

40. Giladi H, Choinière M, Fitzcharles M-A, Ware MA, Tan X, Shir Y. Pregabalin for chronic pain: does one medication fit all? Current medical research and opinion. 2015; 31(7):1403–11. https://doi.org/10.1185/03007995.2015.1040750 PMID: 25868712

41. Baron R, Binder A, Attal N, Casale R, Dickenson AH, Treede RD. Neuropathic low back pain in clinical practice. Eur J Pain. 2016; 20(6): 861–873. https://doi.org/10.1002/ejp.838 PMID: 26935254

42. Taguchi T, Igarashi A, Watt S, Parsons B, Sadosky A, Nozawa K, et al. Effectiveness of pregabalin for the treatment of chronic low back pain with accompanying lower limb pain (neuropathic component): a non-interventional study in Japan. J Pain Res. 2015; 8:487–97. https://doi.org/10.2147/JPR.S88642 PMID: 26346468

43. Orita S, Yamashita M, Eguchi Y, Suzuki M, Inoue G, Miyagi M, et al. Pregabalin for Refractory Radicular Leg Pain due to Lumbar Spinal Stenosis: A Preliminary Prospective Study. Pain Research and Management. 2016; 2016:10.

44. Baron R, Freynhagen R, Tolle TR, Cloutier C, Leon T, Murphy TK, et al. The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy. Pain. 2010; 150(3):420–7. https://doi.org/10.1016/j.pain.2010.04.013 PMID: 20493632

45. Markman JD, Frazer ME, Rast SA, McDermott MP, Gewandter JS, Chowdhry AK, et al. Double-blind, randomized, controlled, crossover trial of pregabalin for neurogenic claudication. Neurology. 2015; 84(3):265–72. https://doi.org/10.1212/WNL.0000000000001168 PMID: 25503625

46. Cohen SP, Hanling S, Bicket MC, White RL, Veizi E, Kurihara C, et al. Epidural steroid injections compared with gabapentin for lumbosacral radicular pain: multicenter randomized double blind comparative efficacy study. BMJ: British Medical Journal. 2015; 350:h1748. https://doi.org/10.1136/bmj.h1748 PMID: 25883095

47. Thorlund K, Imberger G, Johnston BC, Walsh M, Awad T, Thabane L, et al. Evolution of heterogeneity (I2) estimates and their 95% confidence intervals in large meta-analyses. PLoS ONE. 2012; 7(7):e39471. https://doi.org/10.1371/journal.pone.0039471 PMID: 22848355

48. Muehlbacher M, Nickel MK, Kettler C, Tritt K, Lahmann C, Leiberich PK, et al. Topiramate in treatment of patients with chronic low back pain: a randomized, double-blind, placebo-controlled study. Clin J Pain. 2006; 22(6):526–31. PMID: 16788338

49. Spence D. Bad medicine: gabapentin and pregabalin. BMJ (Clinical research ed). 2013; 347:f6747.

50. Mathieson S, Maher CG, McLachlan AJ, Latimer J, Koes BW, Hancock MJ, et al. PRECISE—pregabalin in addition to usual care for sciatica: study protocol for a randomised controlled trial. Trials. 2013; 14(1):213.

51. Clinical Trials Registry. https://clinicaltrials.gov/ct2/show/NCT02273908. Last accessed 22 January, 2017.

52. Clinical Trials Registry. https://www.clinicaltrials.gov/ct2/show/NCT01298466. Last accessed 22 January, 2017.

Supplementary Appendix: S1 Text: Search Strategy for MEDLINE and EMBASE

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 exp Back Pain/ (32247)
2 low back pain.mp. (26237)
3 dorsalgia.mp. (75)
4 back ache.mp. (85)
5 (lumbar adj pain).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1238)
6 exp Coccyx/ or coccydynia.mp. (970)
7 exp Spondylosis/ (6155)
8 lumbago.mp. (1226)
9 back disorder.mp. (116)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (46531)
11 exp Anticonvulsants/ or exp gamma-Aminobutyric Acid/ or gabapentin.mp. (162086)
12 gaba agents.mp. or exp GABA Agents/ (147096)
13 gabapentinoids.mp. (95)
14 pregabalin.mp. or exp Pregabalin/ (2385)
15 lyrica.mp. (88)
16 neurontin.mp. (144)
17 11 or 12 or 13 or 14 or 15 or 16 (212270)
18 10 and 17 (211)

