**Outline**

**This thesis outline will be using the PRISMA Checklist for systematic reviews, so items corresponding to the PRISMA Checklist have their corresponding number appended *(#)*.**

1. Introduction

1. Rationale *(# 3)* 2. Objectives *(# 4)*

1. Optimal dose of morphine 2. Comparison of other opiods with morphine

2. Methods

1. Reproducible Research

2. PRISMA Methods

1. Protocol and Registration *(# 5)* 2. Eligibility Criteria *(# 6)* 3. Information sources *(# 7)* 4. Search Strategy *(# 8)* 5. Study Selection Process *(# 9)* 6. Data Collection Process *(# 10)* 7. Data Items *(# 11)* 8. Risk of Bias Tool (Within Studies) *(# 12)* 9. Summary Measures to Include *(# 13)* 10. Synthesis Methods *(# 14)* 11. Risk of Bias Across Studies *(# 15)* 12. Additional Analyses *(# 16)*

3. Prisma Results

1. Study Flow Diagram *(# 17)* 2. Study Characteristics (Table) *(# 18)* 3. Study Risk of Bias (Table) *(# 19)* 4. Study Results (Table) *(# 20)* 5. Across Study Risk of Bias *(# 23)* 6. Additional Analyses *(# 24)*

4. PRISMA Discussion

1. Summary of Evidence *(# 24)* 2. Limitations *(# 25)* 3. Conclusions *(# 26)*

5. Funding *(# 27)*

**Introduction**

**Rationale *(# 3)***

1. Oligoanalgesia 2. Prior Reviews

**Oligoanalgesia**

Oligoanalgesia is the practise of undertreatment of pain, and this is a common problem for patients with acutely painful conditions who present for emergency care. The processes that lead to undertreatment of pain are complex. One factor that contributes is a difference of opinion on what dosing regime of opioid analgesic is appropriate for treatment of acute pain. Another factor is concern over side effects, such as nausea, vomiting, respiratory depression, or hypotension. A third concern is that treating acute pain may delay making a diagnosis and lead to delay in surgical treatment and subsequent complications.

**Prior Related Reviews**

Several previous systematic reviews have examined the issue of administration of opioid analgesia for acutely painful conditions. They are listed with a brief summary of their findings.

One systematic review and meta-analysis was limited to children with abdominal pain. That review concluded that (a) compared to placebo, opioid analgesia was effective in controlling pain; (b) opioid analgesia did not result in increased perforation or abscesses; and (c) administration of opioids did not result in a delay to diagnosis. It also concluded that, compared to placebo, opioid analgesia did cause increased side effects, as long as continuing to have pain is not considered a “side effect” of placebo. **[1]**

***Analgesia in the emergency department: a GRADE-based evaluation of research evidence and recommendations for practice*.[2]**

A second review is reported in brief only, providing summary statements of findings. Relevant conclusions were: (a) For adults accessing the emergency department with acute pain, fentanyl was more effective than parenteral morphine in management of acute moderate to severe pain; (b) for the same patients, parental hydromorphone was more effective than morphine; and (c) parenteral hydromophone 1 + 1 mg patient-driven protocol was more effective than other intravenous opioids at any dose (physician-driven protocol) All findings were based on reported change in visual analog scale pain ratings. **[2]**

These questions are extremely specific, which limits the usefulness of them, for example, , questions, and may have been driven by the publication of specific articles in the emergency medicine literature, rather than by an *a priori* research question. In addition, the review does not include enough information to make it reproducible.

***Analgesia in patients with acute abdominal pain*.[3]**

A recent Cochrane review addressed the topic of administering opioid analgesia to patients over 14 years of age with acute abdominal pain. Its authors concluded that when compared with placebo, the use of analgesia did not result in “unsuitable treatment decisions” , and that the use of opioid analgesia improved patient comfort . However, the questions of whether the use of opioid analgesia delayed surgery or prolonged hospital stay continue to be unclear. **[3]** ).

