EMERGENCY NURSES ASSOCIATION

Clinical Practice Guideline: Intranasal Medication Administration

How effective is the intranasal medication administration route for emergency care patients?

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Background and Significance

Timely medication administration for patients presenting to the emergency department (ED) is essential and requires ED practitioners to access the quickest, safest, and most effective delivery route. Medication administration routes are affected by numerous variables, including the patient's overall health status, the patient's age, parent/patient/staff preference(s), and the providers' level of knowledge about pharmacological properties (Mudd, 2011). Valuable time can be lost in medication administration if multiple attempts are required to obtain IV access (Del Pizzo & Callahan, 2014; Robinson & Wermeling, 2014). Modern medicine has relied on oral, intramuscular, and intravascular medication administration routes, yet for centuries different cultures throughout the world have used the intranasal route of delivery (Stephen, Lingenfelter, Broadwater-Hollifield, & Madsen, 2012). The use of intranasal (IN) medication administration has received considerable attention in recent years (Del Pizzo & Callahan, 2014), resulting in evidence demonstrating IN medication administration is a safe and effective method for treating patients in the emergency setting.

Medications suitable for intranasal use must be water-soluble, molecularly small enough to be able to permeate the nasal mucosa, and potent enough to be effective in small doses (Humphries & Eiland, 2013). For example, the IN route of opioid administration shows great promise as an alternative to the traditional routes of medication administration, is applicable to both adult and pediatric patients, and is useful in both the in-hospital and out-of-hospital settings, thereby offering a valuable alternative to patients in whom intravenous (IV), oral, or other access is problematic (Prommer & Thompson, 2011). The advantages of IN administration include avoidance of painful injection, avoidance of risks associated with IV access, rapid onset, and high levels of patient acceptability (Merlin et al., 2010). Additionally, because body type does not affect IN medication absorption, the IN route may be advantageous in the obese population (Corrigan, Wilson, & Hampton, 2015).

Metabolically, IN administration bypasses gastrointestinal and hepatic pre-systemic elimination, thereby allowing for an almost immediate effect (Hansen & Dahl, 2013). When an intranasally administered medication makes contact with the nasal mucosa it is absorbed and delivered directly to the cerebral spinal fluid (CSF) and brain via the olfactory nerve pathway, bypassing the blood-brain barrier (Corrigan et al., 2015).

NASAL ANATOMY AND PHYSIOLOGY

The nose is a complex multifunctional organ where the cleansing of inhaled air occurs and the complex olfactory processes begin (Bitter, Suter-Zimmermann, & Surber, 2011). The nose is composed of a bony and cartilaginous foundation where the nasal septum separates the nose into two cavities that posteriorly join the pharynx as the choanae (Del Pizzo & Callahan, 2014). There are three main areas, each with distinct functionalities: the vestibular area, the olfactory area, and the respiratory area (Bitter et al., 2011). The nasopharynx, located in the posterior region of the nasal cavity, consists of ciliated cells and squamous epithelium and is also considered part of the immune system (Bitter et al., 2011). The nasal mucosa has a rich blood supply that contributes to efficient drug absorption and transport to systemic circulation (Robinson & Wermeling, 2014), including bypassing, the blood-brain barrier and first-pass hepatic metabolism. Arterial blood comes from the terminal branches of the internal and external carotid arteries, the maxillary artery, and the ophthalmic artery, while venous drainage is facilitated through the facial vein, retromandibular vein, and internal jugular vein (Del Pizzo & Callahan, 2014). The internal jugular vein empties directly into the superior vena cava, leading to the heart and eventually the systemic circulation, bypassing first-pass hepatic metabolism (Del Pizzo & Callahan, 2014).