Database: Embase <1974 to 2017 May 02>

Search Strategy:

---

1 exp backache/ (86852)
2 backache.mp. (44068)
3 exp Low Back Pain/ (45830)
4 low back pain.mp. or low back pain/ (51243)
5 lumbago.mp. (1637)
6 spondylosis.mp. (8248)
7 or/1-6 (99535)
8 gabapentin.mp. or exp gabapentin/ (25534)
9 anticonvulsants.mp. or exp anticonvulsive agent/ (360788)
10 neurontin.mp. (1950)
11 gabapentinoids.mp. (202)
12 pregabalin/ (10346)
13 pregabalin.mp. (10607)
14 lyrica.mp. (942)
15 or/8-14 (361243)
16 7 and 15 (3035)

17 limit 16 to english language (2864)
18 16 not 17 (171)

Supplementary Appendix S2 Text: Rescaling or Conversion of Pain Scores to a Common 0-10 Numerical Rating Scale.

Conversion to natural units of most familiar/used or reference instrument [0-10 NRS]

- Instrument A (reference instrument of 0-10 NRS); Scale: L_A and U_A; Range: $R = R_A = U_A – L_A$
- Instrument B (another instrument) used in Trial *i*: Scale: L_B and U_B; Range: $R = R_B = U_B – L_B$
- *C*: control group; m^BCi and sd^BCi : mean and sd of control group
- *E*: experimental group; m^BEi and sd^BEi : mean and sd of intervention group

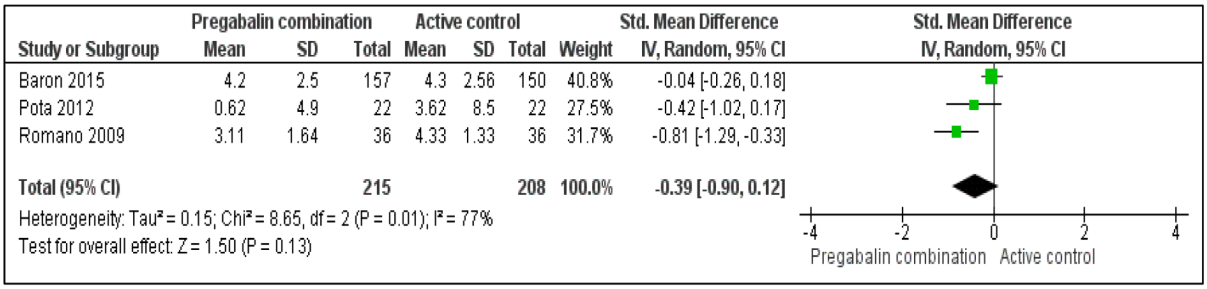
We need to obtain estimates of, m^ACi , sd^ACi , m^AEi , and sd^AEi , of what would have been observed had instrument A been used in trial *i*

$$m^{A}_{Ci} = (m^{B}_{Ci} - L_B)\left(\frac{R_A}{R_B}\right) + L_A \quad \text{and} \quad m^{A}_{Ei} = (m^{B}_{Ei} - L_B)\left(\frac{R_A}{R_B}\right) + L_A$$

$$sd^{A}_{Ci} = sd^{B}_{Ci}\left(\frac{R_A}{R_B}\right) \quad \text{and} \quad sd^{A}_{Ei} = sd^{B}_{Ei}\left(\frac{R_A}{R_B}\right)$$

Supplementary Appendix: S1 Fig. Forest plot showing comparison of studies using pregabalin as an adjunct analgesic compared to active analgesic.

