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# Use of non-opioid analgesics as first line treatment for acute pain management by emergency medical services providers

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**USE OF NON-OPIOID ANALGESICS AS FIRST LINE TREATMENT FOR  
ACUTE PAIN MANAGEMENT BY EMERGENCY MEDICAL SERVICES  
PROVIDERS**

by

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B.S., Santa Clara University, 2017

Submitted in partial fulfillment of the  
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**ABSTRACT**

Pain is the universal symptom of illness and trauma. It affects people of all ages, cultures, and backgrounds, causing distress and suffering. Appearing in a plethora of diagnoses, almost all patients will experience some type of pain as a related symptom during their lifetime. The ubiquitous nature of pain renders it likely that a wide variety of healthcare providers will treat patients reporting pain in both the acute care and longitudinal settings. Many institutions and governing bodies in the medical sphere have emphasized the duty of the medical field to treat pain and thereby alleviate suffering.

It is common for Emergency Medicine (EM) physicians to manage patients presenting to the Emergency Department (ED) in pain. Although these patients' etiologies for their pain may differ, most will be experiencing pain from an acute insult. Emergency Medical Services (EMS) is the extension of EM into the prehospital setting. As such, EMS providers interact with many of the same patients experiencing acute pain. Despite the prevalence of pain and the importance of alleviating it, acute pain management has often been inadequate. Improving pain management should continue to be a high priority.

Opioid analgesics have long been the standard of care for acute pain management. The first opiate, morphine, was isolated in the early 1800's. Opioids are potent analgesics

and are titratable to effect. However, they have a significant adverse effect profile. Among other adverse effects, opioids can cause hypotension and respiratory depression. In addition, the United States opioid epidemic has placed increased pressures on EMS and the entire healthcare profession to utilize opioid alternatives while continuing to improve the quality of acute pain management provided to patients. As a result, non-opioid analgesics have gained increased attention and use in EMS. They generally have fewer adverse effects than opioids and are not typically associated with a potential for addiction and abuse. However, the individual and subjective nature of the pain experience increases the difficulty of achieving improved analgesia.

EMS providers must weigh these various factors and the complexity of the pain experience when determining the most appropriate treatment for acute pain. This review seeks to determine if non-opioid analgesics have potential for use as first line treatment by EMS over opioid analgesics, the standard of care for acute pain management. The purpose of this review of the current literature, especially comparison studies, is to investigate the common EMS analgesics: morphine, fentanyl, acetaminophen, ketorolac, ibuprofen, nitrous oxide, methoxyflurane, and ketamine. The findings are discussed in relation to four important outcome measures identified: effect on pain severity, rescue analgesic use, patient satisfaction, and the consideration of risks. Due to the paucity of research on this important topic, a general recommendation cannot be made for the use of non-opioid analgesics as first line treatment for acute pain management by EMS. However, this review provides several specific suggestions regarding the use of non-

opioid analgesics as first line treatment by EMS. Applicability concerns are addressed, and a protocol is presented that EMS could use to adapt the findings to existing protocols.

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## LIST OF ABBREVIATIONS

ACEP .....	American College of Emergency Physicians
AEMT .....	Advanced Emergency Medical Technician
ARS.....	Adjective Response Scale
CT .....	Computed Tomography
EBP .....	Evidence Based Practice
ED .....	Emergency Department
EM .....	Emergency Medicine
EMS .....	Emergency Medical Services
EMT .....	Emergency Medical Technician
FLACC.....	Face Legs Activity Cry Consolability
IM.....	Intramuscular
IN .....	Intranasal
IO .....	Intraosseous
IV .....	Intravenous
MA .....	Medical Air
NRS.....	Numerical Rating Scale
NSAID .....	Nonsteroidal Anti-Inflammatory Drug
PO .....	Per Os
RCT.....	Randomized Controlled Trial
VAS.....	Visual Analogue Scale
VRS.....	Verbal Response Scale

## INTRODUCTION

Pain is a vital topic in medicine. It does not discriminate, affecting people of all ages, cultures, and backgrounds. Regardless of the diagnosis, most all patients will experience some type of pain as a related symptom during their lifetime. In her article, *A Capsule History of Pain Management*, Dr. Meldrum wrote of pain as the first medical complaint (Meldrum, 2003). This statement highlights the long-standing relationship that society has with pain.

Many different medical providers encounter patients reporting pain as a symptom. Within the field of Emergency Medicine (EM), pain remains a common complaint. Accounts of pain prevalence in the Emergency Department (ED) vary from 38% to 61.2% and 78% (Cordell et al., 2002; Smith et al., 2015; Todd et al., 2007). EM often deals with acutely sick and injured patients.

Another group of medical providers care for a similar patient population. Now common throughout the world, Emergency Medical Services (EMS) is the extension of the ED into the prehospital setting. While there is a facet of EMS that performs other transport duties, such as interfacility transports between healthcare facilities, only the prehospital emergency response and transport of sick and injured patients to the ED will be considered as “EMS” for this review. Prehospital critical care units, both ground and air-based exist and may have expanded scopes of practice based on their provider system. They less commonly provide initial prehospital care and will be excluded from this project.

A survey conducted in 2013 found that approximately 17% of ED patients are brought in by EMS (Augustine, 2014). According to a 2009 United States national estimate, there were approximately 28 million EMS transports in that year (Federal Interagency Committee on Emergency Medical Services, 2012). EMS allows for early medical intervention and transport of sick and injured patients in the prehospital setting to the ED. The capabilities of each EMS system can vary widely based on provider scope of practice and department policies.

The three most common provider levels present on an EMS team in the United States are Emergency Medical Technician (EMT), Advanced EMT (AEMT), and Paramedic. The EMT is trained to perform the most basic and least invasive assessments and interventions in prehospital care. This includes select medication administration, via the oral (PO – “per os”) and buccal routes, that varies slightly from state to state (U.S. Department of Transportation National Highway Traffic Safety Administration, 2007). There is also limited use of the intramuscular (IM) route by EMTs in certain situations such as anaphylaxis. Many states are now permitting intranasal (IN) administration of naloxone for overdose by EMTs. According to these national standards, EMTs are limited to non-pharmacologic treatment of pain (U.S. Department of Transportation National Highway Traffic Safety Administration, 2007). However, there are exceptions. Vermont, as an example, has expanded the EMT scope of practice to include PO administration of acetaminophen for pain management (Vermont Department of Health Office of Public Health Preparedness and Emergency Medical Services, 2018). The AEMT expands on the scope of the EMT by including intravenous (IV) and intraosseous

(IO) route of administration in addition to other skills and medications (such as nitrous oxide for pain) not available to an EMT (U.S. Department of Transportation National Highway Traffic Safety Administration, 2007). The Paramedic is the most advanced level and can administer all the pain medications discussed in this thesis if they are available for use.

There are other organizational differences in EMS. As an example, some organizations are privately owned, while others are a municipal third service and are a part of the government provided services. Yet other services are hospital owned and run. Despite the differences in EMS organizations and provider levels, all EMS providers have the same responsibilities to care for and appropriately treat their patients as every other medical provider. This includes the management of their patients' pain.

There are limited amounts of published reports on the prevalence of pain in the prehospital setting. One study in Paris found that 42% of EMS patients reported acute pain (Galinski et al., 2010). Another study in Australia reported 53% of EMS patients in their study reported pain (Lord, Cui, & Kelly, 2009). These numbers are within the range found by the previous studies investigating the prevalence of pain in the ED. The National Association of EMS Physicians and the American College of Emergency Physicians (ACEP) also acknowledged the high occurrence of pain reported by patients who call 9-1-1 for EMS services (American College of Emergency Physicians, 2016; Gunderson, 2011). With such high occurrences of pain in the ED and EMS settings, the importance of pain management increases.

Pain management has often been found to be inadequate (Albrecht et al., 2013; American College of Emergency Physicians, 2016; Baker, 2017; Brennan, Carr, & Cousins, 2016; Campbell, 1996; Galinski et al., 2010). The inadequacy of pain management was such an important issue that in the *American Pain Society 1995 Presidential Address*, Dr. Campbell suggested elevating the importance of pain by considering it the “fifth vital sign” (Campbell, 1996). In concept, this was an excellent way to increase awareness and promote better pain management. While it succeeded in raising awareness and causing policy changes, much critique has been made about regarding pain as a vital sign (Frieden, 2016; Levy, Sturgess, & Mills, 2018; Morone & Weiner, 2013). One study specifically reported that frequent assessment of pain, as would be done for other vital signs, did not result in improved pain management (Mularski et al., 2006, p. 5). Awareness without action does not improve care. However, the shortcomings of the call to consider pain a vital sign should not diminish the importance of pain management in medicine.

Many institutions including the Institute of Medicine and the American Medical Association have pointed to the ethical, moral, and professional duty of healthcare providers to alleviate suffering through the management of patients’ pain (American Medical Association, n.d.; Pizzo & Clark, 2012). In a policy statement, the ACEP also stated that pain management should be provided by EMS systems (American College of Emergency Physicians, 2016). The World Health Organization and the United Nations went one step further and declared adequate pain management a human right (Brennan et

al., 2016). With so many large and prominent organizations making these statements, pain management should be a priority in medicine and within EMS.

Thus far, pain and the importance of pain management have been discussed and placed into the context of EMS. Inadequacies have been highlighted and the need for continued improvements in prehospital pain management are evident. The remainder of the introduction will describe the different aspects of pain management as it pertains to EMS. Topics will include: a brief review of the pain experience, pain assessments, the appropriate identification of treatment goals, and treatment options.

### **Describing the Pain Experience**

Looking beyond the intuitive understanding of pain, it is important to ask: What is pain? Is it the physical stimulation of nerve endings by various inputs, or the learned response to injury, or something else entirely? The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” and also notes that all pain is subjective (International Association for the Study of Pain, 2018). The experience of pain is not just a stimulation of nerves or a learned response to injury. With this definition, it can be understood that pain is a complex and individual experience.

Pain is an ambiguous term. When considering the acute pain experience, it is useful to identify three broad categories: signal input, descending modulation, and perception. There are four main processes involved in the entire pain experience:

transduction, transmission, perception, and descending modulation. In terms of normal pain signal input, an external or internal noxious stimulus begins the nociception pathway. The recognition of a noxious stimulus by a nociceptor is known as transduction. The second process of pain signal input is transmission; the process by which the neural signal is carried from the afferent nociceptor, through the Dorsal Horn, and terminating in various regions of the brain including the Thalamus. This concludes the process of signal input after a noxious stimulus.

The descending modulation process is a more recently discovered part of the pain pathway (Institute of Medicine (US) Committee on Pain, Osterweis, Kleinman, & Mechanic, 1987). As its name implies, it is a pathway that originates in the brain and acts in the Dorsal Horn region of the spinal cord. Descending modulation signals work on the transmission pathway to inhibit the process of signal input. One of the ways this is achieved is by the release of endogenous opioid-like substances (Ropper, Samuels, & Klein, 2014). Descending modulation affects both the signal input and perception of pain.

Unlike signal input and modulation, the perception of pain is a subjective process. The science underlying pain perception is not entirely understood (Ropper et al., 2014). However, research is beginning to unravel subjective aspect of pain perception. Dr. Coghill published an article highlighting various aspects of this subjectivity. Among them, the article mentions that brain imaging has observed patterns that coincide with individual differences in pain perception (Coghill, 2010). In addition, several factors that contribute to the patient's perception of pain were listed. These include: genetics, sociological factors, attention given to the painful stimulus, prior experiences and

expectations, and other personality and behavioral factors such as anxiety (Coghill, 2010). All these factors can lead to differences in sensitivity, pain tolerance, and the patient's overall response to pain.

While the pain pathway is an important aspect of understanding the pain experience, there are also some other ways of classifying pain. Pain can be classified by duration. Acute pain occurs over a relatively short time period and typically occurs as a result of an acute injury (traumatic or medical in nature). In contrast, chronic pain occurs over an extended period. Pain can also be classified according to location. Visceral pain refers to pain that originates from the internal organs. It is not easily localized and may result from inflammation or other etiologies. Pain located in the integumentary or musculoskeletal systems is referred to as somatic pain and is typically well-localized.

The etiology resulting in a patient presenting to EMS or the ED with pain may vary. Despite the differences in etiology, most patients in these two settings are experiencing pain from an acute insult. One study found that 70.7% of patients reported acute pain in the ED (Mura et al., 2017). Chronic pain is also important. However, it is less prevalent than acute pain in EMS and the management of chronic pain requires a different approach. Since acute pain is more prevalent, it will be the focus of this literature review.

The patient's pain experience is certainly complex and influenced by many factors. There are also many aspects of pain that are not fully understood. However, it is important that EMS providers (and all healthcare providers) understand the many factors that influence a patient's pain experience. This will result in pain management that is

tailored to each patient and ideally leads to better outcomes. To achieve improved outcomes, providers must be proficient in recognizing and assessing a patient's pain.

### **Assessment of Pain**

The first step in pain management is to adequately assess the patient's pain. Acute pain may cause changes in the autonomic nervous system resulting in seemingly objective signs such as tachypnea, tachycardia, and hypertension. However, these signs are not a reliable measure of the presence of or intensity of pain that a patient is experiencing (Bossart, Fosnocht, & Swanson, 2007; Ducharme, 2016; Jennings, Cameron, & Bernard, 2009; Marco, Plewa, Buderer, Hymel, & Cooper, 2006). Due to the lack of correlation between these objective measures and pain, other forms of assessment must be utilized.

Each patient will have their own unique experience with pain. As a result of the individual and subjective nature of pain, the patient's own report of their pain should be the central factor influencing pain assessment and should drive the entire pain management process (American College of Emergency Physicians, 2010, 2017; Ducharme, 2016; Gunderson, 2011; Jennings et al., 2009; Maio et al., 2002). One important element of a patient reported assessment is the severity of the pain. Pain scales are a commonly used tool to assess initial pain severity and the change in severity throughout the pain management process. Although many different versions of pain scales exist, a few of the more common and recommended ones for EMS will be discussed.

The Numerical Rating Scale (NRS) is commonly used in the prehospital setting. It has also been recommended as one of the pain scales best suited for EMS (Jennings et al., 2009; Maio et al., 2002). The NRS asks the patient to rate their pain on a scale of zero (no pain) to ten (worst pain). The range can also be expanded to a scale of 0-100 to increase sensitivity (Maio et al., 2002). Although the scale is often performed verbally, it can also be administered on a physical pain scale card. The verbal administration of the NRS is well suited to EMS as it is easy to administer and does not require a physical pain scale card.

There are several other verbal based pain scales. Another one recommended for EMS is the Adjective Response Scale (ARS) (Maio et al., 2002). It consists of several adjectives that indicate varying levels of pain intensity. For example, the patient might be asked to choose between “none”, “slight”, “moderate”, “severe”, and “agonizing” (Maio et al., 2002). The number of categories and the specific adjectives used can be changed. A 4-point Verbal Response Scale (VRS) is similar in nature to the ARS and consists of four words describing the intensity of the pain. Both scales, while easy to administer in the field, can pose a language barrier. They also limit the number of possible responses, which decreases sensitivity.

The various verbal scales mentioned so far require adequate language knowledge and require the patient to have the capacity to understand the prompts and respond appropriately. Young pediatric patients may not be able to appropriately rate their pain when using those scales. There are two other common types of scales that are more appropriate in this age group. The first are various scales that utilize illustrations or

pictures of faces expressing various levels of pain. These faces may be accompanied by numbers or descriptive words. The assessment is explained to the child and the child is asked to select the face that corresponds with the level of pain the child is experiencing.

The second common type of scale, an observational based scale, for pediatrics is particularly useful in patients who are unable to report their own pain utilizing other scales. It is in this case that healthcare providers must rely on other observational means of pain assessment. The FLACC Scale is an example of this type of scale. It utilizes five different categories (Face, Legs, Activity, Cry, Consolability) which are rated as 0, 1, or 2 based on descriptions provided in the scale (Merkel, Voepel-Lewis, Shayevitz, & Malviya, 1997). Observational based scales provide a framework and scoring system to aid in the assessment of pain.

A final pain scale, though not commonly used in EMS, is important to mention due to its prevalent use in research studies. The Visual Analogue Scale (VAS) consists of a vertical or horizontal line that is usually 10-cm in length (Jennings et al., 2009). Either end of the line is marked with an additional perpendicular line and words indicating which side means no pain and which means the worst pain. The patient is asked to mark where on the line they would rate their pain.