INTRANASAL MEDICATION ADMINISTRATION

Intranasal drug administration is noninvasive, essentially painless, offers a rapid onset of therapeutic effects (Bitter et al., 2011), and is useful in the pre-hospital setting and ED. Medications of appropriate molecular character and concentration delivered intranasally are rapidly absorbed through the capillary network and delivered to the systemic circulation (Corrigan et al., 2015). For optimal absorption and effectiveness, medications administered intranasally should be prepared in volumes of less than 1 mL per nostril (Kerr, Kelly, Dietze, Jolley, & Barger, 2009). Class I (high permeability, high solubility) drugs according to the biopharmaceutical drug classification system have the highest potential for nasal delivery (Bitter et al., 2011). Intranasal medication administration is relatively easy to perform and reduces the discomfort associated with intramuscular or intravenous approaches (Jia, Chen, Hu, & Li, 2013).

Indications: The IN route provides rapid delivery of emergency medications where other routes may be difficult or time-consuming, especially in patients with a history of chronic drug abuse, and malnourished, dehydrated, or pediatric patients (Corrigan et al., 2015). Medications for sedation, analgesia, and the treatment of migraines, opioid overdose, seizures, and breakthrough pain in patients with cancer have all been shown to be effective when administered intranasally (Doe-Simkins, Walley, Epstein, & Moyer, 2009; Pavis et al., 2002).

Contraindications: Contraindications to intranasal administration include nasal septal abnormalities, nasal trauma, epistaxis, excessive nasal mucus or blood, and intranasal damage (Corrigan et al., 2015; Robinson & Wermeling, 2014). Recent use of nasally administered vasoconstrictors such as cocaine, oxymetazoline (used in nasal sprays), and phenylephrine may limit the absorption of IN administered medications (Corrigan et al., 2015).

Table 1: Intranasal Medication Administration-Summary

Advantages	Disadvantages
Easily accessible, non-invasive, painless	Nasal irritation
Rapid and quick onset of action	Mucocilliary clearance
Avoids drug degradation due to GI Tract	Enzymatic barrier to permeability of drug
Bypass first-pass metabolism	Restricted delivery volume
Bypass the blood-brain barrier	High molecular weight compounds cannot be delivered
Higher bioavailability and lower dose requirement	Local side effects and irreversible damage of cilia
Lower risk of overdose	
Minimal side effects due to low dose	
No complex formulation requirement	
No sterility conditions to be maintained	

Adapted from Mundlia, Kumar, & Amardeep, 2015

INTRANASAL MEDICATION DELIVERY SYSTEMS

There are several methods for administration of medications using the intranasal route (Humphries & Eiland, 2013; Kälviäinen, 2015; Wermeling, 2009; Wolfe & Braude, 2010). All methods share some commonalities in requirements for effective medication delivery. First, concentrated doses in small volumes must be used because volumes greater than 1 mL per nare are not reliably absorbed and often result in medication runoff (Wermeling, 2009; Wolfe & Braude, 2010). The ideal volume for intranasal medication administration is 0.2–0.3 mL per nare (Del Pizzo & Callahan, 2014). Medication molecules need to be water soluble and small enough to permeate the nasal mucosa (Humphries & Eiland, 2013). Doses can be split between nares to maximize surface area for absorption (Wolfe & Braude, 2010). If the dose exceeds 1 mL per nare, then it is recommended that the dose be split into partial doses with a period of at least a few minutes between administrations to allow for improved absorption and to prevent runoff (Del Pizzo & Callahan, 2014; Wolfe & Braude, 2010). Additionally, the more surface area that is used in the intranasal administration, the better the absorption; therefore, using a delivery adjunct like a mucosal atomization device will improve the distribution and absorption of medication (Del Pizzo & Callahan, 2014; Kälviäinen, 2015; Wermeling, 2009). Nasal congestion or excess mucous can be a barrier to medication absorption, especially when the patient is crying or seizing. Absorption can be improved by suctioning the nostril prior to medication administration (Wolfe & Braude, 2010).