***Parenteral opioids in emergency medicine–A systematic review of efficacy and safety*.[4]**

A fourth systematic review was limited to adults with acute pain treated in prehospital and emergency settings. A qualitative synthesis was presented because of the heterogeneity of the studies included in the review, some of which compared different opioid regimes. The main conclusion in this review was that (a) opioid analgesia is efficacious in the prehospital setting and in the emergency department. However, the authors concluded that its safety in the prehospital and emergency department is still unclear. **[4]**

Finally, a 2010 paper reported that **[5]**However, it is a mixture of a systematic review and narrative review, with very limited reporting of methods, and is therefore not reproducible. It is also five years old and due for an update, since a number of studies have been published since its literature search ended. Thus an updated and systematic review on this question is due.

***Do opiates affect the clinical evaluation of patients with acute abdominal pain?*[6]**

A 2006 review (part of the JAMA Rational Clinical Exam series) addressed the effect of opiates on management errors of patients with acute abdominal pain. It concludes that opiate administration had no association with management errors. It did not address the issue of dosing for pain control. **[6]**

**Study Objectives**

In emergency conditions morphine is considered the standard against which other analgesics are measured. The effects of morphine are dose-dependent, so it the first question for review is: In patients presenting to prehospital care or the emergency department with an acutely painful condition, is there a treatment regime using intravenous morphine that is more effective in treating pain than usual care?There are other opiates that have different side effect profiles than morphine or a different duration of action, so the second question in the planned review is:In patients presenting to prehospital care or the emergency department with an acutely painful condition, is there another intravenous opioid that is more effective than morphine at treating pain?

**Methods**

**Reproducible Research**

These reviews will be done using the principles of reproducible research There are five key aspect of reproducible research. These are: open formats; open analysis; open access; open publication; and collaboration and tracking tools.

Open formats allow for the use of Free and Open Source Software (FOSS) available to perform a systematic review and metaanalyis. This in turn opens the the study for external review by anyone. There is no lockdown to any particular piece of software.

Open analysis refers to the steps of the analyis being clearly documented and accessible over the web. This increases the transparency of the review process and increases confidence in the process.

Open access over the web to each step of the process improves the reproducibility of the results and will allow the review to be updated easily in the future. Each step of the study will be maintained in a git repository that others can copy and use.

Open publication will allow anyone interested to view the results over the internet without any restrictions. Collaboration and tracking tools refers to the idea that in computer programming, version control software is used to keep track of changes to software and to allow people to collaborate on a project without interfering with each other’s work. Git, an open source program, will be used to provide version control and collaboration for this review.

These reviews will use the PRISMA ( Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [7] statement and checklist as a guide. They will be registered in the PROSPERO [8] database of systematic reviews. At each step below where two reviewers independently make assessments and then compare their results the degree of concordance between the two reviewers will be reported.

1. Inclusion criteria

1. Randomised controlled trials that compare an opioid analgesic to placebo or to another dose of the same or a different analgesic. 2. Cohort studies for evidence on secondary outcomes (adverse effects)

2. Exclusion criteria

1. Abstracts, conference proceedings, that do not contain enough information

**Information sources *(# 7)***

1. Medline 2. Embase 3. CENTRAL 4. CINAHL 5. Clinicaltrials.gov

**Search Strategy *(# 8)***

The search strategiews for each database will be developed in concert with a librarian and then peer-reviewed by another librarian.

**Study Selection Process *(# 9)***

Study selection will be conducted in two steps: first, there will be a review of titles and abstracts of the sudies found by electronic search by two different reviewers using a prespecified data form. The discrepancies between the two reviewers in choosing studies for further analysis at this stage will be resolved by consensus between the two reviewers. Second, the studies identified as potentially relevant in the first stage will be retrieved as full text, and these will in turn be reviewed by two reviewers using a prespecified data form to analyse the studies for quality of methods. Again, the discrepancies will be resolved by consensus.

**Data Collection Process *(# 10)***

Data will be collected by two reviewers using a prespecified data form. Disagreements about the data will be resolved by consensus.