Supplementary file 2: Forest Plot showing comparison of Studies using Pregabalin as an adjunct Analgesic compared to Active Analgesic



Supplementary Appendix S1 PRISMA checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction paragraph 1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction paragraph 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods paragraph 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods paragraph 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods paragraph 3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods paragraph 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods paragraph 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods paragraph 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods paragraph 7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods paragraph 8

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods paragraph 11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods paragraph 11

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods paragraph 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods paragraph 12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results paragraph 1 and figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results paragraph 2 and table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results paragraph 3 and figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results paragraph 4 and 5, and tables 3 and 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results paragraph 4 and 5 and figures 3 and 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results paragraph 8

PRISMA 2009 Checklist

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results paragraph 9 and 10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion paragraph 1
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion paragraph 3
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion paragraph 4
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Abstract

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Chapter 7: Conclusions of the Thesis

This chapter provides an overview of the main findings from the three investigations of analgesic interventions included in this thesis. It also considers the main implications of study findings, directions for future research and clinical practice, and key limitations.

The first part of this thesis described the comparison of morphine (M) versus hydromorphone (HM) in day surgery patients, within the framework of a multicentre randomized control trial (RCT). The study was conducted during February 2015 to May 2018, and randomized 402 patients.

Key findings: The primary finding was that the odds of achieving satisfactory analgesia with minimal emesis (SAME) during stabilisation of patients in post-anesthetic care unit (PACU) were similar between the groups with an odds ratio (OR) of 1.00 (95% Confidence Interval (CI): 0.56, 1.78). The proportion of patients having severe sedation, itching, and respiratory depression were also similar. As another comparison for analgesia, the proportion of patients requesting oral analgesia were nearly equal; 68% in the HM and 66% in the M group. The only significant difference was in the total quantity of opioid analgesia used when considered in equivalent morphine unit ratio of 5:1 (HM:M). The HM group required significantly lesser medication: -0.73 units (95% CI: -1.43, -0.03). We also noted that post-discharge symptoms of average pain, nausea-vomiting, emergency roon visit or readmission rate within the 24 hours, were similar between the groups.

Implications and future directions: This study demonstrated that, although there may be pharmacokinetic differences between the study medications[29], clinically there are no differences either in the achievement of appropriate analgesia or for the side effect rates of patient important outcomes. As the existing literature was unclear about the choice of long-acting opioid to be in acute settings[30-32], our trial provides a much clear picture for the practicing physician or health providers. This finding is in contrast to the review and meta-analysis reporting that HM is more advantageous than M for acute pain, when compared for pain scores[33]. The significant difference in total opioid needed suggests that the potency of HM is more than five times that of M. The ratio of 5:1 (HM:M) is widely quoted and used, although the reported range of potency is variable, from 5:1 to 10:1[34]. Mahler and Forrest looked at the relative potencies of HM and M in postoperative patients and had observed that HM dose of 0.9-1.2 mg could be equi-analgesic to 10 mg of M, which is not a common belief[35]. It is likely that a perception of administering a much smaller dose of opioid with HM creates a subjective bias in health providers who consider HM to be more effective for analgesia. Our study considered patient important outcomes at individual patient level (binary), in contrast to most other studies which report average outcomes. We feel this is especially important, as it not only facilitates the interpretation of treatment effects, but also because opioid side effects can be idiosyncratic and patient dependent. Apart from being a relatively large trial, no differences were observed in our comparison of analgesia and other post-discharge outcomes, indicating consistency with our primary outcome. As it is very unlikely that there are real differences between the study medications, we do not think there would be any benefit in comparing these medications in a similar cohort of patients, and any future clinical decisions should be based on individual patient responses.

Limitations: Since this study involved only patients having day surgeries, it is possible that similar observations may not be valid for PCA therapy, as the effects of M could be cumulative because of an active metabolite. Similarly, our results do not apply for patients with chronic pain.

In chapter 4, we reported the study titled, 'NMDA Antagonists and Steroids for the Prevention of Persisting Post-Surgical Pain after Thoracoscopic Surgeries: A Randomized Controlled, Factorial Design, International, Multicentre Pilot Study'. This was a feasibility study conducted at two sites; St. Joseph's Hamilton, Canada (site 1) and Cleveland Clinic, Cleveland, USA (site 2). The primary objective of the study was to determine the feasibility of recruiting eligible patients and patients completing the three months follow up.