Common methods used for intranasal medication delivery include dripping the solution into the nares, nasal spray, use of a mucosal atomization device, and nebulization of medication (Del Pizzo & Callahan, 2014). The dripping method is accomplished by using a small syringe to slowly drip medication solution into the nares, allowing time between drops for absorption (Del Pizzo & Callahan, 2014). This is best accomplished with the patient in the supine position. The advantage of this approach is that it is easily accomplished using a standard syringe. Disadvantages are: the absorption of medication is unreliable, it requires a compliant patient, and there is increased risk for nasal irritation and a bitter taste following medication delivery (Del Pizzo & Callahan, 2014). Spray bottles are commonly used for over-the-counter medications and some prescription medication but generally do not work well for emergency medication delivery because it is difficult to adjust doses (Wermeling, 2009).

The most common method for administering intranasal medication is a mucosal atomizer device (Del Pizzo & Callahan, 2014; Wermeling, 2009). There are a number of commercially available mucosal atomization devices, including those that can be applied directly to a Luer lock syringe. Advantages of nasal atomizers include improved absorption due to the small size of droplets being delivered and the ability to rapidly cover greater intranasal surface area (Del Pizzo & Callahan, 2014). Thomas, Miller, Couloures, and Johnson (2015) completed a systematic review analyzing extravascular administration of medications and concluded that using a mucosal atomization device (MAD) may be more effective than the dropper method. No disadvantages were identified in the use of atomizer devices for intranasal medication delivery.

Intranasal medication administration also can be accomplished using nebulization. Advantages of this delivery method include a lower incidence of nasal irritation and less incidence of bitter taste. Disadvantages include medication distribution to the mouth, pharynx, and lungs, and the potential for lower medication absorption (Del Pizzo & Callahan, 2014). No studies in humans were identified that evaluated the efficacy of these different delivery methods; therefore, evidence-based recommendations for delivery devices and methods are not included in this Clinical Practice Guideline.

Methodology

This CPG was created based on a thorough review and critical analysis of the literature following ENA's "Requirements for the Development of Clinical Practice Guidelines." All articles and published abstracts relevant to the topic were identified in a comprehensive literature search. The following databases were searched: MEDLINE, PubMed, CINAHL, Cochrane, Joanna Briggs, and Google Scholar. Searches were conducted using a combination of the search terms: *Intranasal medication administration, emergency, adult, pediatric, children, and prehospital.* Searches were limited to English language articles on human subjects from 2005–April 2016. In addition, the reference sections of the selected articles were scanned for pertinent research findings. Following an initial search, the literature was searched a second time using specific medications including *fentanyl, morphine, diazepam, lorazepam, sufentanil, hydromorphone, glucagon, naloxone, ketamine, ketorolac,* and *midazolam* combined with intranasal administration. Older studies (going back to January 2000) related to specific medications were included when there were inadequate more recent studies to address the PICOT question. Meta-analyses, systematic reviews, and research articles from ED settings, non-ED settings, position statements, and guidelines from other sources were reviewed. Clinical findings and levels of recommendation regarding patient management were made by the Clinical Practice Guideline Committee according to ENA's classification of levels of recommendation for practice (Table 2). The articles reviewed to formulate the recommendations in this CPG are described in Appendix 3.