**Data Items *(# 11)***

1. Study eligibility

1. inclusion criteria

2. Study design

1. randomisation 2. allocation concealment

3. Study participants

1. age 2. gender 3. presenting complaint 4. final diagnosis

4. Treatment

1. drug and comparison (placebo or other active drug) 2. dose, fixed or weight based 3. treatment regime, single or multiple dose, patient guided analgesia 4. co-adminstration of other drugs (antiemetics, NSAIDS)

5. Pain (numeric score, VAS, other scoring system, patient satisfaction with treatment)

1. baseline pain 2. pain at other times (fixed interval, at discharge or admission)

6. Adverse events

1. nausea and vomiting 2. respiratory depression (minor: decreased respiratory rate or needing supplemental oxygen, major: needing naloxone or an airway intervention) 3. rescue analgesia 4. persistent pain 5. diagnostic interference (has been assessed in other studies and will not be a major outcome in these reviews)

7. Follow up duration

1. while in emergency 2. after discharge or admission

8. Withdrawals, lost to follow up  
 9. Study risk of bias

**Risk of Bias Tool (Within Studies) *(# 12)***

Randomized controlled trials will be assessed using the Cochrane Risk of Bias Tool. Cohort studies will be assessed using the SIGN tool for cohort studies.

**Summary Measures to Include *(# 13)***

The main summary measure will be the mean difference in pain score. Secondary measures will be rates of adverse events.

**Synthesis Methods *(# 14)*Risk of Bias Across Studies *(# 15)*Additional Analyses *(# 16)***

Subgroups that will be analysed include:

1. prehospital and emergency department studies 2. adult and pediatric patients 3. studies in different risk of bias categories

**Prisma Results**

**Study Flow Diagram *(# 17)***

The results of the literature search and study selection will be presented in a flow diagram.

**Study Characteristics (Table) *(# 18)*Study Risk of Bias (Table) *(# 19)*Study Results (Table) *(# 20)*Across Study Risk of Bias *(# 23)***

There will be a summary of publication bias and risk of biased reporting.

**Additional Analyses *(# 24)***

There will be tables summarizing study characteristics, risk of bias, and results, and additional analyses.

**PRISMA Discussion**

**Summary of Evidence *(# 24)***

The summary of evidence will be done using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[9] guidelines. These guidelines state that…

**Limitations *(# 25)***

The limitations of the review will be discussed.

**Conclusions *(# 26)***

Recommendations will be made as recommended in the GRADE guidelines. [10]

**Funding *(# 27)***

1. Poonai N, Paskar D, Konrad S-L, Rieder M, Joubert G, Lim R, et al. Opioid Analgesia for Acute Abdominal Pain in Children: A Systematic Review and Meta-analysis. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine. 2014 Nov;21(11):1183–92.   
 2. Lipp C, Dhaliwal R, Lang E. Analgesia in the emergency department: a GRADE-based evaluation of research evidence and recommendations for practice. Critical care (London, England). 2013 Mar 19;17(2):212.   
 3. Manterola C, Vial M, Moraga J, Astudillo P. Analgesia in patients with acute abdominal pain. Cochrane database of systematic reviews (Online). 2011;(1):CD005660.   
 4. Niemi-Murola L, Unkuri J, Hamunen K. Parenteral opioids in emergency medicine–A systematic review of efficacy and safety. Scandinavian Journal of Pain. Elsevier; 2011;2(4):187–94.   
 5. Patanwala AE, Keim SM, Erstad BL. Intravenous opioids for severe acute pain in the emergency department. Ann Pharmacother. 2010 Nov;44(11):1800–9.   
 6. Ranji SR, Goldman LE, Simel DL, Shojania KG. Do opiates affect the clinical evaluation of patients with acute abdominal pain? JAMA. American Medical Association; 2006 Oct 11;296(14):1764–74.   
 7. http://www.prisma-statement.org  
 8. http://www.crd.york.ac.uk/PROSPERO  
 9. http://www.gradeworkinggroup.org/index.htm  
 10. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. Journal of clinical epidemiology. 2013 Jul;66(7):719–25.