Pain scales are important tools; however, they are only one aspect of a comprehensive pain assessment. It is important to note that pain scale scores shouldn't be taken as an absolute value. Because of the subjective nature of pain, a 6 on the NRS, for example, will mean different things for each individual patient. Pain scales are most useful for tracking the progress of pain in the same patient. Other assessments are needed

to gain a full picture of the pain the patient is experiencing and to adequately manage each patient's pain (American College of Emergency Physicians, 2017). Simply asking the patient whether or not more analgesics are required is extremely beneficial (Ducharme, 2016). Other important assessments include location, quality, radiation, provocation, alleviation, and function.

### **Goal of Pain Management**

Determination of a pain management goal is an essential aspect of the pain management process. A goal defines what is needed for a treatment to be considered successful. Treatment without a desired outcome is futile. The ethical principles of respect for autonomy, non-maleficence, and beneficence all play important roles in the goal making process.

For some forms of treatment, a universal goal may be applied for all patients. The initial goal of resuscitative measures in cardiac arrest could fairly be set as achieving return of spontaneous circulation. Studies investigating analgesic efficacy may set goals such as achieving no pain, achieving a reduction below a certain preset point on a pain scale, or a percentage decrease in pain as a universal outcome for all patients in the study (Mehta, 2015). However, with an issue as subjective and individual as pain management, a universal goal may not be appropriate.

The most appropriate pain management goal is one that is specific to each patient (American College of Emergency Physicians, 2017). While this approach does not allow for a rigid definition of an ideal goal, there are some important recommendations that can

act as a reference when defining a patient's pain management goal. The first is to include the patient in the decision making process (Lee, 2016; The Joint Commission, 2017; University of Wisconsin Health Pain Care Services, n.d.). This intuitively makes sense given the subjective nature of pain. A study investigating patients' perspectives on acute pain management found that patients desire open communication and involvement in the decision making process; patients also prefer to discuss how their pain is affecting them functionally as opposed to solely relying on a pain score (Smith et al., 2015). Involving patients in their own care also applies the principle of respect for autonomy.

The next recommendation is that zero pain should not be the goal of pain treatment (Gunderson, 2011; Lee, 2016; University of Wisconsin Health Pain Care Services, n.d.). A goal of zero pain is unrealistic, may not be possible, and would likely involve extensive analgesia to the point that the risks of their use begin to far outweigh the benefit of achieving the goal. The Joint Commission and other organizations emphasize the importance of realistic goal setting in pain management (Lee, 2016; The Joint Commission, 2017; University of Wisconsin Health Pain Care Services, n.d.). Alleviating some of the patient's suffering may be a successful outcome in a major trauma patient. It is important to discuss realistic goal setting with the patient.

Realistic goal setting is not only important in the context of adequate pain management, it also has implications for healthcare reimbursement. Patient satisfaction scores are now used as a metric to determine the amount of reimbursement received (Mehta, 2015). This specific topic is too large in scope to be fully considered here. In short, a patient presenting to EMS or the ED with the unrealistic expectation that their

pain should be eliminated will not only be less likely to consider any level of realistic pain management as adequate, they are also likely to negatively impact reimbursement due to not understanding what should be expected out of pain management. Due to unrealistic expectations, these patients may also formally submit a complaint to the Board of Medicine or the Office of Emergency Medical Services, in the case of EMS. In contrast, a patient who comes to a realistic goal regarding pain management after discussing the topic with the provider may be more likely to be satisfied by the level of care provided and less likely to formally submit complaints. These are other important reasons to discuss realistic goal setting with patients.

Goals may also progress or change over time. For example, in the hours following a trauma that requires admission to the hospital, simply achieving tolerable pain with no movement may be the first goal. As healing progresses, the goal may adjust to tolerable pain during physical therapy. This type of goal setting aligns with the recommendations and patient preference for functional goal setting (American College of Emergency Physicians, 2017; Smith et al., 2015; The Joint Commission, 2017; University of Wisconsin Health Pain Care Services, n.d.). Following this recommendation allows the healthcare provider to better balance the principles of beneficence and nonmaleficence with the goal of alleviating suffering.

One final note about acute pain management goal setting is that the patient's and/or the healthcare provider's desire to avoid certain risks or symptoms associated with a possible analgesic choice is a valid aspect of the goal. As with any treatment decision, the risks must be weighed against the benefits. Utilizing these recommendations will aid

the patient and healthcare provider in making the most appropriate goal for the patient's acute pain management.

### **Non-Pharmacologic and Alternative Pain Treatments**

There are many forms of treatment to alleviate acute pain. Non-pharmacologic treatments are readily available to all levels of EMS providers. Among the options are the use of hot and cold packs (Ducharme, 2016). The heat may be soothing, and the ice may help to reduce inflammation. Immobilization and elevation of injured limbs are other procedures that may alleviate pain or prevent further pain from movement. As previously mentioned, there are many behavioral and emotional factors that contribute to a patient's pain (Coghill, 2010). In the prehospital setting, techniques such as distraction and relaxation may help to combat these factors and play a role in pain management.

In addition to the common non-pharmacological pain management treatments utilized in EMS, there are several alternative treatments that have been used in settings outside of EMS. There have been studies demonstrating the efficacy of intensive cryotherapy, aromatherapy, acupuncture, and transcutaneous electrical nerve stimulation in pain management (Ayan et al., 2012; Ducharme, 2016; Fan et al., 2017; Kline, 2017).

There is one final acute pain treatment option that has potential for use in the prehospital setting. That is, the use of nerve blocks by EMS in specific cases of acute pain. A study in Australia investigated the feasibility and efficacy of a fascia iliaca compartment block administered by EMS in the prehospital setting (McRae, Bendall,

Madigan, & Middleton, 2015). They found that the procedure can be effectively performed by paramedics in their setting.

### **Pharmacologic Pain Treatments: Opioids and Non-Opioids**

The pharmacologic treatments utilized in the prehospital setting can be placed into two broad categories: opioids and non-opioids. Analgesics in each category have their advantages and disadvantages. While there are many different opioid and non-opioid analgesics, only those analgesics that are utilized in the prehospital setting will be discussed (Table 1).

**Table 1. Common Opioid and Non-Opioid Analgesics Used in EMS.**

<b>Opioid Analgesics</b>	<b>Non-Opioid Analgesics</b>
Morphine	Acetaminophen
Fentanyl	Ketorolac
	Ibuprofen
	Nitrous Oxide
	Methoxyflurane
	Ketamine

The term opioid is now commonly used to broadly describe any substance that is structurally similar to the natural alkaloids found to act on the opioid receptors (National Institutes of Health LiverTox, 2018). This encompasses both natural and synthetic substances. The umbrella term opioid includes analgesics such as morphine and fentanyl. The natural plant alkaloids are derived from *Papaver somniferum*, the opium poppy. Opiate is the term to describe these naturally derived substances (National Institutes of

Health LiverTox, 2018). Friedrich Wilhelm Sertürner isolated the first opiate, morphine, in 1804; However, the medical use of opiates significantly increased after the invention of the hypodermic needle in the mid-19<sup>th</sup> century (Meldrum, 2003). These substances were initially unregulated and available over-the-counter and only after concerns were raised regarding abuse was regulation put in place (Meldrum, 2003).

Opioids quickly became established as the standard of care, especially in acute pain management. Morphine is described as the standard from which other analgesics are measured against (National Institutes of Health LiverTox, 2018). Given the current understanding of the pain pathways discussed in the *Describing the Pain Experience* section, the analgesic efficacy of opioids is not surprising. The opioid receptors are located throughout the body including the central nervous system. In terms of the pain pathway, opioids produce their analgesic effects by acting on the transmission and perception of pain (Siu, 2015). While this doesn't decrease the transduction of the noxious stimulus, it is still extremely effective in pain management.

Given that opioids have long been the standard of care for acute pain management and indeed, often the only option available to prehospital providers, it is no surprise that EMS would adopt opioids as a standard treatment. Morphine and fentanyl are the two most common prehospital opioid analgesics. They both have a quick onset of action and can be titrated to effect (Ducharme, 2016). Those are both advantages in terms of treating acute pain. Fentanyl, a synthetic opioid, is 100 times more potent than morphine (Ducharme, 2016). While they are effective in their primary function as an analgesic, there are several adverse effects that are disadvantages of their use. The major adverse

effects for morphine are nausea, emesis, constipation, respiratory depression, sedation, hypotension, and euphoria (Abdel-Aziz & Adams, 2017; Ducharme, 2016). Fentanyl's adverse effects are similar to morphine's with the notable exception that Fentanyl causes less cardiovascular depression (Ducharme, 2016).

Opioid medications do have a specific, fast-acting antidote typically available to healthcare provider. Naloxone is a medication that can be used to reverse the effects of opioids in the event of severe adverse effects. It functions at all the opioid receptors as a competitive antagonist (Burillo-Putze & Miro, 2016). Naloxone can be administered via most routes. However, the ability to administer it via the IN route is very beneficial. This allows for rapid administration that does not require the use of needles. It also is incredibly safe to use and rarely ever causes serious complications (Burillo-Putze & Miro, 2016). The use of naloxone has become commonplace in society and is available to the general public (Adams, 2018). This is partly due to its ease of use, relative safety, and efficacy in reversing opioid overdoses.

Another reason naloxone has become commonplace is related to a different disadvantage associated with the use of opioid analgesics: the potential for addiction and misuse. Morphine and fentanyl are both Schedule II controlled substances, indicating they have a high abuse and dependence potential (United States Drug Enforcement Administration, n.d.). The United States opioid epidemic has continued to gain increased attention. From 1999 to 2017 there was a 600% increase in opioid overdose deaths (U.S. Department of Health and Human Services Centers for Disease Control and Prevention, 2018). The CDC reports that an average of 130 people in the United States die from an

opioid overdose every day (U.S. Department of Health and Human Services Centers for Disease Control and Prevention, 2018). This is a large number of deaths each day. However, most of the research has focused on the link between opioid prescription and subsequent addiction. These studies are typically not in the setting of acute pain management. However, some studies have investigated recurrent use or a possible contribution to abuse after opioid exposure or prescription in the ED setting including in opioid-naïve patients (Butler et al., 2016; Hoppe, Kim, & Heard, 2015). Both studies highlighted their limitations and mentioned the need for more research on this topic.

The exact role that EMS providers may play is less clear. In the EMS setting, opioids are administered as intermittent bolus doses. EMS providers do not write prescriptions and if pain is being treated, it is almost always acute pain. This is a very different scenario compared to prescription opioids leading to addiction, diversion or misuse. As described earlier, opioid analgesics have been the standard for acute pain management in EMS.

In the wake of the opioid epidemic, non-opioid analgesics have gained more attention. The push for these alternatives is a result of the possibility for addiction and relapse after an exposure to opioids. Non-opioid analgesics have fewer adverse effects compared to opioids and are typically not associated with addiction due to differing mechanisms of action. While some EMS systems have utilized various non-opioid analgesics for decades, others have only more recently began allowing EMS providers to administer these treatments (M. Miller & Burstein, 2017; Porter, Dayan, Dickerson, & Middleton, 2018). There are also many EMS systems that still do not provide an

alternative to opioids for analgesia. The non-opioid analgesics used in the prehospital setting that will be discussed are acetaminophen, ketorolac, ibuprofen, nitrous oxide, methoxyflurane, and ketamine.

Both ketorolac and ibuprofen belong to a class of drugs referred to as nonsteroidal anti-inflammatory drugs (NSAIDs). In EMS, ketorolac is administered either IV or IM and ibuprofen is administered PO. They act as cyclooxygenase inhibitors and their actions effect the signal transduction portion of the pain pathway (Siu, 2015).

Therapeutically, NSAIDs are particularly useful in acute pain that can be associated with inflammation (Abdel-Aziz & Adams, 2017). The main disadvantage of NSAIDs is that they have more adverse effects than most of the other non-opioid analgesics. One of major adverse effects is their interference with platelets, which increases the risk of hemorrhage and GI irritation (Ducharme, 2016). This can be of concern when the insult causing pain has resulted in bleeding or if it will require operative management. They can also interfere with renal function, though that is more commonly noted in the elderly and in patients with preexisting renal diseases or injuries (Ducharme, 2016). NSAIDs are contraindicated for use in patients with potential hemorrhaging, renal injury, a suspected need for surgery, and in patients who are pregnant (Massachusetts Department of Public Health Office of Emergency Medical Services, 2017). These adverse effects and contraindications limit the potential use of NSAIDs in the prehospital setting.

Unlike the NSAIDs, acetaminophen can be used in almost any patient. This is an advantage when it comes to the selection of analgesics in the prehospital setting. In addition to its use as an analgesic, acetaminophen is also an antipyretic. Unlike the

previous analgesics, the exact analgesic mechanism of action for acetaminophen is still not fully understood (Abdel-Aziz & Adams, 2017). However, it is known not to affect platelets and not to have anti-inflammatory effects (Ducharme, 2016). It is also believed to act on the signal transduction portion of the pain pathway (Siu, 2015). One disadvantage is hepatotoxicity in overdose or in those with other acute or chronic hepatic insult. Despite this, patients with mild renal or hepatic impairment can still receive acetaminophen (Ducharme, 2016). Only patients with severe hepatic impairment, such as liver failure, are contraindicated (Massachusetts Department of Public Health Office of Emergency Medical Services, 2017). The relative safety and lack of adverse effects of acetaminophen along with its ability to be administered in a wide variety of patients are benefits to the use of acetaminophen in EMS.

The next two non-opioid analgesics are administered via inhalation. Nitrous oxide, which is typically delivered as a mixture of 50% nitrous oxide and 50% oxygen, has a fast onset and offset (Ducharme, 2016). The fast onset makes it especially useful for acute pain in the prehospital setting. Nitrous oxide is reported to indirectly effect the descending modulation portion of the pain pathway (Sanders, Weimann, & Maze, 2008). The two primary adverse effects are nausea and emesis (Ducharme, 2016). Due to the nature of the gas, nitrous oxide use is contraindicated in patients with head injury or altered mental status, or in conditions where there is already air in unwanted body compartments such as in a pneumothorax or perforated bowel (Ducharme, 2016). As with other analgesics, this can be problematic as such conditions may be difficult to detect in the prehospital setting without diagnostic equipment. Two other considerations for its use

in the prehospital setting are the additional bulk of carrying another gas tank on the ambulance and the ability to effectively ventilate the ambulance to avoid provider exposure to the gas.

The second inhaled analgesic is methoxyflurane. Although it is not currently licensed for use in the United States, this particular analgesic has been in use in Australia for several decades (Porter et al., 2018). Methoxyflurane's analgesic mechanism of action is not fully known (National Institutes of Health National Cancer Institute, 2011). Although its use as an anesthetic at higher doses resulted in nephrotoxicity, it has not been shown to have this affect when used at lower doses as an analgesic (Porter et al., 2018). In fact, Porter et al. describes high patient satisfaction with its use and minimal adverse effects such as dizziness and headache. Like nitrous oxide and other analgesics, the onset of action of methoxyflurane is very fast (Porter et al., 2018). One advantage of methoxyflurane is that it is administered via a relatively small inhalation device and does not require a bulky tank of gas like nitrous oxide. This eliminates a potential barrier to its use in the prehospital setting.

The final non-opioid is sub-dissociative dose or low dose ketamine. Traditionally used as an anesthetic, it acts as an analgesic in lower doses (American College of Emergency Physicians, 2017). The main mechanism of action is the antagonism of the N-methyl D-aspartic acid receptor (Kurdi, Theerth, & Deva, 2014). This effects the perception and descending modulation portion of the pain pathway. Ketamine is a relatively recent addition to civilian EMS analgesia protocols. However, it has been recommended in mountain rescue since 1999 and is effectively used in military medicine

(Wedmore & Butler, 2017). Ketamine offers many benefits over the opioid analgesics. It has minimal effect on respiratory drive and acts as a sympathetic nervous system stimulant, which results in increased blood pressure, heart rate, and cardiac output (Kurdi et al., 2014). Low dose ketamine has few contraindications including patients under three months old, patients with a history of schizophrenia, and cautioned in patients who may not tolerate hyperdynamic states (Pourmand, Mazer-Amirshahi, Royall, Alhawas, & Shesser, 2017; Wedmore & Butler, 2017). Previous contraindications for head and ocular injury patients have been disproven, with the exception of hydrocephalus (Wedmore & Butler, 2017). However, ketamine is also associated with adverse effects including emergence reactions, hallucinations, dizziness, nausea, emesis, sedation, hypersalivation, and laryngospasm (Ducharme, 2016; Kurdi et al., 2014; Motov, Mai, et al., 2017; Wedmore & Butler, 2017). The most dangerous adverse effect, laryngospasm, was found to only occur in 0.3% of cases in one study investigating the adverse effects of ketamine used for sedation (Green et al., 2009). Notably, the median dose in this study is approximately four times higher than the doses recommended for low dose ketamine.