Table 2. Levels of Recommendation for Practice

Level A recommendations: High
• Reflects a high degree of clinical certainty • Based on availability of high-quality level I, II, and/or III evidence rated using the Melnyk and Fineout-Overholt grading system (Melnyk & Fineout-Overholt, 2015) • Based on consistent and good quality evidence; has relevance and applicability to emergency nursing practice • Is beneficial
Level B recommendations: Moderate
• Reflects moderate clinical certainty • Based on availability of Level III and/or Level IV and V evidence rated using the Melnyk and Fineout-Overholt grading system (Melnyk & Fineout-Overholt, 2015) • There are some minor inconsistencies in quality evidence; has relevance and applicability to emergency nursing practice • Is likely to be beneficial
Level C recommendations: Weak
• Has limited or unknown effectiveness • Level V, VI, and/or VII evidence rated using the Melnyk and Fineout-Overholt grading system (Melnyk & Fineout-Overholt, 2015) - Based on consensus, usual practice, evidence, case series for studies of treatment or screening, anecdotal evidence, and/or opinion • There is limited or low quality patient-oriented evidence; has relevance and applicability to emergency nursing practice
Not recommended for practice
• No objective evidence or only anecdotal evidence available; or the supportive evidence is from poorly controlled or uncontrolled studies • Other indications for not recommending evidence for practice may include: ◦ Conflicting evidence ◦ Harmfulness has been demonstrated ◦ Cost or burden necessary for intervention exceeds anticipated benefit ◦ Does not have relevance or applicability to emergency nursing practice • There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. For example: ◦ Heterogeneity of results ◦ Uncertainty about effect magnitude and consequences ◦ Strength of prior beliefs ◦ Publication bias

Summary of Literature Review

Intranasal medication administration is advantageous for patients requiring analgesia, sedation, anxiolysis (antianxiety), termination of seizures, management of hypoglycemia, narcotic reversal, and benzodiazepine reversal both in the ED and pre-hospital settings when ready access to other routes may be difficult to obtain (Corrigan et al., 2015). Corrigan and colleagues (2015) completed a literature review and concluded that fentanyl, sufentanil, ketamine, hydromorphone, midazolam, haloperidol, naloxone, and glucagon may be safely and effectively administered intranasally in the emergency and prehospital settings. Studies evaluating the use of IN ketorolac, morphine, diazepam, and lorazepam are also included in this clinical practice guideline. The following is a summary of the evidence as it relates to intranasal administration utilizing specific medications and classes of medication.

ANALGESICS

Fentanyl (Opiate): Fentanyl is the most commonly administered intranasal opioid for the provision of analgesia in place of parenteral opioids (Graudins, Meek, Egerton-Warburton, Oakley, & Seith, 2015). Fentanyl is approved for the relief of postoperative pain, acute pain, procedural wound-care pain, and breakthrough pain in patients with cancer (Fortuna, Alves, Serralheiro, Sousa, & Falcão, 2014). Fentanyl alters the transmission of pain signals, diminishes the perception and emotional response to pain, and has a rapid onset, yet is short acting, with a decreased histamine release compared with morphine, and has fewer cardiovascular effects than other opioids (Mudd, 2011; Seith, Theophilos, & Babl, 2012). The pharmacokinetic profile of fentanyl makes it a suitable agent to be used intranasally, bypassing first-pass metabolism and achieving bioavailability of 70%–89% (Borland, Milsom, & Esson, 2011; Fortuna et al., 2014). The use of IN fentanyl (1.5 mcg/kg) has been associated with a reduced time to analgesic administration when compared with traditional IV morphine administration for children with acute pain (Holdgate, Cao, & Lo, 2010).

In a prospective intervention study, intranasal fentanyl (1.5 mcg/kg) was administered to children 1–3 years of age with moderate to severe pain and shown to provide effective and rapid analgesia (Cole, Shepherd, & Young, 2009). In a prospective, nonblinded interventional trial, IN fentanyl at 2 mcg/kg provided effective analgesia for patients 3–18 years old within 10 minutes of initial administration (Saunders, Adelgais, & Nelson, 2010). Karlsen, Pederson, Trautner, Dahl and Hansen (2014) conducted a prospective observational study, demonstrating IN fentanyl in doses of 50 and 100 mcg was safe, well-tolerated, and appeared to provide effective analgesia in a wide range of patients in the prehospital setting. Mudd (2011) completed a systematic review, which included a total of 12 studies, and found intranasal fentanyl is equivalent or superior to IV, IM, or orally administered morphine, and equivalent to IV-administered fentanyl in children. Murphy et al. (2014) also conducted a systematic review evaluating the safety and efficacy of IN fentanyl in children 3–15 years of age. Three studies with a total of 313 participants were identified to be included in the review. Murphy et al. (2014) found IN fentanyl "may be an effective analgesic for the treatment of patients with acute moderate to severe pain, and its administration appears to cause minimal distress to children" (p. 2). Murphy and colleagues (2016) conducted a follow-up study to evaluate the safety and efficacy of IN fentanyl in the pediatric population when administered by paramedics in the prehospital setting. This prospective cross-sectional study included 94 children between the ages of 1–16 years who were treated for acute pain in Ireland's emergency medical services. Findings from this study indicated IN fentanyl can be safely used to provide effective pain management for children in the prehospital setting (Murphy et al., 2016).

