Thesis proposal

**Summary of the Problem: Patients in emergencies are not consistently well-treated for pain.**

Background: Oligoanalgesia is the inadequate treatment of pain, and in the Emergency Department setting, the term is usually reserved to describe the experience of patients who present for emergency care with acutely painful conditions, and who do not get adequate analgesia.{Wilson:1989da} The processes that lead to undertreatment of pain are complex.{Rupp:2004bk} It has been traditional to think that the administration of opioid analgesia may lead to complications. Sir Vincent Zachary Cope, the author of \*Cope's Early Diagnosis of the Acute Abdomen\*, a standard text of general surgery, said in 1929:

“There are many acute abdominal pains for which a dose of

morphine is the correct treatment—such, for example, as

renal and biliary colic, gastric crises, diaphragmatic

pleurisy with pain referred to the abdomen—but there are

other conditions of an apparently similar nature for which

to give a dose of morphine is, to say the least, an unwise

and, to say the most, a possibly fatal, procedure.”{Cope:1929we}

This fairly nuanced expression was taken as a prohibition against giving opioids to patients with acute abdominal pain.{Yealy:1996wq}

Different physicians presented with the same clinical presentation may make widely disparate decisions about treatments for acute pain.{TamayoSarver:2004jw} Even within the same clinical setting, the treatment of pain varies widely among clinicians, both in emergency medical services{Albrecht:2013dv} and in the emergency department setting.{Heins:2006gb}

Factors Contributing to Oligoanalgesia

A number of factors have been identified as contributing to oligoanalgesia. These include lack of clinician education about how to manage pain; treatment of pain not being included in quality improvement initiatives; fears of patients becoming addicted to or abusing opioids; concerns over side effects, such as nausea, vomiting, respiratory depression, or hypotension; and differential treatment according to membership in racial and ethnic groups contribute to the undertreatment of pain.{Miner:2006ie} Caregivers’ attitudes, such as the belief that pain is an accepted part of the process of disease and that patients pain experience is not valid, also contribute to oligoanalgesia.{Ducharme:2013bp}

One common concern about providing adequate treatment for acute pain is that such treatment may delay diagnosis and surgical treatment and lead to subsequent complications has been addressed in three systematic reviews, which all conclude that treatment of acute pain does not lead to these problems.{Poonai:2014hv}{Manterola:2011fk}{Ranji:2006ki}

**The best outcome for research and clinical use is patient oriented: “enough pain treatment”.**

Pain is a subjective experience that, unlike temperature, pulse, blood pressure and oxygen saturation, cannot be measured by an external instrument; yet it has considered to be the "Fifth Vital Sign" in medicine.{Campbell:1996gb} The intent behind designating pain this way is to promote the treatment of pain by recognizing significant abnormalities and taking action to bring these abnormalities back into an acceptable range; and to prioritize the treatment of patients in pain.

As pain is a patient reported outcome (PRO), based on self-report of symptoms, pain researchers have developed methods of measuring pain so as to make an individual patient's symptoms reproducible from one time to the next, and to measure and aggregate multiple patients' intensity of pain. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)] group has published recommendations for PROs in clinical trials for chronic pain, {Turk:2006kf}{Dworkin:2008ej} and acute pain,{Cooper:2016kl} but these recommendations are not addressed at the emergency department. The two most commonly used pain measurements in emergency department pain research are: 1) a visual analogue scale (VAS), which is a 100 mm line, anchored by descriptors on each end (typically, “no pain” and “the worse pain imaginable”) on which the patient marks the point representing their perception of their pain intensity; and 2) an eleven point verbal numerical rating scale (VNRS) that goes from 0 to 10 (typically, with the instructions: “on a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your pain”) . These two scales do not seem to differ significantly when compared to each other. {Marquie:2008bq} These scales have been shown to be reproducible within patients,{Bijur:2001uo} but in clinical practice different raters can elicit different pain scores from the same patient.{Harting:2013cd} Furthermore, t: other factors such as considerations of side effects or fear of addiction will affect their decisions to accept treatment.{Tanabe:1999co}

There have been multiple studies conducted in emergency department settings aimed at identifying the minimally detectible pain score difference (sometimes called the minimally important difference (MID) or the minimally clinically important difference (MCID)), which usually works out to be an improvement between than 1 and 2 cm on a VAS.{Todd:1996uv}{Kelly:1998th}{Kendrick:2005gf} This is the amount of change on a VAS that is associated with patients saying that they feel either a little better or a little worse. These changes are averaged over the group in the study and then reported. There are two problems with using this approach to estimate the effectiveness of pain control in the emergency department setting: first, the detection of a minimal difference is not the same as adequate control of pain, and second, the MID may not apply to individuals. For example, a larger decrease in pain ratings may not reflect “feeling a little better” for a given individual, and conversely, some patients have an increase in pain ratings, yet still report feeling a little better.{Todd:1996uv} Finally, feeling "a little better" should not be confused with having the desired amount of pain relief.{Barden:2007uw}