Ketamine also has a disadvantage compared to the other non-opioids because it is a Schedule III controlled substance, which means it has abuse potential (United States Drug Enforcement Administration, n.d.). In a policy statement, ACEP recognizes the efficacy and potential benefit of ketamine as an analgesic when compared to opioid analgesics (American College of Emergency Physicians, 2017). However, it is noted that more randomized clinical trials are needed to better define how to most appropriately utilize ketamine in this setting. There are also many administrative and political hurdles

that would need to be overcome in order for ketamine to be used as an analgesic (American College of Emergency Physicians, 2017). Due to these challenges and drawbacks, ketamine will be considered separately from the other non-opioid analgesics. Overall, each of the prehospital analgesics presented have their own set of risks and benefits that must be considered when determining the appropriate treatment for each individual patient (Table 2).

**Table 2. Advantages and Disadvantages of Prehospital Analgesics.** Table highlighting the main advantages and disadvantages for each of the analgesics discussed as it pertains to EMS.

	<b>Advantages</b>	<b>Disadvantages</b>
<b>Morphine</b>	Fast onset Can be titrated to effect Easy reversal with naloxone Long standing standard of care for acute pain	Numerous adverse effects (nausea, emesis, constipation, euphoria, and sedation) Respiratory depression Hypotension Schedule II controlled substance Opioid analgesic
<b>Fentanyl</b>	See morphine 100 times more potent than morphine	See morphine Less cardiovascular depression compared to morphine
<b>Ketorolac</b>	NSAID - Anti-inflammatory property useful for pain associated with inflammation Non-opioid analgesic	Platelet interference - increased risk of hemorrhage and GI irritation More adverse effects and contraindications than other non-opioids
<b>Ibuprofen</b>	See ketorolac	See ketorolac
<b>Acetaminophen</b>	Usable in almost any patient Relative safety and relative lack of contraindications and adverse effects Non-opioid analgesic	Contraindicated in patients with severe hepatic impairment
<b>Nitrous Oxide</b>	Fast onset and offset Adverse effects self-limiting due to patient-controlled administration Non-opioid analgesic	Bulk of equipment Nausea and emesis Contraindicated in certain patients
<b>Methoxyflurane</b>	Same as nitrous oxide Smaller device than nitrous oxide	Not yet available in United States Dizziness and headache
<b>Ketamine</b>	Fast onset Does not cause hypotension Minimal effects on respiratory drive Less potential for abuse than opioids Non-opioid analgesic	Numerous adverse effects (emergence reactions, hallucinations, dizziness, nausea, emesis, sedation, hypersalivation, and laryngospasm) Schedule III controlled substance

## **SPECIFIC AIMS**

This thesis seeks to do the following:

1. Complete a thorough literature review of the efficacy of non-opioid analgesics as compared with common opioid analgesics used in the prehospital setting.
2. Discuss the findings to answer the following question: Can non-opioid analgesics be successfully used as first line treatment for acute pain in the prehospital setting?

This review hopes to provide recommended guidelines for the use of non-opioid analgesics as first line treatment for acute pain by EMS providers including guidelines for pain management education of EMS providers.

## REPORT OF CURRENT LITERATURE

Prehospital emergency care is a relatively new area of healthcare. Within the United States, the birth of EMS can be traced to the first published EMS curriculum in 1969 (Edgerly, 2013). This curriculum was established in response to a report in 1966 that demonstrated a need for out of hospital medical intervention (National Academy of Sciences (US) and National Research Council (US) Committee on Trauma & National Academy of Sciences (US) and National Research Council (US) Committee on Shock, 1966). Since that time, EMS has rapidly grown and evolved. The scope of practice for EMS providers has continued to expand and involve more complex treatments and interventions. In 2010, EMS became an official medical subspecialty for physicians in the United States (M. H. Wilson et al., 2015).

Despite the recognition of the importance of EMS, specific research into prehospital emergency care is slim. Two common EMS specific journals, *Prehospital Emergency Care* and *Prehospital and Disaster Medicine*, weren't established until 1997 and 1985, respectively. A study searching the Cochrane Library conducted in 2005 found that there were only 413 studies performed in the prehospital setting, 63% of which pertained to resuscitation and cardiac care (Smith et al., 2007). A lack of prehospital research does not mean that the research shouldn't be performed or isn't important. In fact, the truth is quite contrary. The importance of research in prehospital care appears to be universally recognized (Bigham & Welsford, 2015; Cone, 2007; Sayre, White, & Brown, 2001; E. Smith et al., 2007; M. H. Wilson et al., 2015).

Like all areas of medicine, research allows for Evidence Based Practice (EBP). The National Highway Traffic Safety Administration reported that the lack of EBP was an area of concern in the EMS system (Sayre et al., 2001). However, evidence is a requirement of increasing the utilization of EBP. One solution is to continue pushing for and pursuing prehospital research. This solution, while important, presents significant obstacles. The prehospital setting lacks the controlled environment that is important for research protocols. There are many different personnel involved in the prehospital setting and the study is not conducted in a centralized location. It is also more difficult to acquire consent in EMS research. This particular challenge was addressed in one study using a two part consent process: initial phone consent with a study physician at the ED and formal written consent upon arrival at the hospital (Ducassé et al., 2013). However, the EMS units were staffed by nurses who have additional education and training beyond typical EMS providers.

Another option is to consider the translation of EM research into the prehospital setting. Depending on the research subject, both options may be valid. The topic of applying EM research to EMS is addressed in an article by Drs. Brigham and Welsford. While their article emphasizes that careful consideration be made before applying EM practices to EMS, they mention that analgesic administration is an appropriate example of this practice (Brigham & Welsford, 2015). With this in mind, and due to the relative lack of prehospital specific studies pertaining to non-opioid analgesic administration, both EMS and EM studies will be considered in this review of the literature.

### **Non-Opioid Analgesic Studies**

The different non-opioid analgesic studies will be presented in groups according to the non-opioid analgesic investigated in the study. The emphasis is on studies that compared a non-opioid analgesic with an opioid analgesic. However, a few additional studies investigating the efficacy of certain non-opioid analgesics will also be highlighted. A summary of certain study characteristics for all the comparison studies can be found in Table 3.

**Table 3. Randomized Trial Characteristics for Studies Comparing Non-Opioid Analgesics to Opioid Analgesics.** *ED – Emergency Department, EMS – Emergency Medical Services, y.o. – years old, m.o. – months old*

Non-Opioid	Opioid	Setting (ED/ EMS)	Blinded	Source of Pain	Ages Included	Trial
Acetaminophen	Fentanyl	ED	Yes	Renal colic	16-65 y.o.	Al et al.
	Morphine	ED	Yes	Renal colic	18-55 y.o.	Bektas et al.
		ED	Yes	Renal colic	18-55 y.o.	Serinken et al.
		ED	Yes	Renal colic	18-65 y.o.	Pathan et al.
		ED	Yes	Isolated diaphyseal long bone fracture	18-60 y.o.	Deloee et al.
		ED	Yes	Isolated limb pain caused by trauma	15-65 y.o.	Craig et al.
		ED	Yes	Mechanical low back pain	18-55 y.o.	Eken et al.
Ketorolac	Morphine	ED	Yes	Isolated limb injury (non-penetrating)	≥16 y.o.	Rainer et al.
Ibuprofen	Morphine	ED	Yes	Musculoskeletal injury	6-17 y.o.	May et al.
		ED	Yes	Uncomplicated extremity fracture	5-17 y.o.	Poonai et al.
Nitrous Oxide	Fentanyl	ED	No	Isolated extremity fracture or dislocation	15-85 y.o.	Kariman et al.
Ketamine	Fentanyl	ED	Yes	Extremity injury	8-17 y.o.	Frey et al.
	Morphine	ED	Yes	Renal colic	≥16 y.o.	Farnia et al.
		ED	Yes	Extremity, low back, flank, abdominal	18-59 y.o.	Miller et al.
		ED	Yes	Musculoskeletal, back, flank, abdominal	18-55 y.o.	Motov et al., 2015
		ED	No	Mild to moderate blunt trauma	18-70 y.o.	Shimonovich et al.
		EMS	No	Trauma	≥30 m.o.	Tran et al.

## **Acetaminophen**

There were more studies comparing acetaminophen to the common prehospital opioid analgesics than any of the other non-opioid analgesics considered in this literature review. Four of those studies investigated pain management in the context of renal colic pain (Al et al., 2018; Bektas et al., 2009; Pathan et al., 2016; Serinken et al., 2012).

Although renal colic is an extremely painful condition that is seen in the prehospital setting, those studies did not examine another common cause of pain for patients in the prehospital setting. That is, acute pain resulting from trauma. Three studies investigated this etiology resulting in pain (Craig, Jeavons, Probert, & Bengner, 2012; Deloee, Zarmehri, Pishbin, Najafi, & Salehi, 2017; Eken, Serinken, Elicabuk, Uyanik, & Erdal, 2014).

*Al et al., 2018:*

A randomized controlled trial (RCT) investigating acute pain from renal colic conducted in Turkey included IV acetaminophen (10 mg) and fentanyl (2 µg/kg) in two of the three drug groups (Al et al., 2018). There were a total of 100 patients per drug group included in the trial. The VAS was used to assess pain and 93.3% of patients reported initial pain between 7 cm and 10 cm with 52% between 9 cm and 10 cm. The patients were monitored for 30 minutes, reassessing pain at the 15- and 30-minute mark. This study demonstrated that at both the 15- and 30-minute assessments, there was no significant difference between the pain relief provided by fentanyl and acetaminophen. However, approximately half of the patients in both groups required additional

medication at the end of the measured study time. The type of rescue medication used was left to provider discretion. It is not mentioned whether the difference in rescue medication use between acetaminophen and fentanyl is statistically significant.

*Serinken et al., 2012:*

This RCT compared acetaminophen (1g in 100 mL normal saline) to morphine (0.1 mg/kg in 100 mL normal saline) in acute renal colic patients (Serinken et al., 2012). After patient exclusions, there were 38 and 35 patients in the acetaminophen and morphine groups, respectively (Serinken et al., 2012). Both the VAS and a 4-point VRS were assessed at baseline, 15, and 30 minutes.

Numerically, the results indicated a 7.1 mm difference in mean reduction in VAS scores at 30 minutes (Serinken et al., 2012). However, this proved not to be statistically significant. As acknowledged by the author, the sample size was not large enough to prove equivalence since the study was initially planned as a superiority trial. 15.8% of the patients receiving acetaminophen and 20% receiving morphine required rescue medication at the end of the trial. The results demonstrated that the acetaminophen group experienced fewer adverse events (5.3%) when compared with the morphine group (15.3%).

*Bektas et al., 2009:*

This randomized, placebo-controlled trial investigating acute renal colic pain included three groups: acetaminophen (1 g in 100 mL normal saline; 46 patients),

morphine (0.1 mg/kg in 100 mL normal saline), and placebo (100 mL normal saline) (Bektas et al., 2009). Pain was assessed at baseline, 15, and 30 minutes using both the VAS and the 4-point VRS. The initial mean pain scores were 71 mm for acetaminophen and 74 mm for morphine.

This study reported that fewer patients in the acetaminophen group experienced adverse effects (24% vs. 33% in the morphine group); however, statistical significance for adverse events was not specifically reported between the two analgesics (Bektas et al., 2009). The mean reduction in VAS were: 43 mm acetaminophen, 40 mm morphine, and 27 mm placebo. The authors mention that the results of the 4-point VRS paralleled these results. While both medications were effective at reducing pain, there was no difference between the analgesics after statistical analysis. Bektas et al. also did not have a large enough sample size to prove equivalency, however they did conclude that acetaminophen is safe and effective in this patient population.

*Pathan et al., 2016:*

The final RCT pertaining to renal colic pain has the largest sample size (Pathan et al., 2016). Pathan et al. designed the double-blind, multigroup trial to overcome deficiencies of past trials including small sample sizes and a lack of an intention-to-treat group. They included 1644 participants in the intention-to-treat group, 1316 of which remained in the protocol group after confirmation of ureteric calculi (Pathan et al., 2016). The medications investigated are acetaminophen, morphine, and diclofenac. The dosages of acetaminophen and morphine are the same as the previous studies: acetaminophen (1 g

in 100 mL normal saline) and morphine (0.1 mg/kg in 100 mL normal saline). Pain was measured initially (median initial score: 8) and at 30, 60, and 90 minutes post medication administration and post-study follow up occurred up to two weeks after the trial. This is the only renal colic study that extended the trial beyond 30 minutes. Unlike the previous studies, this study used a NRS of 0-10 (Pathan et al., 2016). This beneficial as it is a commonly used method for prehospital pain assessment.

Pathan et al. also took a different approach in defining the primary outcome: percentage of patients having a 50% reduction in their pain score at 30 minutes. The results of this study showed statistical significance between acetaminophen and morphine (Pathan et al., 2016). At 30 minutes, 68% of patients in the acetaminophen group achieved the primary outcome compared with 60% in the morphine group (Pathan et al., 2016). As a secondary outcome, 83% of patients in the acetaminophen group had achieved at least a 3-point reduction in NRS scores at 30 minutes compared with 78% in the morphine group. 23% of the acetaminophen group patients required rescue analgesia (25% for morphine). Finally, the acetaminophen group experienced fewer acute adverse events compared to the morphine group (1% vs. 4%). The authors did note that the low adverse event rates for the morphine group may have been due to the patient population of the study.

*Deloee et al., 2017:*

The first of three small studies investigating pain related to trauma compared IV acetaminophen to IV morphine in patients presenting to the ED with isolated diaphyseal

long bone fractures (Deloee et al., 2017). The initial mean VAS score was 90 mm, which was assessed after non-pharmacologic pain management had been provided. After allocation, 26 patients received 0.1 mg/kg morphine and 24 patients received 15 mg/kg of acetaminophen. This was the only acetaminophen study that utilized a weight-based dosage for the acetaminophen group. Both upper extremity and lower extremity fractures were distributed between both groups without a statistically significant difference between groups (Deloee et al., 2017). Using the VAS assessment at 0, 5, and 30 minutes, Deloee et al. only found a statistically significant difference in pain score at the 5-minute mark (mean difference of 14.57 favoring morphine); neither medication was superior to the other at 30 minutes. In addition to the small sample size, this study also didn't report adverse effects or the need for rescue analgesia.

*Craig et al., 2012:*

A RCT conducted in the U.K. also compared IV acetaminophen (27 patients at 1 g) and IV morphine (28 patients at 10 mg), but in the context of isolated acute limb pain caused by trauma (Craig et al., 2012). To be included in the study, patients had to report an initial NRS of at least 7/10. One main difference in this study is that the medications were infused over a longer time period (15 minutes). The VAS was used to assess pain at 0, 5, 15, 30, 45, and 60 minutes. No significant difference between the two medications was shown at any point throughout the trial. However, the morphine group had significantly more adverse reactions (8 patients vs. 2 for acetaminophen). In addition, one of the secondary outcome measures was patient satisfaction. This was an important

measure to include given the subjective nature of the pain experience for patients.

However, the results on patient satisfaction did not reach statistical significance (Craig et al., 2012).

*Eken et al., 2014:*

The final acetaminophen study included dexketoprofen in addition to acetaminophen (1 g in 100 mL of normal saline) and morphine (0.1 mg/kg in 100 mL of normal saline) (Eken et al., 2014). Pain was assessed initially and at 15 and 30 minutes after analgesic administration using both the VAS and 4-point VRS. To be included in the study, patients must report moderate or severe pain on the initial 4-point VRS. There were a total of 46 patients in the acetaminophen group and 45 in the morphine group. Though still a relatively small study, it is the largest study found comparing acetaminophen to a common prehospital opioid for traumatic pain. Specifically, acute mechanical low back pain was investigated in this study (Eken et al., 2014). The results showed consistency between the VAS and 4-point VRS scores. Although the study did not reach significance in terms of rescue analgesic administration and adverse events, it did demonstrate that morphine was not superior to acetaminophen at the end of the trial. However, the reduction of the mean VAS score for morphine was 11 mm greater than the score for the acetaminophen group at 15 minutes (statistical significance not stated). The clinical significance of this difference will be addressed in the discussion section.