Kress et al. (2009) conducted a randomized, controlled, double-blind study evaluating the use of IN fentanyl to treat opioid-tolerant patients with cancer. Intranasal fentanyl at 50, 100, and 200 mcg was associated with an onset of analgesia within 10 minutes and was an effective treatment for breakthrough pain in this population of adult patients (Kress et al., 2009).

Findings from these studies indicate that IN fentanyl may be safely and effectively used to treat moderate to severe pain in the emergency setting. There are no commercially available fentanyl concentrations in the U.S. other than the 50 mcg/mL. Therefore, when administering a dose greater than 100 mcg (1 mL per nostril) there may be drug loss and/or decreased efficacy due to nasal runoff (Corrigan et al., 2015).

Ketamine (NMDA antagonist): Ketamine is a phencyclidine derivative used in humans for its analgesic and anesthetic properties (Afridi, Giffin, Kaube, & Goadsby, 2013; Jia et al., 2013). Intranasal ketamine (25 mg) was demonstrated to be a safe and effective treatment for reducing a prolonged aura in patients with migraine (Afridi et al., 2013). A prospective observational study of 40 adult

patients with orthopedic injuries examined the feasibility, effectiveness, and adverse effects of 0.5 mg/kg IN ketamine for analgesia in the ED. Results indicated a clinically significant reduction in visual analogue (VAS) pain scores with only minor, transient adverse effects and no changes in vital signs requiring clinical intervention (Andolfatto et al., 2013). Yeaman, Oakley, Meek, and Graudins (2013) conducted a pilot study to investigate the effectiveness of IN ketamine as an analgesic for children in the ED. Results indicated 1 mg/kg IN ketamine provided an adequate level of analgesia by 30 minutes that was maintained for more than 60 minutes (Yeaman et al., 2013). In a study of 72 adult patients presenting to the ED with pain requiring analgesia, a clinically significant VAS reduction was observed in only 56% of subjects who received 1 mg/kg of IN ketamine (Yeaman, Meek, Egerton-Warburton, Rosengarten, & Graudins, 2014). These results were not as favorable as those reported in other studies, indicating additional research is needed to evaluate the efficacy of using IN ketamine for analgesia in the emergency setting.

Ketamine and Fentanyl: Graudins, Meek, Egerton-Walburton, Oakley and Seith (2015) conducted a double-blind, randomized, controlled trial comparing the analgesic efficacy of intranasal fentanyl and ketamine in children aged 3 to 13 with isolated limb injuries and a pain score of 6 or higher during triage. A total of 80 children were enrolled in the study (40 per arm) and all participants were treated with oral ibuprofen in addition to the randomized intervention. Graudins et al. (2015) found statistically similar pain reduction for IN ketamine and IN fentanyl; however, IN ketamine was associated with a higher rate of mild, adverse events as well as sedation. Despite the increase in adverse events, IN ketamine could be considered for those who have contraindications to fentanyl or other opioids (Graudins et al., 2015).