Other studies have looked at a different measure, confusingly also called the minimally clinically important difference, which is defined as the change in VAS associated with adequate relief of pain. These studies have shown that the amount of change on a pain scale that is associated with adequate relief of pain varies with the initial severity of the pain. the Minimally Clinically Important Difference is sometimes reported as a certain distance on the scale, and sometimes as a percentage change from an initial value. In one study conducted in the emergency department setting, the average MCID associated with adequate pain relief was an improvement of 3 cm on the VAS, and the average change in pre-treatment pain score was an decrease of 30% from the initial score.{Lee:2003wl} The findings were similar in a postoperative setting,{Cepeda:2003bo} and in a rheumatology clinic.{tenKlooster:2006je} This is again problematic for assessing the adequacy of pain management in individual cases, as it is a group average rather than a measure that applies to every patient. The relationship between individual patient’s experiences of having a sufficient relief of pain and a change in a pain score is inconsistent: as above, some people have reported sufficient relief of pain even though their final pain score is higher than their initial score. In addition, one of these studies had sensitivities and specificities of only about 70% for their 3 cm cutoff,{tenKlooster:2006je} which leads to substantial misclassification of whether or not an individual patient had adequate pain relief.

**The standard treatment for acute pain is morphine and the doses in clinical use vary considerably.**

Morphine is the “gold standard” opioid which is often used as a comparison in studies of other analgesics in the emergency department, yet the dose of morphine that is used in clinical practice is lower than the equivalent doses of other opioids.{Bijur:2012jy}{OConnor:2010hu}{OConnor:2006gk} Education about pain management and protocols for analgesia have the possibility to improve the treatment of pain. In order to effectively treat pain we need to know the optimal doses of morphine for analgesia, and that is the purpose of this thesis.

**Research on morphine dosing often uses outcomes that are not patient-oriented.**

Research on morphine dosing most often uses a change in pain score as the outcome of interest,{MacKenzie:2016gx}{Patanwala:2010er} but does not relate this score to the proportion of patients that say they have been adequately treated for pain. Some research has used overall patient satisfaction as an outcome, but overall satisfaction does not correlate with pain relief, as patients may be satisfied with their care while continuing to be in severe pain,{DeLaney:2015fj} or patient satisfaction may increase after an intervention even though no more analgesia is given.{Taylor:2016fw}

I propose doing a set of two systematic reviews. The aim of the first review is to answer the question: “In patients presenting to the emergency department with acute painful and receiving a treatment for pain; does an lowering the pain score below a threshold, or reaching an absolute or relative change in pain score, best predict the patient’s expressed statement that they have had enough pain treatment?” Clarifying the current knowledge on the linkage between “enough pain treatment” and other outcomes will make the research using those other outcomes easier to interpret and utilize. .

**A systematic review of morphine dosing that translates other outcomes to “enough pain treatment” will be a better guide to morphine dosing.**

The second question of interest is: “In patients presenting to the emergency department with acute pain, what standardised dosing regimen of morphine, compared with usual care, will relieve the acute pain as judged by the patient expressed goal of enough pain treatment?” This will aid in guiding the optimal dosage of morphine for acute pain by clarifying the current knowledge on the linkage between “enough pain treatment” and other outcomes used in the morphine dosing literature.

**Methods.**

There will be two systematic reviews. Each review will be registered in the PROSPERO database (<http://www.crd.york.ac.uk/PROSPERO/)> and will be prepared following the checklist in the PRISMA-P statement.(31) The search strategies will be developed with a librarian. The databases searched will be MEDLINE, EMBASE, and CINAHL. The included studies will be randomised controlled trials and cohort studies that address the questions (more specific inclusion criteria to be developed) . Articles will be excluded if they are case reports, reviews, abstracts or editorials. Two authors will independently review the articles found by the search and rate their relevance according to the inclusion and exclusion criteria. Any conflicts will be resolved by discussion until the reviewers reach consensus. Following selection of articles, two reviewers will independently rate the methodological quality of each article using a critical appraisal form based on the Cochrane risk of bias tools for randomised{Higgins:2011cg} and non-randomised{Sterne:2016jn} studies. Data from the articles will be summarized in tables. There will be a qualitative synthesis of the results. The GRADE guidelines will be used to rate the quality of the evidence across the studies.{Guyatt:2011ef} If the studies contain sufficient detail and are judged to be homogenous enough after the qualitative synthesis then a meta-analysis will be included.

For the first review concerning the relationship between pain scale measures and “enough pain treatment” there will be an attempt to derive a bias analysis tool{Lash:2011kd} to more easily translate the pain scale measures into the endpoint of “enough pain treatment”, that can then be used in the second review for studies that do not use that endpoint.