## **Ketorolac**

There were numerous RCTs investigating the use of ketorolac for analgesia in other settings and comparing ketorolac with certain opioid and non-opioid analgesics. However, there were a lack of RCTs that compared ketorolac to one of the common prehospital opioid analgesics in the EMS or ED settings (excluding studies investigating surgical procedures). There were no prehospital RCTs and only one ED based RCT (Motov, Yasavolian, et al., 2017; Rainer et al., 2000). In addition to that study, one other RCT will be presented as it demonstrates the efficacy of ketorolac in the ED (Motov, Yasavolian, et al., 2017).

*Motov, Yasavolian, et al., 2017:*

This study investigated the efficacy of IV ketorolac at three difference doses (Motov, Yasavolian, et al., 2017). The patients were included if their chief complaint at the ED was acute pain with a score of 5 or greater on the NRS. 80 patients were included in each of the three dosage groups (10 mg, 15 mg, and 30 mg). Pain scores were recorded at 15, 30, 60, 90, and 120 minutes in addition to baseline pain scores prior to analgesic administration. The primary outcome was a reduction in pain scores at 30 minutes. The patients in the 10 mg group went from a mean NRS score of 7.7 to 5.2 at 30 minutes, which was statistically significant. Of note, there was not a significant difference in the analgesic efficacy between the three doses studied.

*Rainer et al., 2000:*

A double blind RCT in Hong Kong compared IV ketorolac with IV morphine in patients presenting to the ED with isolated limb injury (Rainer et al., 2000). The primary goal was a cost analysis of the two analgesics. The secondary outcomes were pain relief (both at rest and with movement), adverse events, time spent in the ED, and patient satisfaction. Pain scores were assessed using a VAS at baseline and then at various timepoints up until one and a half hours followed by one final assessment at six hours. The median initial pain was approximately 4/10 at rest and 8/10 with movement. Pain relief was reported as a likelihood of reaching 50%, 75%, and 100% pain reduction (100% was not recorded for the with movement assessment) and as a rate of pain decrease per hour.

A total of 149 patients were divided between the two study groups: 75 for ketorolac and 74 for morphine (Rainer et al., 2000). Ketorolac was given with an initial 10 mg dose followed by additional 5 mg doses every 5 minutes with a maximum of 30 mg. Morphine was given as 5 mg initially followed by 2.5 mg every 5 minutes up to 15 mg total. Medication administration would cease if there was complete resolution of pain at rest.

The clinical results of the study showed that the morphine group was 16 times more likely to experience adverse effects compared with ketorolac (Rainer et al., 2000). In fact, three patients were admitted to the hospital from the morphine group due to adverse events (none from the ketorolac group). In both measures of pain relief at rest, morphine was not superior to ketorolac. With activity, the likelihood of a 50% reduction

in pain was not statistically significant between the two groups. However, ketorolac was shown to be more likely to achieve a 75% reduction in pain with movement compared to morphine. In addition, the per hour rate of decrease in pain score was greater with ketorolac. Patients in the ketorolac group were also more satisfied with their pain management.

This study is also useful as it provides a cost analysis between morphine and the more expensive ketorolac (three times more expensive at the time of the study) (Rainer et al., 2000). When admissions costs were taken into consideration there was no significant difference in total costs between ketorolac and morphine. Ketorolac becomes the cheaper medication to administer when the analysis is done for the cost to only the ED and pharmacy. Morphine, due to adverse events, also increases the time that nursing and physician staff takes managing each patient given that medication. Finally, patients in the ketorolac group were discharged from the ED significantly sooner than patients in the morphine group. The study by Rainer et al. was the only study found that performed a cost analysis of a non-opioid vs. opioid analgesic.

## **Ibuprofen**

Similar to ketorolac, ibuprofen is also an NSAID. No RCTs were found that compared ibuprofen with a parenteral administration of morphine or fentanyl in an appropriate context for EMS. There were two studies that compared a PO administration of ibuprofen with PO morphine (May et al., 2017; Poonai et al., 2014). These two studies exclusively investigated the pediatric population. Although they will be presented, the

significant limitations in applying the findings to EMS will be discussed in the *Limitations in Reported Literature* section.

*Poonai et al., 2014:*

The first study compared the analgesic efficacy of normal release PO morphine (0.5 mg/kg, max of 10 mg) to PO ibuprofen (10 mg/kg, max of 600 mg) in patients being discharged from the ED after a confirmed extremity fracture (Poonai et al., 2014). The study was conducted by patients and their guardians after discharge from the ED using instructions and survey forms. A revised faces scale, which gave each face a value from 0 – 5, was used to assess pain severity before and 30 minutes after each dose was given. A maximum of four doses of the study medication were available, with instructions to take every six hours as needed and to use acetaminophen as a rescue analgesic if needed.

The primary outcome of the study was the difference in pain score measured after the first dose was given (Poonai et al., 2014). There were 66 participants in the morphine group and 68 in the ibuprofen group all 5-17 years old. The median pain score recorded at discharge was 2; however, only the differences in pain scores were reported for the self-administered doses after discharge. While both medications resulted in a clinically significant decrease in pain, there were no significant differences reported between groups. The study also reported no significant difference in rescue analgesia use and significantly more adverse effects in the morphine groups. It is mentioned that the study

was not adequately powered to detect between group differences in these secondary outcome measures.

*May et al., 2017:*

The second study compared the analgesic efficacy of PO morphine (0.2 mg/kg, max of 15 mg), PO ibuprofen (10 mg/kg, max of 600 mg), and a PO combination of both morphine and ibuprofen combined at the same dose as the individual groups in patients presenting to the ED with a musculoskeletal injury to one limb (May et al., 2017). The entire study was conducted in the ED and utilized the 100 mm VAS scale for pain assessment at baseline and 30, 60, 90, and 120 minutes after analgesic administration. Participants were 6-17 years old. There were 201 patients each in the two groups containing morphine and 99 patients in the ibuprofen group.

The participants had an approximate initial mean VAS of 61 mm in all groups (May et al., 2017). The primary outcome for each group was the number of participants achieving a VAS less than 30 mm at the 60-minute assessment. At 60 minutes, there was no significant difference between groups in the percentage of patients achieving the primary outcome (33% for ibuprofen, 29% for morphine, and 30% for the combination group). May et al. also reported no significant difference between groups after separating each group into two groups based on initial pain severity (a 30 mm – 69 mm group and a group with at least 70 mm).

This RCT also reported the mean VAS decrease, rescue analgesic use, and adverse effects (May et al., 2017). The 120-minute assessment was the only timepoint

that reported a significant difference in the mean VAS decrease between the morphine group (-16.5 mm) and ibuprofen group (-27.1 mm), not the combination group. That is a 10.6 mm difference between those groups. Both the combination group and the morphine group had significantly more adverse effects compared to the ibuprofen group (21.5%, 20.7%, and 6.6%, respectively) (May et al., 2017). Only five patients in total required rescue analgesia, and the significance of the difference between groups was not reported.

### **Nitrous Oxide**

Nitrous oxide is the first of two inhalation analgesics that will be discussed. It is typically administered as a mixture with oxygen. All of the studies being considered utilized a mixture of 50% nitrous oxide and 50% oxygen (Ducassé et al., 2013; Kariman et al., 2011; Triner, Bartfield, Birdwell, & Raccio-Robak, 1999). For simplicity, the mixture will be referred to as “nitrous oxide” going forward. Only one of the three studies compared nitrous oxide with an opioid analgesic (Kariman et al., 2011). However, the other two efficacy studies, comparing to placebo, demonstrate notable results (Ducassé et al., 2013; Triner et al., 1999).

#### *Triner et al., 1999:*

A small double-blind, randomized, pilot study compared nitrous oxide to 100% oxygen in patients diagnosed with a migraine history presenting to the ED with an acute migraine (Triner et al., 1999). Although this study did not compare nitrous oxide with a common prehospital analgesic, it is useful to consider given the results on the efficacy of

nitrous oxide on acute pain in the ED. The 100 mm VAS was used to assess pain prior to treatment and after treatment was discontinued (Triner et al., 1999). Patients had access to the treatment, which was supplied via a demand valve device, for 20 minutes, however they were not required to use the gas continuously. Patients were monitored for an additional 20 minutes to record the use of additional analgesics agents after discontinuing the study treatment.

There were 10 patients in the nitrous oxide group and 12 in the oxygen group with no significant difference in initial median VAS scores (69 mm for nitrous oxide group and 78.5 mm for oxygen group) or other baseline characteristics (Triner et al., 1999). The oxygen group did not have a significant reduction in pain scores at the end of treatment. The median score decreased to 21 mm in the patients receiving nitrous oxide. Only 20% of patients receiving nitrous oxide required rescue analgesics at the end of treatment (84% for oxygen group). 20 minutes after nitrous oxide was discontinued, 60% of patients in that group still did not require rescue analgesics and were discharged having only been treated with nitrous oxide. The study was not large enough to report on adverse events and did not follow up with patients after the 40-minute period.

*Kariman et al., 2011:*

The next study investigated if nitrous oxide was superior to a single dose of fentanyl in patients presenting to the ED with an isolated extremity fracture or dislocation confirmed by X-ray (Kariman et al., 2011). Patients were required to have a VAS score of at least 4 out of 10 to be included in the trial. Unlike the previous study, this study was

not blinded. The authors cite the difficulty of blinding considering the equipment required to administer nitrous oxide. Pain was recorded prior to treatment and at 3, 6, 9, and 60 minutes after treatment began, although additional analgesics were allowed prior to 60 minutes.

There were 50 patients in each group (Kariman et al., 2011). Patients in the nitrous oxide group self-administered the treatment for a maximum of 15 minutes or until their pain was controlled. Patients in the fentanyl group received 6 L/min of oxygen and fentanyl at 2 µg/kg with no maximum dose limit. There was no significance between the two groups at 3, 6, and 60 minutes. However, the nitrous oxide group had a statistically significant difference in the VAS assessment at 9 minutes (2.2 vs. 3.1 for fentanyl). The authors caution that the clinical significance of that is unclear.

*Ducassé et al., 2013:*

While the final study only assessed the efficacy of nitrous oxide compared to medical air (MA) rather than to an opioid analgesic, it did so in the prehospital setting in France (Ducassé et al., 2013). Nitrous oxide is also currently in the state protocols of at least three states in the United States: Alabama, New Hampshire, and Vermont (Alabama Department of Public Health Office of Emergency Medical Services, 2018; New Hampshire Department of Safety Division of Fire Standards and Training and Emergency Medical Services, 2018; Vermont Department of Health Office of Public Health Preparedness and Emergency Medical Services, 2018). The EMS system where the study took place includes ambulances staffed by nurses (Ducassé et al., 2013). These nurses, in

conjunction with a physician at the ED, enrolled and treated qualifying patients according to the study protocol. This study included any patient with acute traumatic pain with a NRS score between 4 and 6 out of 10. Each treatment group included 30 patients.

Patients were treated in their randomly assigned group for 15 minutes (Ducassé et al., 2013). After 15 minutes, all patients were treated with nitrous oxide until arrival at the hospital. Assessments were conducted initially and on five-minute intervals for 30 minutes. If they had not reached the hospital at 30 minutes, assessments continued every 15 minutes until arrival. Once at the hospital, patients and nurses were asked to report their satisfaction with analgesia. Keep in mind, both groups would have received nitrous oxide treatment at that point.

Analgesic efficacy results were reported as a percentage of patients with an NRS score of 3 or below after 15 minutes of treatment (Ducassé et al., 2013). They also reported median pain scores. After 15 minutes of treatment, 67% of the nitrous oxide group achieved the efficacy goal compared to 27% of the MA group. The nitrous oxide group also reported a lower median NRS score at 15 minutes (2 vs. 5 for MA), which was statistically significant starting on the first assessment at 5 minutes. Ducassé et al. reported no significant difference in the baseline characteristics between the two study groups. In addition, at 20 minutes (5 minutes after all patients received nitrous oxide treatment) there was no longer a significant difference between the two groups.

While most studies reported pain relief, this was one of the few studies to record patient and provider satisfaction with treatment. Upon arrival at the ED, with all patients having received nitrous oxide treatment, all but one of the 60 patients involved in the

study reported being either satisfied or very satisfied with the analgesic treatment (Ducassé et al., 2013). Similarly, all but two of the prehospital nurses involved in the study were equally as satisfied as the patients.

### **Methoxyflurane**

The second inhalation analgesic is methoxyflurane. It has been used as an analgesic to treat acute pain for over 40 years in Australia and is approved for use in many other countries (Porter et al., 2018). Despite the length of time it has been in use, there are few completed RCTs demonstrating its efficacy. The STOP! study is a double-blind RCT that was conducted in the UK and compared methoxyflurane to placebo in patients presenting to the ED with acute pain from minor trauma (Frank Coffey et al., 2014). To be included, the initial NRS score was required to be between 4 and 7. A total of 149 patients were included for analysis in each group (approximately 40% between the ages of 12 and 18). The primary outcome was the change in VAS score at 5, 10, 15, and 20 minutes after treatment began.

Patients in the methoxyflurane group received one inhaler device (3 mL) to self-administer the medication at the start of treatment (Frank Coffey et al., 2014). The placebo group received the same inhaler device filled with 5 mL of a saline placebo. Both groups were given the option of receiving a second inhaler or rescue medication at any time throughout the study if the patient requested it.

The study demonstrated that the change in VAS score was significantly greater for the methoxyflurane group compared to placebo at all time points (Frank Coffey et al.,

2014). The greatest change was seen at 15 minutes with a decrease of 18.5 mm from initial pain score. It took four minutes (median value) for patients receiving methoxyflurane to report initial pain relief. In total, 87.2% of patients in the methoxyflurane group had pain relief and only 1.3% requested rescue analgesia.

Two follow up sub-group analysis abstracts reported on the efficacy of methoxyflurane for patients reporting a NRS of 7 (severe pain) initially (Coffey, Mirza, & Lomax, 2018a, 2018b). These results demonstrated that in the severe pain sub-group, methoxyflurane still had a significantly shorter time to initial pain relief (Coffey et al., 2018b). Finally, the percentage of patients experiencing at least a 30% decrease in pain was significantly higher in the methoxyflurane group compared to placebo up to 90 minutes after treatment began (Coffey et al., 2018a). Although methoxyflurane is available in other countries across the world, the United States does not currently have access to this medication. A report by a company that sells the methoxyflurane delivery device indicates that United States approval is currently in progress (Wilson, 2019).

## **Ketamine**

Ketamine is more well known as an anesthetic agent at higher doses. Its use as an analgesic at lower, sub-dissociative, doses is also understood and becoming more common. As an example, as of January 1<sup>st</sup>, 2018, New Hampshire has added low dose ketamine for analgesia to their statewide EMS protocols (New Hampshire Department of Safety Division of Fire Standards and Training and Emergency Medical Services, 2018). Six RCTs compared ketamine to morphine or fentanyl in the setting of acute pain (Farnia

et al., 2017; Frey et al., 2019; Miller, Schauer, Ganem, & Bebarta, 2015; Motov et al., 2015; Shimonovich et al., 2016; Tran et al., 2014). These studies varied in the etiology resulting in pain and the routes of administration for the analgesics. Only one study exclusively investigated the pediatric population (Frey et al., 2019).

*Farnia et al., 2017:*

The first RCT investigated IN ketamine (1 mg/kg; 20 patients) and IV morphine (0.1 mg/kg; 20 patients) in patients at least 16 years old presenting to the ED with renal colic pain (Farnia et al., 2017). In addition, the study utilized a placebo morphine and ketamine so that each patient received both an IN and an IV administration. Fentanyl was offered as a rescue analgesic after 30 minutes. The VAS was used to assess pain prior to and 5, 10, 15, and 30 minutes after medication administration. Although the VAS is reported in other studies in millimeters, this study reported the VAS score on a scale of 0.00-10.00. This likely translates to a centimeter representation of the scale, however this was not stated in the study.

The mean initial pain score was statistically significant between the ketamine and morphine groups (8.35 and 7.4, respectively) (Farnia et al., 2017). This study took this difference in baseline score into account during analysis. There was no significant difference reported between the study groups at 15 and 30 minutes. However, the difference between mean scores at 5 minutes favored morphine, but only marginally (0.79 mean difference). The clinical significance of this will be addressed in the discussion. The study showed no significant difference in rescue analgesia use (Farnia et

al., 2017). Eight patients in the morphine group experienced hypotension and six patients in the ketamine group experienced an emergence reaction.