Hydromorphone: Hydromorphone is an opiate analgesic eight times more potent than morphine. However, because of low lipophilicity, it is not considered an ideal agent for intranasal administration (Corrigan et al., 2015). There is limited evidence regarding the effectiveness of IN hydromorphone. However, in a multicenter, open-label, escalating dose-range trial, single doses of 2, 4, 6, 8, and 10 mg IN hydromorphone HCl were administered to 113 patients presenting with acute traumatic injuries. Most patients received initial pain relief within 10–15 minutes, a 30% reduction in pain intensity by 30 minutes, and 50% or greater pain intensity reduction at 60 minutes (Wermeling et al., 2010), which demonstrates IN hydromorphone at certain doses may be effective for treatment of acute pain.

Ketorolac (NSAID): Ketorolac is a nonsteroidal anti-inflammatory (NSAID) used for the treatment of inflammation and pain (Brown, Moodie, Bisley, & Bynum, 2009). No studies comparing IN ketorolac with other routes of administration in the emergency setting were identified. Intranasal ketorolac has been studied in other environments and with healthy adult volunteers, however, and Garnock-Jones (2012) completed a review of four well-designed phase II and III studies and found IN ketorolac was effective in providing short-term pain relief in postoperative adult patients, noting minimal and transient adverse effects. Drover, Hammer, and Anderson (2012) conducted an open label study analyzing the pharmacokinetics of intranasal ketorolac in adolescent surgical patients. Findings were comparable to adult studies and indicated IN ketorolac was well-tolerated, effective in managing pain, and resulted in minimal adverse effects (Drover et al., 2012). Additional studies are needed to evaluate the safety and efficacy of IN ketorolac in the emergency setting and in the pediatric population.

Morphine: Morphine is the standard opioid administered to alleviate moderate to severe pain and is one of the most hydrophilic compounds among opioid medications (Fortuna et al., 2014; Grassin-Delyle et al., 2012). Orally administered morphine is commonly recommended for the relief of breakthrough pain in patients with cancer despite the 20- to 30-minute onset of pain remission (Pavis et al., 2002). The bioavailability of a simple solution of morphine when delivered intranasally is approximately 10% compared with intravenous administration (Illum et al., 2002). To improve the bioavailability of IN morphine, the addition of chitosan, a bioadhesive linear polysaccharide that interacts with the nasal mucus layer and nasal epithelial cells, provides a longer time for drug transport across the nasal membrane (Illum et al., 2002). In phase I human clinical trials, nasal administration of 0.5% chitosan and morphine hydrochloride rapidly established peak plasma concentrations that were well-tolerated and well-accepted (Illum et al., 2002).

Stoker et al. (2008) completed a randomized, double-blind, dose-ranging study to compare the safety and efficacy of IN morphine with IV morphine and a placebo. A total of 187 healthy adult patients, 18–76 years old, undergoing bunionectomy surgery were administered 3.75 mg, 7.5 mg, 15 mg, or 30 mg IN morphine via nasal spray, 7.5 mg IV morphine, or a placebo. Results indicated both 7.5 mg and 15 mg IN morphine were effective as evidenced by decreased pain scores and tolerability. Christensen and colleagues (2008), in a randomized, double-blind clinical trial with 225 healthy volunteers experiencing moderate to severe postsurgical pain after molar extractions, found single doses of IN morphine 7.5 mg and 15 mg quickly provided reduction in pain and were safe and well-tolerated. These researchers also found IN morphine 15 mg was similar to IV morphine 7.5 mg in onset, level of analgesia, and duration of effect.