Key findings: We initiated the trial at site 1 on 3rd May 2017 and at site 2 on 5th April 2018. Out of the estimated sample size of 48 patients, we recruited 27 patients, and had to stop recruitment on April 20th, 2018 because the packaged study medications were expiring and there was no available supply of 5 mg memantine tablets from our source. The recruitment rate per week (95% CI) were 0.63 (0.47–0.79); and 1 (0.83–1.17), respectively, at sites 1 and 2. The percentage of randomized patients with follow-up at three months after randomization was 100% and 66.7% (one of the three patients was lost to follow up) at site 1 and 2, respectively. Overall, we were unable to demonstrate feasibility based on lower than expected recruitment rate, and other logistical challenges that did not allow us to complete the full study recruitment. The study assessed clinical endpoints as secondary outcomes. At three months post randomization, the number of patients having any persistent post-surgical pain (PPSP) (resting score >0 in 0–10 numerical rating scale (NRS), and PPSP on movements (>3 in 0–10 NRS) were four, and two patients respectively. There were no important differences in any other clinical outcomes.

Implications and future directions: Our trial is a good example of the need for a feasibility study, before embarking on a larger trial[36]. We planned it as an international trial as we appreciated the need to involve other centres beyond Canada. We faced several challenges during the conduct of the trial: requirements for regulatory approvals, acquisition and packaging of study medications, individual site ethics approval, and the need to ensure study completion before the expiry of study medications. Although we were able to overcome the challenges of satisfying regulatory requirements, we had a significant delay at the 2nd site due to other trial logistics. We also observed that the increasing use of robotic surgery for lung resections can affect patient recruitment at both sites[37]. The 2nd aspect to consider is the rate of baseline risk of PPSP in this population so that a reasonable estimate for a future study sample can be made. The incidence of PPSP after video assisted thoracoscopic surgeries (VATS) lobectomies is not consistent across studies and can vary between 22 to 63%[38-40]. We estimated a lower limit of 20% incidence with movement, based on available literature. In our trial, we observed a PPSP rate of 15% at rest and 7% with movement (clinically important PPSP). We believe that appropriate changes to study population, such as including other populations at higher

risk of PPSP along with VATS lobectomy patients, with stratification based on surgical type, should be considered to make a larger trial feasible.
Limitations: This being a pilot study, it is not appropriate to infer about potential treatment effects of study interventions. Although we have highlighted a good scientific rationale behind our study interventions, we need to acknowledge that there is limited data on the optimal dosing and timing of our study interventions to prevent PPSP.

In our third part of the thesis, we reported on the background, methodology and our systematic review and meta-analysis of RCTs assessing the benefits and safety of gabapentinoids in chronic low back pain (CLBP).
Key findings: We identified 8 RCTs that assessed the benefits of using gabapentin (GB) or pregabalin (PG) in CLBP. Out of them, six had a risk of selection bias, six for allocation concealment and three for sequence generation, and four involved a risk of detection bias. GB compared to placebo (3 studies, n = 185) showed only minimal improvement of pain compared to placebo (mean difference (MD) = 0.22 units, 95% CI [−0.5 to 0.07] I^2 =0%; GRADE: very low), and pain relief with PG was inferior compared to the active analgesic group (MD = 0.42 units, 95% CI [0.20 to 0.64] I^2 = 0; GRADE: very low). Studies using PG as an adjuvant (n =423) were not pooled due to heterogeneity, but the largest of them showed no benefit of adding PG to tapentadol. Both GB and PG were associated with increased risk of dizziness and GB was additionally associated with increased risk of fatigue, visual disturbances, and difficulties with mentation compared with placebo.
Implications and future directions: Considering the overall burden of CLBP, appropriate management of this condition is a health priority[20,41]. CLBP is a challenging and frequently recurring condition, with unsatisfactory results using routine analgesic medications. As there are multiple observations about the increased use of gabapentinoids for CLBP, our review serves an important purpose in the present context. Our results indicate that there is not only limited evidence to support the use of gabapentinoids in nonspecific CLBP, the existing evidence suggests increased risk of adverse effects with only minimal or no benefit. From the standpoint of clinical practice, it has important implications, and their continued use in CLBP merits caution. It is notable that the results of our review were considered as important signals for clinical practice by National Institute of Health Research, UK (https://discover.dc.nihr.ac.uk/content/signal-000515/two-nerve-drugs-are-not-suitable-for-treating-long-term-low-back-pain). As the existing studies are small, it is important for any future study assessing the benefit of gabapentinoids to be large, and to stratify patients to possible neuropathic and non-neuropathic pain category, as gabapentinoids have better evidence in neuropathic pain conditions.
Limitations: Non-inclusion of studies with patients of predominant leg pain or spinal stenosis can be considered a limitation. This was done to limit the heterogeneity within our study population. Heterogeneity has been shown to be an issue with meta-analyses involving a smaller number of trials or events. Also, topiramate (another anticonvulsant medication used for chronic pain conditions) was not considered in this review, as it has a slightly different mechanism of action and is not commonly used for CLBP. At the same