*Tran et al., 2014:*

This RCT did not utilize a blinded protocol and was carried out in a rural, low-resource, prehospital setting (Tran et al., 2014). The study included any patient over 2.5 years old that was in need of analgesia after a trauma (Tran et al., 2014). There were 308 participants included in the analysis. The study participants had many notable characteristics: 24 patients under 15 years old, 28 patients with multiple injuries considered major, 91% of patients suffered a blunt trauma, 61% of injuries were from a road accident, and 24% were from falls. The study excluded patients with transport times less than 10 minutes and had a mean prehospital treatment time of 2.2 hours.

The study was conducted by physicians who responded into the field and transported the patient either by ambulance or taxi (Tran et al., 2014). The two medication groups were IV ketamine (169 patients at 0.2-0.3 mg/kg) and IM morphine (139 patients at 10 mg for adults and 5 mg for children). The initial pain severity was not reported. The VAS was used to assess pain. Unlike other studies, the physician rated the patient's pain instead of the patient. The study concluded that both analgesics were equally effective in reducing pain severity and that transport time and the severity of the initial injury did not affect the efficacy. Nausea and vomiting were significantly more often reported in the morphine group (19% of patients) than the ketamine group (5% of

patients). The proportion of patients experiencing agitation was reported as statistically significant between the two groups (11% for ketamine and 1.5% for morphine).

*Shimonovich et al., 2016:*

The second unblinded study compared IN ketamine (24 patients at 1 mg/kg) to IM morphine (27 patients at 0.15 mg/kg) and IV morphine (24 patients at 0.1 mg/kg) in adult patients presenting to the ED with acute pain after a mild to moderate blunt trauma (Shimonovich et al., 2016). The VAS was used to assess initial pain and every five minutes for the first hour after medication administration. To be included in the study, participants had to have an initial pain score of at least 80 mm. The initial mean pain score was approximately 91 mm for all groups.

The study included several outcome measures: time to achieve a 15 mm VAS decrease, time to reach and extent of maximum pain reduction, adverse effects, and patient satisfaction (Shimonovich et al., 2016). There was no significant difference found in the time to reach or extent of maximum pain reduction of the IM or IV morphine groups compared to the IN ketamine group. The difference in time to onset and rate of reduction in pain scores of IN ketamine and IV morphine were also found not to be statistically significant. IN ketamine did have a significantly shorter time to onset: 14.3 minutes versus 26 minutes for IM morphine. IM morphine was also shown to have a slower rate of pain score reduction than either of the other medication groups. The satisfaction rating, as measured by patients marking a position on a VAS line, was not found to be statistically significant between the groups.

The adverse effects were categorized as difficulty concentrating, dizziness, confusion, and dry mouth (Shimonovich et al., 2016). These categories were reported as the percentage of patients experiencing each adverse effect. Ketamine was statistically significant compared to the two morphine groups in both the difficulty concentrating (58.3% for ketamine, 20.8% for IV morphine, and 22.2% for IM morphine) and the dry mouth (25% ketamine, 79.2% IV morphine, and 63% IM morphine) categories. More patients in the IN ketamine group experienced dizziness compared to the IM morphine group (79.2% and 22.2%, respectively) with no statistical difference between IN ketamine and IV morphine. The IN ketamine group experienced more confusion than the IV morphine group (50% and 12.5%, respectively).

*Frey et al., 2019:*

This study also investigated IN ketamine, but compared it to IN fentanyl (Frey et al., 2019). This RCT investigated patients with an extremity injury, was double-blinded, and utilized a non-inferiority trial. Only pediatric patients with a VAS pain score greater than 35 mm were included in the study (8-17 years old). Opioid analgesic use prior to arrival at the ED excluded patients; however, non-opioid use prior to arrival was allowed. The IN ketamine group (1.5 mg/kg, max of 100 mg) analyzed 43 patients and the IN fentanyl group (2 µg/kg, max of 100 µg) analyzed 42 patients.

The VAS was used to assess pain at baseline and 15, 30, and 60 minutes after analgesic administration (Frey et al., 2019). The mean of the two initial pain scores for both groups was 73.4 mm. The primary outcome measure, the difference in mean

decrease in pain score from baseline, was assessed at 30 minutes. The study demonstrated that IN ketamine is non-inferior to IN fentanyl. There were also no significant differences in the lowest pain score, vital signs, or sedation scores between groups. Adverse effects were reported as minor and transient with the only significant difference between groups noted at the 15-minute assessment. Overall, 77% of ketamine patients and 31% of fentanyl patients reported adverse effects. Finally, there was no significant difference in the use of rescue analgesia, with 23% of all patients requiring a rescue analgesic.

*Miller et al., 2015:*

IV ketamine (0.3 mg/kg) was compared to IV morphine (0.1 mg/kg) in this double-blind RCT conducted in the ED with adult patients (J. P. Miller, Schauer, Ganem, & Bebart, 2015). The medications were administered over 5 minutes. The study investigated patients presenting to the ED with acute abdominal, flank, low back, or extremity pain from any etiology. Patients were included in the study if the physician felt that opioid analgesics were warranted and if opioids or tramadol had not been used in the past four hours. The NRS was utilized for pain assessment. There were 24 patients analyzed in the IV ketamine group (maximum dose of 25 mg allowed) and 21 patients analyzed in the IV morphine group (maximum dose of 8 mg allowed). Patients were allowed a second dose at their request as early as 20 minutes; however, requesting a third dose resulted in the termination of data collection for that patient. Repeat dosing in this study was used instead of a separate rescue analgesic. In addition, midazolam and

naloxone were available to providers for adverse effects if needed. However, no patient received those medications throughout the course of the study.

The initial mean pain severity in both treatment groups was 7.1 out of 10 on the NRS (Miller et al., 2015). Pain was also assessed at 5, 10, and 20 minutes, and then every 20 minutes for 2 hours with time starting after the infusion had finished. The maximum change in NRS score was achieved significantly earlier for ketamine (4.9-point reduction from baseline at 5 minutes) compared to morphine (5-point reduction from baseline at 100 minutes). It was noted that despite its fast onset, ketamine did not sustain its analgesic effect as well as morphine. The mean pain score reduction achieved at least a 50% reduction from baseline at all timepoints after 20 minutes. No significant difference was observed in the proportion of patients requiring additional doses between the groups. It is important to note that patients in both the ketamine and morphine group required a third dose (25% and 14%, respectively).

The number of adverse events reported was also not statistically significant between groups (Miller et al., 2015). Hallucinations and dysphoria were only noted in the ketamine group and headache and drowsiness were only noted in the morphine group. There was no difference reported in the sedation and agitation scale used by the study. This study also assessed physician and nurse satisfaction. While the nurse satisfaction was slightly higher in the ketamine group, it was reported as not clinically significant. No other differences in satisfaction were observed.

*Motov et al., 2015:*

The final ketamine study investigated patients complaining of acute abdominal, flank, back, and musculoskeletal pain with an initial pain score of at least 5 out of 10 on the NRS (Motov et al., 2015). Patients were excluded if opioids were used in the past four hours. The two groups were IV ketamine (0.3 mg/kg; 45 patients) and IV morphine (0.1 mg/kg; 45 patients). The medication was administered over 3-5 minutes. Rescue fentanyl was available for patients if needed at 30 and 60 minutes. Pain was assessed using the NRS every half an hour for two hours and at 15 minutes.

The initial mean pain score for both groups was approximately 8.5 on the NRS (Motov et al., 2015). There was no difference noted in the mean reduction of pain scores between groups at the 15- and 30-minute assessments. Interestingly, at 15 minutes, more patients in the ketamine group reported complete resolution in pain compared to the morphine group (31% difference between groups). This difference was no longer present by 30 minutes. None of the complete resolution of pain patients used rescue analgesia. There was no significant difference noted in the proportion of patients achieving at least a 3-point reduction in pain score. There was a 38% difference in the proportion of patients experiencing adverse effects, more in ketamine group, immediately and at 15 minutes after medication administration. The difference was no longer noted at the 30-minute assessment. Although ketamine is a non-opioid analgesic, it is still considered a controlled substance with abuse potential. As such, these results will be discussed separately from the other non-opioid analgesics.

## **Non-Opioid Analgesics as First Line Treatment**

After evaluating the efficacy of non-opioid analgesics on pain relief and patient satisfaction, it is important to consider the application aspect of non-opioid analgesics as first line treatment. The Maimonides Medical Center in Brooklyn, New York, underwent a study that ran for eight hours to investigate the application of a non-opioid first protocol (Cohen et al., 2015). They took an approach termed channel enzyme receptor-targeted analgesia to develop their non-opioid first protocol. This protocol outlined what non-opioid medications should be used based on pain severity (NRS from 0-10) and underlying cause. Notably, the protocol utilized more types of analgesics than are used in EMS.

Every patient seen in the ED over the course of one eight hour shift, with a chief complaint of pain, was treated using the study protocol (Cohen et al., 2015). Pain was recorded prior to analgesic administration and at 30 and 60 minutes after administration. A rescue dose of opioid analgesics was available only after 30 minutes. In addition to pain assessment, adverse events, and whether patients were satisfied were also recorded.

Of the 17 patients treated during the study, 12 of them had acute pain (Cohen et al., 2015). The median NRS pain score for all patients prior to analgesic administration was 8. 41% of patients reported at least a 30% reduction in pain by 30 minutes. Only one patient received rescue analgesia. In the acute pain group, 83% of patients were satisfied with their pain relief at 30 minutes. IV ketorolac, IV acetaminophen, and oral ibuprofen were the three most common analgesics used during the study.

More recently, a level 1 trauma, burn, and stroke center in Colorado investigated the application of a non-opioid first protocol over a three month period (Duncan, Smith, Maguire, & Stader, 2019). The protocol gave first-line treatment, second-line treatment, and alternative options based on the cause of the pain. The protocol also utilized more analgesics than are available to EMS. This study looked at the percentage of patients receiving opioid and non-opioid analgesics before and after implementing the protocol (Duncan et al., 2019). In addition, patient satisfaction was recorded using the Press Ganey survey.

Almost 30,000 patients were analyzed in both the pre- and post-implementation periods (Duncan et al., 2019). After the protocol was implemented there was a 20% reduction in IV opioid administration. IV acetaminophen had a 29.5% increase in use and IV ketorolac had a 73.7% increase. The study found that there was no significant difference in patient satisfaction before or after the implementation of the study protocol.

## EVALUATION OF CURRENT LITERATURE

### Limitations in Reported Literature

The strength of evidence is an important consideration when discussing an alternative treatment to the standard of opioid analgesics. With two exceptions, only RCTs were used as the main source of evidence as they represent a rigorous study design and provide the strongest initial evidence (Guyatt et al., 2011). The two exceptions were two studies that reported on non-opioid first protocols in practice in the ED and will be discussed separately. However, there are several reasons why the level of evidence from an RCT may be weaker than initially assumed or why strong evidence may not lead to a strong conclusion. One concern is the ability to generalize the study results to the EMS population in question. One aspect of generalization is having a representative research population. The similarities in patient population between EM and EMS have been previously discussed. Although careful consideration should be made, research in analgesic administration in EM can be successfully applied to EMS (Bigham & Welsford, 2015). This section will address the significant limitations in the reported RCTs.

#### *Non-Opioid Studies, Excluding Ketamine:*

There are six publications that did not include an opioid analgesic as a comparison group (Coffey et al., 2018a, 2018b; Coffey et al., 2014; Ducassé et al., 2013; Motov, Yasavolian, et al., 2017; Triner et al., 1999). The three publications by Coffey et al. were the only studies reported that investigated methoxyflurane (Coffey et al., 2018a,

2018b; Coffey et al., 2014). Since they cannot be utilized in isolation to compare non-opioid analgesics to opioid analgesics and because they are the only studies investigating methoxyflurane, those three studies will not be considered as evidence in the non-opioid group. The other three studies investigated the same non-opioid analgesic utilized in other comparison studies (Ducassé et al., 2013; Motov, Yasavolian, et al., 2017; Triner et al., 1999). However, one study exclusively investigated migraine headache (Triner et al., 1999). This study is excluded from the review as the etiology resulting in pain is not represented in the comparison studies. The other two studies can be used as additional supporting evidence in conjunction with the other comparative studies.

The only two studies investigating ibuprofen utilized PO morphine as the comparison group (May et al., 2017; Poonai et al., 2014). PO morphine is not commonly utilized by EMS. In addition, the PO route is subject to the first pass effect, which causes only a portion of the administered medication to reach systemic circulation. Without an additional study comparing to IV or IM morphine, which are commonly used in EMS, the ability to generalize these results to EMS is significantly limited. As such, Ibuprofen will not be considered in the conclusions.

In the remaining comparison RCTs, there is one significant dose discrepancy that should be noted. One study investigating acute pain from renal colic administered a 10 mg dose to the acetaminophen group (Al et al., 2018). This dose is significantly lower than the 600 mg – 1000 mg typically administered by EMS. Results in this study favoring fentanyl may have been skewed by the low dose in the acetaminophen group. In isolation, the results of this study present weaker evidence when generalizing to EMS due to this

disparity between the doses. This study will be included as evidence since there are three other studies with an acetaminophen group investigating renal colic that administered a dose typical of EMS.

The age of the patients included in the remaining nine comparison RCTs is another limiting factor to generalizability. Only two studies had a minimum age of 15 years old, but they also included adult patients in the study (Craig et al., 2012; Kariman et al., 2011). These studies only provide limited evidence for patients who are 15 years old. Due to these age limitations, the conclusions in this review should only be utilized for patients who are at least 16 years old.

There are also several limitations to the different etiologies resulting in pain that are included in the remaining comparison studies. Multisystem trauma patients and patients in extremis are not well represented in the reported literature. In addition, several RCTs specified that the study was investigating isolated limb trauma. The only non-traumatic etiology resulting in pain was renal colic. The narrow scope of patients included in these trials prevents a general statement regarding the use of non-opioid analgesics as first line treatment by EMS. More specific conclusions will be made in the remaining sections of the review.

#### *Ketamine Studies:*

Three of the ketamine studies contained significant limitations (Farnia et al., 2017; Frey et al., 2019; Tran et al., 2014). However, none of the limitations resulted in the study being completely excluded from use as evidence. There was only one study that

investigated ketamine and an opioid, morphine, in patients presenting to the ED with acute pain specifically from renal colic (Farnia et al., 2017). Due to the small sample size of this study, 20 patients per group, this study does not present enough evidence to support a specific recommendation for ketamine regarding pain from renal colic. This study will be used in combination with the other ketamine studies to make a more general recommendation.

The EMS study has a severe limitation that prevents it from being used as evidence in the effect on pain severity outcome measure. In this study, the physicians reported their observed pain severity instead of having the patients report their level of pain (Tran et al., 2014). The importance of patient reported assessments in pain management is why this study will not be utilized to compare the analgesic efficacy of ketamine to the opioid analgesics.

The final study with a significant limitation is the only ketamine study to exclusively investigate the pediatric population. The study investigated extremity injuries in patients 8-17 years old and utilized a non-inferiority design (Frey et al., 2019). This study presents significant evidence, despite being the single study investigating pediatric patients, because of the strength of the non-inferiority design. The limitation of this study comes from the narrow etiologies included. Only a specific recommendation for pediatric patients experiencing pain from an extremity injury can be made from this study.

Similar to the other non-opioid studies, multisystem trauma patients and patients in extremis are not well represented in the ketamine studies. Except for the separate recommendations resulting from the pediatric study, the recommendations from the

remaining five ketamine studies should only be utilized for patients who are at least 18 years old. As such, a general statement regarding ketamine use by EMS cannot be made. As was the case with the other non-opioid studies, more specific conclusions regarding ketamine will be made in the remaining sections of this review.

#### *Non-Opioid First Studies:*

There were three significant limitations in the studies that reported on the implementation of a non-opioid first protocol in the ED (Cohen et al., 2015; Duncan et al., 2019). For one study, it was not apparent whether protocol use was mandated in all patients (Duncan et al., 2019). This is a limitation as it changes the significance of the findings. Both studies shared the two remaining limitations. First, neither of these studies are RCTs (Cohen et al., 2015; Duncan et al., 2019). The results of these studies are not as strong as a RCT. Secondly, the protocols in both studies include more analgesics than are available to EMS (Cohen et al., 2015; Duncan et al., 2019). This limits the ability to generalize the results of these studies to EMS. However, these studies demonstrate successful implementation of non-opioid first protocols that can guide changes in EMS.

#### **Importance and Use of Outcome Measures in the Reported Literature**

While there are many outcome measures that can be important in considering an effective first-line treatment for acute pain in EMS, four important outcomes were identified for this literature review: effect on pain severity, patient satisfaction, rescue analgesic use, and the consideration of risks. The use of these outcome measures by the

17 RCTs that were not completely excluded in the *Limitations of Reported Literature* section are summarized in Table 4. Measuring the effect on pain severity requires an adequate pain assessment. In research, more objective measures typically provide more rigorous data. However, vital signs are not a reliable measure of pain intensity (Bossart et al., 2007; Ducharme, 2016; Jennings et al., 2009; Marco et al., 2006). In practice, pain scales are often utilized to measure pain severity (Table 4). Sixteen of the publications reported their results in terms of absolute reduction in pain scores.

**Table 4. Use of Four Identified Outcome Measures in Randomized Trials.** Indicates the presence of each outcome measure in RCTs not excluded from use as evidence.

<b>Trial</b>	<b>Effect on Pain Severity</b>	<b>Patient Satisfaction</b>	<b>Rescue Use</b>	<b>Adverse Effects</b>
<b>Comparison Studies</b>				
Al et al.	Absolute reduction	No	Yes	Yes
Bektas et al.	Absolute reduction	No	Yes	Yes
Craig et al.	Absolute reduction	Yes	Yes	Yes
Deloee et al.	Absolute reduction	No	No	No
Eken et al.	Absolute reduction	No	Yes	Yes
Farnia et al.	Absolute reduction	No	Yes	Yes
Frey et al.	Absolute reduction	No	Yes	Yes
Kariman et al.	Absolute reduction	No	No	Yes
Miller et al.	Absolute reduction Proportion obtaining percentage reduction	No (Provider satisfaction is reported)	Yes	Yes
Motov et al., 2015	Absolute reduction Proportion obtaining percentage reduction Proportion $\geq$ 3-point reduction	No	Yes	Yes
Pathan et al.	Absolute reduction Proportion obtaining percentage reduction Proportion $\geq$ 3-point reduction	No	Yes	Yes
Rainer et al.	Absolute reduction Proportion obtaining percentage reduction	Yes	No	Yes
Serinken et al.	Absolute reduction	No	Yes	Yes
Shimonovich et al.	Absolute reduction	Yes	No	Yes
Tran et al.	Excluded in <i>Limitations in Reported Literature</i> section	No	No	Yes
<b>Efficacy Studies</b>				
Ducassé et al.	Absolute reduction Proportion obtaining specified threshold	Yes (Provider satisfaction also reported)	No	Yes
Motov, Yasavolian, et al., 2017	Absolute reduction	No	Yes	Yes

Although a study might report a statistically significant decrease in pain score, that does not inherently indicate a meaningful reduction in pain for the patients. One study reported that 13 mm is the minimum change in VAS to be considered clinically significant (Todd, Funk, Funk, & Bonacci, 1996). That study did not indicate whether the initial pain severity level affected this value. Another study reported 13 mm as the minimal clinically significant change only for patients with VAS scores less than 34 mm; patients with VAS scores at or above 67 mm required a 28 mm change in order to be clinically significant (Bird & Dickson, 2001).

Instead of reporting results based on absolute pain reduction, seven studies also utilized different approaches (Table 4). These different assessment methods can demonstrate a reduction in pain severity or the percentage of patients achieving a specified goal. They serve as useful tools when comparing the ability of two analgesics to reduce pain, which is important in determining the most appropriate first-line treatment. The usefulness of these measures to identify adequate pain control is less clear. These types of goals do not completely consider how initial pain severity or other subjective factors may affect what a patient perceives as adequate analgesia. With the high prevalence of inadequate pain control, a measure of adequacy is an important outcome to consider.

The physiologic nature of pain (signal input and modulation) through pain pathways and the perception of pain are the targets of analgesics. However, it would be impractical to assess the adequacy of pain by measuring the activity of these pathways.

This is because a multitude of factors play a role in the subjective pain experience beyond the more well understood physiology of pain (Coghill, 2010).

Both patients and providers agree that an adequate pain goal should involve the patient, include realistic expectations and functional goals, be patient specific, and appropriately consider all aspects of the pain experience beyond solely relying on pain scales (American College of Emergency Physicians, 2017; Gunderson, 2011; Lee, 2016; Smith et al., 2015; The Joint Commission, 2017; University of Wisconsin Health Pain Care Services, n.d.). One way that this has been addressed in research is through the reporting of patient satisfaction. Despite its significance, only four of the publications included patient satisfaction as an outcome measure (Table 4). Two studies included a report of provider satisfaction with the analgesic treatment (Table 4).

Realistic expectations and functional based pain goals may influence patient and provider satisfaction. For example, an initial prehospital goal may be to alleviate the pain enough for initial treatment and transport of the patient to be tolerable. A second goal may be to alleviate pain that is interfering with proper assessment. A patient's understanding of what realistic pain management might look like may influence their pain goal and subsequently their reported satisfaction. None of the studies reviewed mentioned a script or dialogue with the patient to address the concept of realistic and functional pain management (Craig et al., 2012; Ducassé et al., 2013; J. P. Miller et al., 2015; Rainer et al., 2000; Shimonovich et al., 2016). The differences in the baseline definition of satisfaction between groups was not indicated and therefore may have skewed the satisfaction results.

The final useful measure of adequate pain management identified in this review is the use of rescue analgesics. In total, 11 of the publications recorded the percentage of patients in each group requiring rescue analgesia (Table 4). If a patient requires or requests a rescue analgesic, it can be inferred that the initial treatment was not considered adequate by the patient. A difference between group use of rescue analgesia is an indication that one treatment was more efficacious.

The last outcome measure is the consideration of risks associated with analgesic use. This is the combination of adverse effects, contraindications, and other factors. Adverse effects were reported in 16 of the studies (Table 4). While the previous outcome measures are arguably more important in deciding which treatment should be utilized as first-line treatment for acute pain in EMS, a significant difference in adverse effects between groups or the presence of specific undesired adverse effects for any one treatment may influence the final decision. This is especially true when the other outcome measures do not strongly favor one analgesic over the other.

As noted in the *Goal of Pain Management* section, individual patient and/or healthcare provider preferences to avoid certain risks associated with a specific analgesic are both valid when deciding which treatment to utilize in a clinical setting. However, such personal preferences are not well integrated into comparison and efficacy RCTs as it would interfere with the randomization of the participants. That would be undesirable as randomization strengthens the validity of the results in an RCT.

## DISCUSSION

Pain is the oldest reported symptom (Meldrum, 2003). The high prevalence of pain make it likely that a wide variety of healthcare providers will treat patients reporting pain. EMS providers are no exception. Reports of pain prevalence in EMS patients vary in range from 42% to 53% (Galinski et al., 2010; Lord et al., 2009). The importance of pain management is also widely recognized (American College of Emergency Physicians, 2016; American Medical Association, n.d.; Brennan et al., 2016; Pizzo & Clark, 2012). With the high prevalence of pain and the recognition of the importance of adequate analgesia, it might be expected that optimal pain management strategies would be well understood and practiced. However, this is not the case. Pain management is often inadequate (Albrecht et al., 2013; American College of Emergency Physicians, 2016; Baker, 2017; Brennan et al., 2016; Campbell, 1996). As such, improving pain management should continue to be a high priority for healthcare providers.

The two major groups of analgesics utilized in the prehospital setting are opioid and non-opioid analgesics. Opioids have long been used for acute pain management in the prehospital setting. Non-opioids are a more recent addition and have gain increased attention in the wake of the opioid epidemic. This literature review seeks to determine if non-opioid analgesics can be utilized as first-line treatment for acute pain in the EMS environment.

## **Results of Outcome Measures in the Reported Literature**

There are four broad results possible for each outcome measure. The result may not be reported by a study. The result may be reported, but the statistical significance may not be reported. One analgesic may be favored over the other as demonstrated by the results within an outcome measure. The final possible result is that no significant difference is found between the study groups. While no significant difference is not the same as equivalence, it indicates that neither group is superior to the other for the outcome being measured. This finding is significant when considering an alternative to the standard of care for acute pain, opioid analgesics.

There are some considerations that are unique to EMS and are also significant when selecting a first line treatment for acute pain management by prehospital providers. These considerations apply to all the non-opioid analgesics investigated in this section. In EMS, there is typically only one provider with the patient in the ambulance during transport. The single provider must perform all patient care tasks during transport. These tasks include assessing, monitoring, and treating the patient, and managing adverse effects. The confined space of the ambulance coupled with the additional noise and movement associated with transportation increase the difficulty of successfully managing the heavy task load. The most critical cases, including cardiac arrest, may result in more providers present during transport. However, significantly more tasks are also performed in these critical cases. This contrasts with the ED where there are frequently additional providers (nurses, technicians, physicians, etc.) who assist with different aspects of patient care if needed.

There are also additional considerations regarding resource availability, education, scope of practice, and culture of EMS. The limited availability of resources extends beyond the number of providers present during transport. Prehospital providers have limited equipment available for diagnostic testing. This complicates the creation of protocols that adequately address the various contraindications and indications for administering certain analgesics, and other medications. As will be more fully discussed in later sections of the review, the culture of EMS practice is heavily protocol driven. This is in part related to the limited educational training and scope of practice of prehospital providers and contrasts with the extensive training and more free form decision making process that is typical of physicians. As a result, these unique characteristics have a significant role when considering analgesic administration by EMS. These EMS circumstances will be considered throughout the remaining sections of the review as it applies to each analgesic.

*Non-Opioid Studies, Excluding Ketamine:*

After the exclusions made in the *Limitations in Reported Literature* section, there are three non-opioids (acetaminophen, ketorolac, and nitrous oxide) and nine comparison studies remaining. One study was mentioned in that section, but wasn't excluded (Al et al., 2018). While the results of this study did not demonstrate a significant difference, it should be reiterated that the limitation favored fentanyl due to a low dose of acetaminophen. The remaining studies administered doses that are representative of EMS protocols. The initial pain scores of most studies were in the top quarter of the pain scale,

which contributes to the generalizability of the results. If an analgesic is effective for severe pain, it is a safer generalization that it would be effective for lower levels of pain than generalizing studies with low initial pain scores to high pain severity patients. These studies can be separated into two groups: pain from renal colic and pain from trauma.

An aspect of the unique circumstances of EMS favors all three of the non-opioid analgesics in this subsection. The adverse effects outcome measure may be more significant in EMS than in the ED. More adverse effects increases the total tasks the single EMS provide must perform during transport. Opioids are known to have more adverse effects than these three non-opioids. Adverse effects of opioids, such as emesis, hypotension, and respiratory depression, require additional management and monitoring of the patient. The non-opioid analgesics may be preferred as they have fewer adverse effects and reduce the total task load of the provider.

Acetaminophen is the only non-opioid represented in the renal colic group (Table 5). Only one study demonstrated significant differences between groups for the effect on pain severity outcome measure, all of which favored acetaminophen to varying degrees. One study reported that the morphine group used more rescue analgesia than the acetaminophen group. Two of the studies reported significantly more adverse effects in the morphine group. Pathan et al. analyzed approximately 440 patients per group, which significantly strengthens the results of that study (Pathan et al., 2016). Overall, all three of the four outcome measures utilized in these studies favor acetaminophen over opioid analgesics.

**Table 5. Results of Four Outcome Measures in Non-Opioid Comparison Studies Investigating Acute Renal Colic Related Pain, Excluding Ketamine.** *APAP* – Acetaminophen, *NR* – Not Reported, *NSD* – No Significant Difference, *PS* – Patient Satisfaction, *SSNR* – Statistical Significance Not Reported.

<b>Trial</b>	<b>Groups</b>	<b>Effect on Pain Severity</b>	<b>PS</b>	<b>Rescue Use</b>	<b>Adverse Effects</b>
<b>Al et al.</b>	Acetaminophen Fentanyl	NSD	NR	SSNR	SSNR
<b>Bektas et al.</b>	Acetaminophen Morphine	NSD	NR	NSD	NSD
<b>Serinken et al.</b>	Acetaminophen Morphine	NSD	NR	NSD	Morphine significantly more (14.3% vs. 5.3%)
<b>Pathan et al.</b>	Acetaminophen Morphine	Percent patients achieving 50% reduction by 30 min greater for APAP (68% vs. 60%) Mean score at 30 min lower for APAP (3.3 vs. 3.8) Reduction of at least 3-points - SSNR Percent patients with pain at 60 min less for APAP (30% vs. 38%)	NR	Morphine significantly more (23% vs. 20%)	Morphine significantly more (3% vs. 1%)

In the case of renal colic, there are other factors that strengthen the findings in the literature. Non-opioids are currently recommended as first line treatment over opioids for acute pain from renal colic (Engeler, Schmid, & Schmid, 2008). It should be noted that within non-opioids, the current recommendations favor NSAIDs over acetaminophen. As mentioned in the *Pharmacologic Pain Treatments: Opioids and Non-Opioids* section, opioids are known to have more adverse effects and contraindications compared to acetaminophen, which can be given to most any patient. The relative lack of contraindications for acetaminophen is important given the limited diagnostic testing equipment available to EMS. In addition, the fixed adult dosing of acetaminophen avoids

the calculation of a weight-based dose in the hectic EMS environment. This is advantageous as it reduces the task load of the EMS provider.

None of the other non-opioids, excluding ketamine, considered in this literature review investigated renal colic pain. Therefore, there is not enough evidence to support a general recommendation that non-opioids, as a group, be utilized as first line treatment for the treatment of acute renal colic pain in EMS. There were three outcome measures available in the four renal colic studies. All three favored acetaminophen to varying degrees and were strengthened by other factors outside of the reported comparison studies. There is enough evidence in this literature review to support using acetaminophen over opioids for acute renal colic pain in EMS. Acute renal colic pain should be treated by EMS using analgesics, excluding ketamine, in the following order: NSAIDs, acetaminophen, opioids.

One significant limitation of this recommendation pertains to the limited ability of EMS to diagnose renal colic. The recommended equipment for definitive diagnosis include computed tomography (CT) scans and ultrasound (Carter & Brown, 2017). Although ultrasound has been studied for use in EMS, it is not commonplace. EMS providers must rely on patient report, if a current diagnosis of renal colic has already been given, or signs and symptoms. These usually include unilateral acute onset flank pain that may radiate to the groin, ipsilaterally (Carter & Brown, 2017). In addition, approximately 90% of cases will present with hematuria (Carter & Brown, 2017). Hematuria is reliant on the patient recognizing and reporting it to EMS, which may present a limitation for that presentation of renal colic. Careful recognition of these signs and symptoms, and

specific exclusions such as associated trauma, may provide enough of an indication to base treatment on.

There are five studies investigating trauma related pain (Table 6). All four outcome measures are represented in this group of studies. The effect on pain severity outcome measure is variable in this group. Two studies demonstrate three outcomes that favor the non-opioid analgesics. However, the study by Kariman et al. does not report if their outcome favoring nitrous oxide is clinically significant (Kariman et al., 2011). There are also two studies that favor the opioid analgesic at the first assessment. The 11 mm difference observed in one study favoring the opioid analgesic is below the clinically significant threshold noted by two different studies (Bird & Dickson, 2001; Todd, Funk, Funk, & Bonacci, 1996). That result is unlikely to represent a meaningful reduction for the patient. The 14.5 mm difference favoring an opioid demonstrated in the other study may represent a meaningful reduction for the patient using the 13 mm threshold (Todd et al., 1996). However, the 14.5 mm difference is below the 28 mm threshold given the high initial pain severity (Bird & Dickson, 2001). Taking this into consideration, two pain reduction outcomes favor the non-opioids and one may favor the opioids.