time, it is important to note that a subsequently published review, which considered the population of lumbar radicular pain with or without CLBP, and expanded to include any anticonvulsants, also came to a similar result and conclusion as ours[42].

Final Conclusions: This thesis includes investigations involving analgesic interventions in three different context and patient population, using methodological framework of an RCT; factorial design feasibility RCT; and a systematic review and meta-analysis. It identified no difference between morphine and hydromorphone in day surgery patients; need for appropriate modifications to protocol for a definitive factorial design trial; and limited evidence for using gabapentinoids for CLBP, respectively.

REFERENCES FOR CHAPTER 1 (Introduction) and 7 (Conclusion)

1. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. Pain. 1979;6(3):249.
2. Brennan F, Carr DB, Cousins M. Pain Management: A Fundamental Human Right. Anesthesia & Analgesia. 2007;105(1):205-21.
3. Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet. 2011;377(9784):2215-25.
4. Sommer M, de Rijke JM, van Kleef M, Kessels AG, Peters ML, Geurts JW, et al. The prevalence of postoperative pain in a sample of 1490 surgical inpatients. Eur J Anaesthesiol. 2008;25(4):267-74.
5. Troy AM, Cunningham AJ. Ambulatory surgery: an overview. Current opinion in anaesthesiology. 2002;15(6):647-57.
6. Shnaider I, Chung F. Outcomes in day surgery. Current opinion in anaesthesiology. 2006;19(6):622-9.
7. Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. Anesthesia and analgesia. 1999;89(3):652-8.
8. Chatterjee S, Rudra A, Sengupta S. Current concepts in the management of postoperative nausea and vomiting. Anesthesiology research and practice. 2011;2011:748031.
9. White PF. Pain management after ambulatory surgery - where is the disconnect? Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2008;55(4):201-7.
10. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367(9522):1618-25.
11. Werner MU, Kongsgaard UE. I. Defining persistent post-surgical pain: is an update required? British journal of anaesthesia. 2014;113(1):1-4.
12. Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2009;36(1):170-80.
13. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-15.
14. Schmid RL, Sandler AN, Katz J. Use and efficacy of low-dose ketamine in the management of acute postoperative pain: a review of current techniques and outcomes. Pain. 1999;82(2):111-25.
15. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008;70(18):1630-5.
16. Ellis A, Bennett DL. Neuroinflammation and the generation of neuropathic pain. British journal of anaesthesia. 2013;111(1):26-37.
17. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database Syst Rev. 2013;7:CD008307.