**Table 6. Results of Four Outcome Measures in Non-Opioid Comparison Studies Investigating Acute Trauma Related Pain, Excluding Ketamine.** *NR – Not Reported, NSD – No Significant Difference, PS – Patient Satisfaction.*

<b>Trial</b> (Source of Pain)	<b>Groups</b>	<b>Effect on Pain Severity</b>	<b>PS</b>	<b>Rescue Use</b>	<b>Adverse Effects</b>
<b>Deloee et al.</b> (Isolated diaphyseal long bone fracture)	Acetaminophen Morphine	14.5 mm difference in reduction at 5 min favoring morphine NSD at 30 min	NR	NR	NR
<b>Craig et al.</b> (Isolated limb trauma)	Acetaminophen Morphine	NSD	NSD	NSD	Morphine significantly more (8 vs. 2 patients)
<b>Eken et al.</b> (Mechanical low back)	Acetaminophen Morphine	11 mm difference at 15 min favoring morphine NSD at 30 min	NR	NSD	NSD
<b>Rainer et al.</b> (Non-penetrating Isolated limb trauma)	Ketorolac Morphine	Odds of 75% reduction with activity favors ketorolac. NSD for 50% (100% NR) nor at rest for 50%, 75%, 100%. Per hour rate of reduction greater for ketorolac with activity (1.09 vs. 0.87). NSD at rest.	Favors ketorolac	NR	16 times more likely for morphine
<b>Kariman et al.</b> (Isolated extremity fracture or dislocation)	Nitrous oxide Fentanyl	Mean score for nitrous oxide significantly less at 9 min (2.2 vs. 3.1) NSD at 3 and 6 min	NR	NR	NSD

Although there is only one study reporting a limitation of non-opioid use due to a slower onset of analgesia, this limitation is potentially significant in the context of EMS. Many EMS systems have short transport times. For example, an urban city likely has most transports under 10 minutes while a suburban city may have transport times that extend to 15 or 20 minutes. Only rural EMS systems are likely to have extended

transports beyond 30 minutes. The short transport times increase the importance of administering an analgesic with rapid onset. The coadministration of another non-opioid analgesic with acetaminophen may mitigate the potential limitation, although small in magnitude, reported by the one study.

The study investigating ketorolac reported two outcomes that indicated ketorolac was superior to morphine when patients moved their injured extremity (Table 6). Another unique aspect of EMS is that the patient is transported in a moving vehicle. The transport is often jarring for the patient. In addition, significant movement of the patient may be required at the scene of the emergency to get the patient onto the stretcher and loaded into the ambulance. It would be advantageous to have an analgesic, such as ketorolac, that is known to significantly outperform opioid analgesics when the patient is moving.

The use of rescue analgesia does not favor either group of medications (Table 6). One of the two studies reporting patient satisfaction demonstrated a significant difference; patients are more satisfied with the non-opioid analgesic. The EMS study investigating nitrous oxide in trauma patients found that all but one patient and all but two providers were satisfied or very satisfied with the non-opioid treatment (Ducassé et al., 2013). This additional information strengthens the support for non-opioid analgesics in EMS. Adverse effects are reported in four of the studies, two of which found morphine to have significantly more adverse effects. This finding parallels the known adverse effects profiles noted in the *Pharmacologic Pain Treatments: Opioids and Non-Opioids* section.

There are additional external factors that contribute to the reported literature. The task load by EMS providers is reduced when these non-opioid analgesics are selected due to the fixed dosing. Nitrous oxide has an additional benefit that it is self-administered by the patient and does not require IV/IM/IN/IO administration. This allows the patient to control the level of analgesia administered and allows the patient to self-limit any adverse effects that may be experienced. These advantages are not possible with opioid analgesia in EMS as patient controlled analgesia devices for opioids are not commonly found in this setting.

All four outcome measures are utilized in the studies investigating acute pain from a chief complaint that is traumatic in nature. Non-opioid analgesics are marginally favored in their ability to decrease the pain severity. A potential solution exists to address the possible limitation of acetaminophen having a slower analgesic effect. While neither group of analgesics are superior in the number of patients requiring rescue analgesia, the non-opioid analgesics are favored both in terms of patient satisfaction and the consideration of risks. Non-opioid analgesics are also favored in various factors that consider the aspects unique to EMS. Although there are limitations in the generalizability of these results, as discussed in the *Limitations in Reported Literature* section, there is enough evidence to support a more specific recommendation. The use of acetaminophen, ketorolac, and nitrous oxide as first line treatment by EMS for patients with acute pain resulting from an isolated extremity trauma is supported. While not the focus of this review, coadministration of non-opioid analgesics is a reasonable consideration to maximize the analgesic effect.

*Ketamine Studies:*

None of the six ketamine studies were completely excluded in the *Limitations in Reported Literature* section. As mentioned in that section, five of the studies support conclusions for patients 18 years old and older and the final study provides significant evidence to state a pediatric conclusion. There was more diversity in the route of administration studied in the six different ketamine RCTs than the other non-opioid RCTs. IN/IV ketamine, IN fentanyl, and IM/IV morphine were all represented between the six studies (Table 7 and Table 8). The ability to use the IN route is particularly useful in patients where it may be difficult or especially distressing to obtain IV access, such as pediatric patients. However, fentanyl can also be administered IN so route of administration alone does not favor ketamine over the opioid analgesics.

The consideration of risks outcome measure is more complex for ketamine compared to the other non-opioids. The adverse effects results are comparable between the pediatric and adult ketamine studies. As such, the consideration of risks for both groups will be considered simultaneously. As mentioned in previous sections, ketamine is a controlled substance with the potential for abuse. In the United States, ketamine is listed as a Schedule III drug, which means it has at most a moderate potential for dependence, both physical and psychological (United States Drug Enforcement Administration, n.d.). This is important to note, as one of the driving factors in the search for opioid alternatives is the pressures placed on the ED and EMS to find alternatives to opioids as a result of the opioid epidemic. However, by function of its classification, there is less potential for

ketamine abuse than opioids. Morphine and fentanyl, which are Schedule II drugs, have a high abuse and dependence potential (United States Drug Enforcement Administration, n.d.). While the potential for abuse is less in ketamine, it still exists. The other non-opioids, such as acetaminophen and ketorolac, are not controlled substances and do not pose a risk of abuse. There may be cases where the opioids, ketamine, and the other non-opioids could all be equally considered as first line treatment after considering all other outcome measures. In these cases, it is reasonable to suggest that analgesics be selected based on the consideration of risks outcome measure barring any specific contraindications related to other risks. That order begins with the other non-opioids, followed by ketamine, and lastly, the opioids.

The other risks to consider for ketamine are its known effects, which are typically reported in studies investigating ketamine. The adverse effects reported for ketamine include reemergence reactions including hallucinations, dizziness, hypersalivation, nausea, emesis, sedation, and laryngospasm (Ducharme, 2016; Green et al., 2009; Kurdi et al., 2014; Motov, Mai, et al., 2017; Pourmand et al., 2017; Wedmore & Butler, 2017). These adverse effects must be weighed against the common adverse effects of the opioid analgesics, especially morphine, which include hypotension, respiratory depression, euphoria, sedation, and constipation (Abdel-Aziz & Adams, 2017; Ducharme, 2016). The most concerning of the opioid analgesics are the respiratory depression and hemodynamic effects. Ketamine is favored in this regard as its effects on respiratory drive are minimal and it is known to stimulate the sympathetic nervous system resulting in increased blood pressure, heart rate, and cardiac output (Kurdi et al., 2014).

All six of the ketamine RCTs reported some variation in the comparison of adverse effects (Table 7 and Table 8). Two studies reported that the ketamine group experienced significantly more minor adverse effects than the morphine or fentanyl group, but that the difference was soon after administration and transient. Three studies reported that specific adverse effects are more prevalent in one analgesic or the other with no significant trend favoring either analgesic (Table 8).

The initial increase in adverse effects may be related to the rapid administration of the medication. A study comparing ketamine administered via an IV push over 5 minutes to an IV infusion over 15 minutes demonstrated a significant reduction in adverse effects when the administration time was increased without any significant difference noted in analgesic effect or rescue analgesic use (Motov, Mai, et al., 2017). This suggests that the initial prevalence of adverse effects of ketamine can be reduced by changing the administration time. In the United States, the state of Vermont already requires a 15 minute infusion when ketamine is used by EMS providers for pain management (Vermont Department of Health Office of Public Health Preparedness and Emergency Medical Services, 2018). Notably, the 15-minute infusion should not require the use of an infusion pump, which is not common in EMS. The manual IV administration sets commonly used by EMS providers have a predefined drops per milliliter rate (gtt/mL) that can be used to set a 15-minute infusion. The short transport time previously noted for urban EMS systems may result in arrival at the ED prior to the completion of the infusion. This is likely to be of limited concern because no significant difference in analgesic efficacy was found between the administration times (Motov, Mai, et al., 2017).

Furthermore, it may be advantageous to have time remaining at the ED to bridge the gap between prehospital care and analgesic administration by an EM provider. This gap is created due to the time it takes for registration, assignment to a bed, and the time between the physician's order for analgesic administration and actual administration of an analgesic.

Overall, ketamine does not have the benefit of reduced task loading on EMS providers noted for the other non-opioid analgesics. The preservation of the respiratory drive, lack of hypotension, and reduced potential for abuse are all advantages of ketamine. The lack of hypotension and potential for an increase in the sympathetic nervous system may actually delineate significant benefits for ketamine. This is especially true for patients where hypotension or an increased concern for hypotension may contraindicate opioid analgesic use by EMS. In addition, the ability to reduce the early adverse effects using a slower infusion without sacrificing analgesic efficacy mitigates the one major concern reported by the ketamine studies for the consideration of risks outcome measure when IV ketamine is administered. The various factors pertaining to the consideration of risks outcome measure supports the recommendation for a 15-minute infusion time when IV ketamine is used by EMS for pain management.

**Table 7. Results of Four Outcome Measures in a Pediatric Ketamine Comparison Study Investigating Acute Trauma Related Pain.** *Fent – Fentanyl, IN – Intranasal, Ket – Ketamine, NR – Not Reported, NSD – No Significant Difference, PS – Patient Satisfaction.*

<b>Trial</b> (Source of Pain)	<b>Groups</b>	<b>Effect on Pain Severity</b>	<b>PS</b>	<b>Rescue Use</b>	<b>Adverse Effects</b>
<b>Frey et al.</b> (Extremity injury)	IN: Ketamine Fentanyl	Ket non-inferior to fent in reduction at 30 min NSD in mean difference from baseline NSD in lowest pain scores achieved	NR	NSD	All minor and transient. Larger overall proportion in ket (77% vs. 31%). NSD except at 15 min. NSD in max sedation score NSD in vital signs.

The one study exclusively investigating extremity trauma in a pediatric population will be considered separately for the remaining outcome measures (Table 7). Although it wasn't a large study, it was the only RCT to utilize a non-inferiority design (Frey et al., 2019). This style of design provides more significant evidence than a superiority design (when superiority is not demonstrated) because a lack of superiority does not equate to equivalence or non-inferiority. In this case, ketamine was not inferior to fentanyl in all pain severity measures. The study acknowledged the use of higher doses of medication in both groups, but mentioned that it did not result in increased analgesic effect compared to previous studies (Frey et al., 2019). This finding is important when generalizing to EMS due to the lower doses of both medications that are used in that setting. The high initial pain score, as mentioned previously, also supports generalizability.

Patient satisfaction was not reported (Table 7). However, no significant difference was found for rescue analgesic use. The strength of the non-inferiority design coupled with the consideration of risks previously discussed allows a specific recommendation to

be made based on these results. In the pediatric population suffering from acute pain after an extremity injury, ketamine should be considered by EMS for use as first line treatment over opioid analgesics. This suggestion is strengthened in patients where the concern for the hemodynamic and respiratory drive effects of opioids or the concern for opioid addiction relapse or opioid tolerance is greater.

**Table 8. Results of Four Outcome Measures in Ketamine Comparison Studies Investigating Acute Pain.** *HCP – Healthcare Provider, IM – Intramuscular, IN – Intranasal, IV – Intravenous, Ket – Ketamine, Mor – Morphine, NR – Not Reported, NSD – No Significant Difference, PS – Patient Satisfaction.*

<b>Trial</b> (Source of Pain)	<b>Groups</b>	<b>Effect on Pain Severity</b>	<b>PS</b>	<b>Rescue Use</b>	<b>Adverse Effects</b>
<b>Farnia et al.</b> (Renal colic)	IN: Ketamine IV: Morphine	Mean difference between groups at 5 min favors mor (7.9 mm difference). NSD at 15 and 30 min.	NR	NSD	Hypotension in 8 mor and emergence in 6 ket patients
<b>Miller et al.</b> (Extremity, low back, flank, abdominal)	IV: Ketamine Morphine	Max reduction: Ket (-4.9 at 5 min) Mor (-5 at 100 min) Ket mean percent reduction approximately 50% for 2 hours despite poor sustained analgesia	NR  NSD for HCP	NSD	NSD overall NSD in agitation and sedation Systolic blood pressure higher for ketamine at 5 and 10 min
<b>Motov et al., 2015</b> (Musculo-skeletal, back, flank, abdominal)	IV: Ketamine Morphine	Ket 31% more complete resolution at 15. NSD at 30 min. NSD in reduction at 15 and 30 min NSD in percent achieving at least 3-point reduction	NR	Ket 17% more at 120 min. NSD at 30 and 60 min.	Only minor effects. Difference favors mor at 15 min (38% difference). NSD at 30 min.
<b>Shimonovich et al.</b> (Mild to moderate blunt trauma)	IN: Ketamine IV: Morphine IM: Morphine	IN ket faster rate of reduction than IM mor until NSD at 45 min NSD in rates of reduction for IV mor and IN ket NSD in max reduction or time to reach max	NSD	NR	Difficulty concentrating IN ket more than IV/IM mor (58.3% vs. 20.8%/22.2%). Dizziness IN ket more than IM mor (79.2% vs. 22.2%). Confusion IN ket more than IV mor (50% vs. 12.5%). Dry mouth IV/IM mor more than IN ket (79.3%/63% vs. 25%) NSD in vital signs
<b>Tran et al.</b> (Trauma)	IV: Ketamine IM: Morphine	Excluded in <i>Limitations in Reported Literature</i> section	NR	NR	More nausea and emesis for mor (19% vs. 5%; difference of 8-22%). More agitation for ket (11% vs. 1.5%; difference of 4-16%)

The remaining five studies covered a broad range of acute pain, both traumatic and non-traumatic in nature, in an adult population (Table 8). As previously mentioned, the doses used are generalizable to EMS and the high initial pain scores are an added strength of the studies. Overall, ketamine is found to have a significantly more rapid onset of analgesic effect compared to opioid analgesics (Table 8). One study reported the opposite finding. However, the difference reported was 39% lower than the 13 mm clinically significant difference threshold (Bird & Dickson, 2001; Todd et al., 1996). As mentioned in the discussions regarding the other non-opioids, a rapid onset of action is advantageous for EMS.

One limitation reported in two studies, one via effect on pain severity and one via rescue use, is that ketamine does not provide sustained analgesia as well as the opioid analgesics (Table 8). Despite these results, Miller et al. found that the mean percentage reduction in pain score was still at least 50% for two hours in the ketamine group. In addition, one study reported that IN ketamine and IV morphine have similar rates of reduction (Table 8). This is an important finding as it demonstrates the analgesic efficacy of ketamine administered via the IN route compared to an IV route of administration for an opioid. An IN analgesic can be administered more quickly and is less invasive than an IV analgesic. This is especially pertinent in patients where an IV access is difficult to obtain. The rescue use result was only significant at the 120-minute assessment (Table 8). This result is not significant for most EMS systems. A 120-minute transport time would be an abnormally long transport for the typical United States EMS system. As such, this

specific result is not well suited to generalize to EMS use of ketamine. The other rescue analgesic results and the satisfaction results did not favor either medication.

In the five adult ketamine RCTs included, all four of the outcome measures were utilized in at least one RCT. After considering the unique circumstances of EMS, only two outcome measures had enough evidence to favor one analgesic over the other. The consideration of risks, although more complicated for ketamine compared to the other non-opioids, favors ketamine over the opioid analgesics. The effect on pain severity outcome measure also favors ketamine. Due to diversity in the locations and causes of acute pain studied in ketamine, a more general statement can be supported for adult patients. In adult patients, ketamine should be considered by EMS for use as first line treatment over opioid analgesics. Just as in the pediatric population, this suggestion is strengthened in patients with increased concern for opioid addiction relapse or opioid tolerance and in patients whose hemodynamic or respiratory status may increase the risk of opioid analgesic use.

### **Applicability of Recommendations to EMS**

All the studies reported in this review were performed by higher level providers with a scope of practice and education beyond the EMS paramedic. Within the United States, most Advanced Life Support EMS providers operate under the license of a medical director, who is a physician. Most medical directors and EMS services are required to follow statewide protocols, also written and presided over by physicians. Standing orders, written in a protocol document, govern the scope of practice for each

EMS provider level. Most patient care by EMS is performed utilizing these protocols. The EMS provider can also contact online medical direction, typically a phone call to an affiliated physician, to request additional orders or input. The EMS provider's limited scope of practice and lack of an independent license necessitate rigid protocols that account for the knowledge, skillset, and equipment that each level of provider has access to. As mentioned in the introduction, paramedics represent the most advanced level of EMS provider for this review and can utilize all the recommendations.

Protocols must also consider another unique aspect of EMS care. EMS often interacts with undifferentiated patients. While EM also cares for undifferentiated patients, EMS is unique in that the limited resources hinder diagnostic evaluation. This has implications for EMS protocols and the non-opioid analgesic recommendations. The recommendations made in this review would have to be written into protocols that consider these unique aspects of EMS practice.

Perhaps the most significant consideration in writing rigid protocols based on these recommendations is including appropriate and explicitly defined inclusion and exclusion criteria that only utilizes resources available to EMS. This presents a barrier to the implementation of the research findings because many of the studies utilized blood work and other imaging technologies (ultrasound, X-Ray, CT, etc.) in their research protocols. The different non-opioid analgesics included in the recommendations are acetaminophen, ketorolac, nitrous oxide, and ketamine. They each have varying contraindications that have been previously discussed in detail. All four non-opioids are currently utilized in at least one EMS system in the United States. The state protocols of

these EMS systems provide reference for the contraindications of these analgesics in ways that are appropriate for EMS administration (Alabama Department of Public Health Office of Emergency Medical Services, 2018; Massachusetts Department of Public Health Office of Emergency Medical Services, 2017; Vermont Department of Health Office of Public Health Preparedness and Emergency Medical Services, 2018).

The two specific etiologies resulting in pain represented in the recommendations of this review are renal colic and extremity trauma. Extremity trauma, without further explanation, is a sufficient inclusion parameter for EMS providers. The identification of renal colic cannot be definitively made in the prehospital setting. However, a protocol could be written to allow for the use of non-opioid analgesics in patients with a high index of suspicion for renal colic. This protocol may include the presence of flank pain not associated with trauma and difficulty or pain with urination. Of course, patients who state their pain is from a current diagnosis of renal colic would also be indicated. The adult ketamine recommendation is more general in nature and does not require rigid etiology-based inclusion criteria.

The development of non-opioid first protocols is only one aspect of implementing these recommendations in EMS. Changes and updates to pain management education would likely improve the result of new protocols on acute pain management in EMS. Both studies reporting on a non-opioid first protocol incorporated provider education (Cohen et al., 2015; Duncan et al., 2019). Based on the topics discussed throughout this review, it is reasonable to propose that EMS provider education should include the following outcomes:

1. Awareness of high prevalence of acute pain and inadequate analgesia.
2. Awareness of the importance of pain management.
3. Describe the pain experience including the subjective nature of pain.
4. Perform a comprehensive pain assessment and understand the limitations of pain scales.
5. Discuss realistic pain management expectations and goals with patients.
6. Understand the relative advantages and disadvantages of each analgesic.
7. Appropriately utilize non-opioid and opioid analgesics including an understanding of certain indications where non-opioid analgesics should be successfully administered as first-line treatment.
8. Understand the potential implications of EMS provided pain management on the entire patient experience.

Given the scarcity of EMS research on acute pain management outcomes, only the potential impact on the entire patient experience can be discussed. The first situation to consider is the exclusive use of opioid analgesics by EMS. This is likely to result in continued inadequate pain management. Many patients with minor to moderate pain may not be offered a potent analgesic such as morphine or fentanyl. Also, only paramedics will have access to an analgesic. The patients who are given analgesics will only receive opioids. This presents a potential limitation in patients concerned with relapse, patients who have developed an opioid tolerance or are taking medications such as methadone, or patients where opioid analgesics may be contraindicated.

Only having opioid analgesics available also limits the ability of the EMS provider to include the patient in the pain management process, which was identified as an important component from the patient perspective (R. J. Smith et al., 2015). Treating all patients with opioids may also lead to an unrealistic expectation that more opioids should be given by the physician in the ED. However, the EM physician has access to non-opioid analgesics in addition to opioid analgesics. The ED provider may believe that

a non-opioid analgesic is the preferred choice for a patient. The unrealistic expectation resulting from opioid use by EMS may increase the difficulty of discussing non-opioid options in the ED. The pressure to continue with opioid treatment may also be increased due to the implications on healthcare reimbursement mentioned in the *Goal of Pain Management* section.

Pressures to continue opioid treatment in the ED may also increase the potential for a short course opioid prescription upon discharge. Two studies presented in the *Pharmacologic Pain Treatments: Opioids and Non-Opioids* section reported a potential contribution of opioid exposure or prescription for acute pain in the ED to future recurrent use or abuse (Butler et al., 2016; Hoppe et al., 2015). This potential for abuse is receiving increased attention due to the opioid epidemic in the United States. Recommending non-opioid use by EMS has the potential to address all these concerns and provide additional benefits.

EMS administration of non-opioid analgesics should allow for increased treatment of any severity of pain, increased patient involvement in pain management, discussion of realistic expectations and appropriate goals, and provide an alternative for patients at a higher risk with opioid analgesic use. The prehospital initiation of non-opioid treatment and discussion of realistic pain management will mitigate the barriers present upon arrival to the ED in the previous scenario. The availability of non-opioid analgesics may also allow EMTs and AEMTs to administer pharmacologic analgesia. Some states in the United States currently allow specific non-opioid analgesic administration by EMTs and AEMTs (Alabama Department of Public Health Office of

Emergency Medical Services, 2018; New Hampshire Department of Safety Division of Fire Standards and Training and Emergency Medical Services, 2018; Vermont Department of Health Office of Public Health Preparedness and Emergency Medical Services, 2018). A final benefit to non-opioid use is that fewer resources are required to manage patients receiving non-opioids, possibly except for ketamine, compared to opioids. One of the comparison studies reported that patients in the ED receiving a non-opioid were discharged more quickly, did not require as many resources to manage adverse effects, and resulted in lower ED and pharmacy costs (Rainer et al., 2000). These potential advantages warrant significant consideration of non-opioid analgesic use by EMS.

### **Application of Non-Opioid First Protocols in Practice**

There are two studies that reported on a non-opioid first protocol being implemented in the ED (Cohen et al., 2015; Duncan et al., 2019). In one study a 20% reduction in IV opioid use was reported along with a 29.5% increase in acetaminophen use and a 73.7% increase in ketorolac use (Duncan et al., 2019). Importantly, Duncan et al. reported no significant difference in patient satisfaction before or after the implementation of the protocol. The Colorado chapter of the ACEP includes the non-opioid first protocol used by Duncan et al. in their 2017 guidelines (Colorado Chapter of the American College of Emergency Physicians, 2017).

The other study only had 17 patients, but all were treated with the non-opioid first protocol (Cohen et al., 2015). Interestingly, by 30 minutes, 41% of patients had at least a

30% reduction in pain, 83% were satisfied with their pain relief, and only one patient throughout the entire study period received rescue analgesia. This is with a median initial pain score of 8 out of 10. Ketorolac, acetaminophen, and oral ibuprofen were the three most common analgesics administered (Cohen et al., 2015). As mentioned in the *Limitations in Reported Literature* section, the generalizability of these results to EMS is limited due to the use of a wide variety of analgesics not available to EMS.

Despite the limitations, both studies demonstrate the success of a non-opioid first protocol. These studies, the current recommendations made, and the discussion regarding the application of the recommendations to EMS in conjunction with the information presented throughout this review presents compelling evidence that non-opioid analgesics should be administered as first-line treatment by EMS in specific situations. A potential EMS protocol incorporating considerations made throughout this review and allowing for the application of all recommendations made is presented in Figure 1. Only specific information supported by the review is included in the protocol. Although one of the recommendations allowed for use in patients 16 years old and older, the figure only delineates between adult (18 years and older) and pediatric (under 18 years old) to simplify the EMS protocol. This protocol would be added in addition to the existing pain management protocols for an EMS system that details the contraindications and additional doses and routes of administration allowed for each analgesic. As mentioned previously, education should be provided to the EMS providers to maximize the benefit the protocol may have to patients.

**EMS Acute PAIN Analgesic Priorities** *PAIN: Pain Algorithm Integrating Non-opioids*

**Important:** Indicated in patients reporting acute pain. Contraindicated in cardiac related pain.

**Doses: Check for contraindications**

- Acetaminophen: 1000 mg IV
- Ketorolac: 10 mg IV
- Nitrous oxide: 50% administered by patient
- Ketamine: 0.3 mg/kg IV over 15 minutes or 1 mg/kg IN

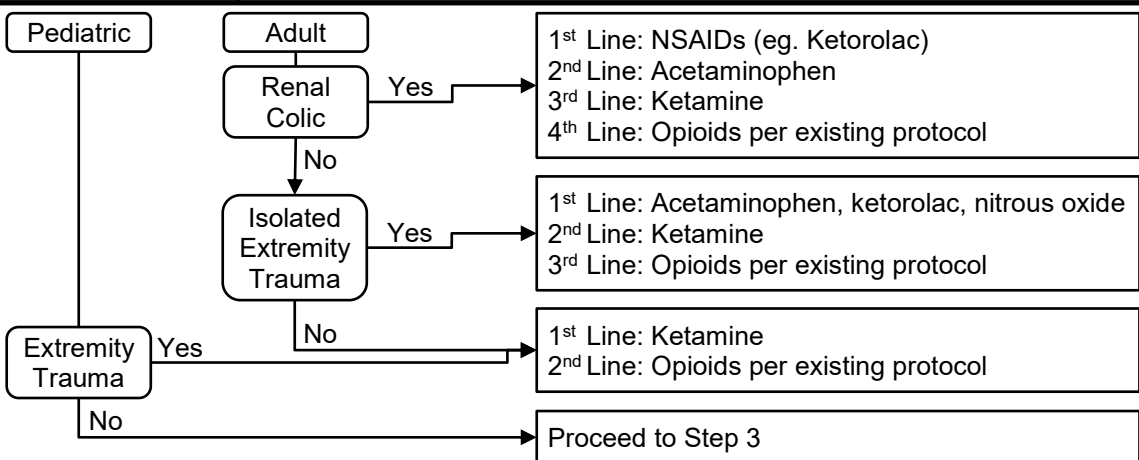
**Note:** May consider other doses/routes if existing protocols allow.

**Step 1 Determine Starting Point**

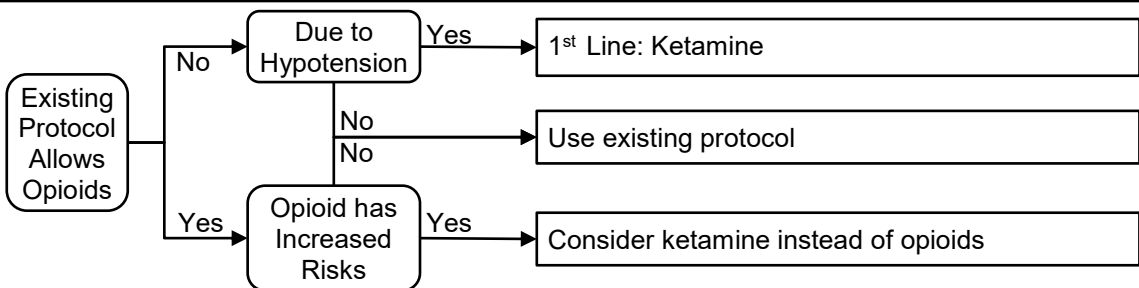
Any apply, start at Step 3. None apply, Step 2.

- Patient is in extremis
- Patient sustained multisystem trauma

**Step 2 Etiology Based Treatment Recommendations**



**Step 3 Consideration of Risks Based Treatment Recommendations**



**Notes**

- Renal colic: typically, acute onset unilateral flank pain, may radiate to groin ipsilaterally, and hematuria present in most cases.
- Increased risks for opioids: concern for hemodynamic or respiratory depression effects of opioids, opioid addiction relapse, opioid tolerance, or use of opioid abuse/addiction treatment medication (eg. methadone).
- Ketamine IV preferred when possible as slow infusion decreases adverse effects.
- Consider other non-opioids before ketamine and opioids if allowed by existing protocols.
- No minimum pain requirement for ketamine due to subjective nature of pain reporting. However, adverse effects should be weighed against pain severity and discomfort.

**Figure 1. EMS Acute PAIN Analgesic Priorities.** EMS specific Pain Algorithm Integrating Non-opioids (PAIN) that applies information contained in this review; intended as an adjunct to a preexisting pain management protocol. *IN* – Intranasal, *IV* – Intravenous.

## **Limitations and Future Research**

There are several limitations of this thesis. This is a literature review and no prospective research was conducted. As such, the thesis is dependent on the quality of the results and information contained in the current published literature. This was also not a rigorous meta-analysis and the literature presented in the report of current literature does not represent every published study. Publications that were not available in English and publications that could not be accessed in full were not used in the *Report of Current Literature* section of this thesis, with one exception. There were two subgroup analysis publications that were only accessible in abstract (Coffey et al., 2018a, 2018b). However, these abstracts were used in the report of current literature as the initial study was available in full.

Care was taken to consider high quality evidence, but there were various limitations and weaknesses present in the reported literature. The first major limitation was the paucity of EMS research, especially regarding pain management. Secondly, the inherent difficulty of objectively measuring a patient's pain, which is itself a largely subjective process, further impedes research on this subject. The subjective nature of pain and adequate pain control also increases the difficulty of establishing clinically relevant outcome measures. Other limitations specific to each study were discussed in the *Limitations in Reported Literature* section and taken into consideration when making conclusions. However, the ability to generalize the results of the published literature to EMS further limited the conclusions that could be supported. Multimodal analgesia is another important consideration in pain management. However, this thesis specifically

investigated single agent comparisons. Due to these various limitations, the conclusions made in this thesis should not be relied on as the sole source of information when selecting an analgesic to administer. Rather, this thesis should provide a guide used as a part of the decision-making process to select an appropriate analgesic.

Given the importance of pain management in EMS and the high rates of inadequate pain management, research in this topic should continue being performed. It is evident that more EMS specific research is required. There are several topics of research that should be conducted or expanded on given the information noted in this thesis. More comprehensive outcome measures that better represent the complex and subjective nature of the pain experience should be investigated. Special attention should be given to the identification of adequate pain management, while considering the current recommendations that goals should be patient specific, realistic, and consider the many complex factors at play in a patient's pain experience. Those outcome measures should then be utilized in future research endeavors to allow for the most clinically relevant results and comparison between studies. Those future endeavors should include a patient population that covers a wider range of the patients treated by EMS for acute pain. There is also a need for research into the pediatric patient population. These research studies should include investigating the efficacy of different analgesics and comparisons between various analgesics in the diverse EMS specific patient population.

## CONCLUSION

The high prevalence of acute pain reported in EMS patients, the lack of adequate pain management reported, and many calls to improve analgesia have made the importance of this topic clear. The severity of the opioid epidemic has placed additional pressures on healthcare providers at all scopes of practice to utilize opioid alternatives while attempting to improve the quality of pain management provided to patients. This literature review sought to determine if non-opioid analgesics can be utilized as first line treatment for EMS patients with acute pain.

Due to the paucity of research relevant to this topic, a general recommendation for non-opioid analgesics cannot be supported. However, more specific suggestions can be supported by the reported literature. In addition to existing recommendations that NSAIDs be used as first line treatment for patients with acute renal colic pain, this literature review supports the use of acetaminophen over opioid analgesics for these patients. The use of acetaminophen, ketorolac, and nitrous oxide as first line treatment by EMS for patients with acute pain resulting from an isolated extremity trauma is also supported.

Some conclusions regarding ketamine were also supported. Specifically, in pediatric patients with an acute extremity injury, EMS should consider ketamine over opioid analgesics. A more general and stronger suggestion can be made for adult patients. Ketamine should be considered by EMS for use as first line treatment over opioid analgesics. Both ketamine conclusions are strengthened in patients where opioid addiction relapse, opioid dependence, or the negative hemodynamic and respiratory drive

effects of opioid analgesics are of heightened concern. Patients in extremis and patients below the age of 16 years old are not well represented and are excluded from all these conclusions, except for the pediatric specific suggestion for ketamine.

An EMS protocol was proposed that summarized the recommendations and considered the important applicability aspects discussed. Potential implications of both exclusive opioid analgesic use and non-opioid analgesic use by EMS were also considered. The importance of EMS education, in addition to non-opioid protocols, was discussed. It is important to note that a suggestion for first-line treatment is not suggesting exclusive or sole use of that analgesic. It is only suggesting that it be considered first, prior to other analgesics. This thesis provides a guide to be used as a part of the decision-making process to select an appropriate analgesic rather than the sole source informing the decision. Due to the paucity of research, further research on this important topic may either strengthen or disprove one or more of these conclusions and is needed to improve the quality of acute pain management provided by EMS.

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**CURRICULUM VITAE**