18. Montgomery AA, Peters TJ, Little P. Design, analysis and presentation of factorial randomised controlled trials. BMC medical research methodology. 2003;3:26-.
19. Deyo RA, Weinstein JN. Low back pain. The New England journal of medicine. 2001;344(5):363-70.
20. Hoy D, Bain C, Williams G, March L, Brooks P, Blyth F, et al. A systematic review of the global prevalence of low back pain. Arthritis Rheum. 2012;64(6):2028-37.
21. Murray CJ, Atkinson C, Bhalla K, Birbeck G, Burstein R, Chou D, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. Jama. 2013;310(6):591-608.
22. Patel R, Dickenson AH. Mechanisms of the gabapentinoids and alpha 2 delta-1 calcium channel subunit in neuropathic pain. Pharmacol Res Perspect. 2016;4(2):e00205.
23. Bennett MI, Simpson KH. Gabapentin in the treatment of neuropathic pain. Palliat Med. 2004;18(1):5-11.
24. Gajraj NM. Pregabalin: its pharmacology and use in pain management. Anesth Analg. 2007;105(6):1805-15.
25. Goodman CW, Brett AS. Gabapentin and Pregabalin for Pain - Is Increased Prescribing a Cause for Concern? The New England journal of medicine. 2017;377(5):411-4.
26. Maizels M, McCarberg B. Antidepressants and antiepileptic drugs for chronic non-cancer pain. Am Fam Physician. 2005;71(3):483-90.
27. England PHEaN. Pregabalin and gabapentin: advice for prescribers on the risk of misuse 2014 [cited 2019 August 22]. Available from: https://www.gov.uk/government/publications/pregabalin-and-gabapentin-advice-for-prescribers-on-the-risk-of-misuse.
28. Mack A. Examination of the evidence for off-label use of gabapentin. J Manag Care Pharm. 2003;9(6):559-68.
29. Murray A, Hagen NA. Hydromorphone. Journal of Pain and Symptom Management. 2005;29(5):57-66.
30. Chang AK, Bijur PE, Baccelieri A, Gallagher EJ. Efficacy and safety profile of a single dose of hydromorphone compared with morphine in older adults with acute, severe pain: a prospective, randomized, double-blind clinical trial. Am J Geriatr Pharmacother. 2009;7(1):1-10.
31. Goodarzi M. Comparison of epidural morphine, hydromorphone and fentanyl for postoperative pain control in children undergoing orthopaedic surgery. Paediatric anaesthesia. 1999;9(5):419-22.
32. Patanwala AE, Keim SM, Erstad BL. Intravenous opioids for severe acute pain in the emergency department. The Annals of pharmacotherapy. 2010;44(11):1800-9.
33. Felden L, Walter C, Harder S, Treede RD, Kayser H, Drover D, et al. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. British journal of anaesthesia. 2011;107(3):319-28.
34. Inturrisi CE. Clinical pharmacology of opioids for pain. Clin J Pain. 2002;18(4 Suppl):S3-13.
35. Mahler DL, Forrest WH, Jr. Relative analgesic potencies of morphine and hydromorphone in postoperative pain. Anesthesiology. 1975;42(5):602-7.

36. Rosenthal R, Kasenda B, Dell-Kuster S, von Elm E, You J, Blumle A, et al. Completion and Publication Rates of Randomized Controlled Trials in Surgery: An Empirical Study. Annals of surgery. 2015;262(1):68-73.
37. Onugha O, Ivey R, McKenna R. Novel Techniques and Approaches to Minimally Invasive Thoracic Surgery. Surg Technol Int. 2017;30:231-5.
38. Gottschalk A, Cohen SP, Yang S, Ochroch EA. Preventing and treating pain after thoracic surgery. Anesthesiology. 2006;104(3):594-600.
39. Pluijms WA, Steegers MA, Verhagen AF, Scheffer GJ, Wilder-Smith OH. Chronic post-thoracotomy pain: a retrospective study. Acta Anaesthesiol Scand. 2006;50(7):804-8.
40. Freixinet JL, Canalis E, Julia G, Rodriguez P, Santana N, Rodriguez de Castro F. Axillary thoracotomy versus videothoracoscopy for the treatment of primary spontaneous pneumothorax. The Annals of thoracic surgery. 2004;78(2):417-20.
41. Morlion B. Pharmacotherapy of low back pain: targeting nociceptive and neuropathic pain components. Current medical research and opinion. 2011;27(1):11-33.
42. Enke O, New HA, New CH, Mathieson S, McLachlan AJ, Latimer J, et al. Anticonvulsants in the treatment of low back pain and lumbar radicular pain: a systematic review and meta-analysis. Canadian Medical Association Journal. 2018;190(26):E786-E93.