Morphine also has been studied using aerosolized medication administration. Nebulization of morphine for patients with chronic pulmonary disorders such as COPD, end-stage lung cancer, and emphysema has been used for the symptomatic treatment of dyspnea (Brown, Eichner, & Jones, 2005). Since dyspnea episodes are often short in nature, the use of drugs with a short onset are more likely to reduce a patient's distress (Bausewein & Simon, 2014). Morphine decreases the respiratory drive and is thought to act locally in the lungs to alleviate dyspnea (Brown et al., 2005). In a randomized controlled trial, Bruera and colleagues (2005) demonstrated that both nebulized and subcutaneous morphine decreased baseline dyspnea over several hours, which supports the potential use of morphine for the treatment of dyspnea. However, although individual patients may experience relief of dyspnea, current evidence does not support the use of inhaled nebulized and intranasal opioids for the treatment of dyspnea (Bausewein & Simon, 2014; Brown et al., 2005).

Sufentanil (Synthetic Opiate): Sufentanil is a synthetic opiate that is five to eight times more potent than fentanyl (Corrigan et al., 2015; Stephen et al., 2012). Sufentanil is 100% bioavailable at 30 minutes, with an onset of action within 20 minutes. IN sufentanil exhibits a lower rate of adverse respiratory effects compared with IV sufentanil (Corrigan et al., 2015). Stephen and colleagues (2012) conducted a prospective, open-label, pilot study (N = 15) in ED patients to establish a safe and effective dose of IN sufentanil when treating moderate to severe pain in patients with an isolated extremity injury. After administering IN sufentanil 0.5 mcg/kg, participants reported a 4.3-point average decrease in pain scores, maintained a Ramsay sedation score of 2 (cooperative, tranquil, and oriented), and had an average satisfaction score of 4.5 out of 5. Steenblik and colleagues (2012) conducted a nonrandomized, observational study on patients who presented with acute extremity injuries. Each participant (N = 40) was administered IN sufentanil 0.5 mcg/kg. All but two participants reported adequate pain relief, with initial average pain scores of 9 reducing by 4.7 (95% CI, 3.67–5.57) at 10 minutes, by 5.79 (95% CI, 3.67–5.57) at 20 minutes, and by 5.75 (95% CI, 4.72–6.67) at 30 minutes, with 78% of the participants reporting they were very satisfied with their pain relief. Stephen et al. (2012) and Steenblik et al. (2012) demonstrated IN sufentanil at 0.5 mcg/kg provided rapid, effective analgesia in patients with moderate to severe pain. Both studies were small, pilot studies, therefore there is insufficient evidence to make recommendations for IN sufentanil.

ANTIHYPOGLYCEMICS

Glucagon: Glucagon, which is typically administered via the subcutaneous or intramuscular route, is used as an emergency intervention to treat hypoglycemia in patients with diabetes (Pontiroli, 2015). Glucagon is primarily useful in the treatment of hypoglycemia in unresponsive patients in the out-of-hospital environment (Pontiroli, 2015; Rickels et al., 2016). Intranasal glucagon has potential indications for use in the emergency setting as well as in out-of-hospital settings. Boido, Ceriani, and Pontiroli (2014) conducted a systematic review and meta-analysis to evaluate the effectiveness of glucagon, compare glucagon and dextrose, and compare IN glucagon with parenteral glucagon. Findings from this study reinforced that glucagon administered via all routes has variable efficacy and may require a second dosing to achieve intended outcomes. Five studies were reviewed to evaluate the effectiveness of intranasal glucagon in addressing hypoglycemia, finding IN glucagon administration has similar efficacy to IM glucagon (Boido et al., 2015). Additionally, the authors concluded IN glucagon may be easier for lay caregivers to administer in the out-of-hospital setting (Boido et al., 2015). Rickels et al. (2016), completed a randomized, crossover, non-inferiority study comparing IN glucagon with IM glucagon in 75 adult patients with type I diabetes who had hypoglycemia induced with IV insulin in a controlled environment. In this study, IN glucagon was determined to be effective in correcting insulin-induced hypoglycemia in adult type I diabetic patients and resulted in minimal adverse effects, including facial and head discomfort (Rickels et al., 2016).

BENZODIAZEPINES

Diazepam: In the treatment of seizures, diazepam is a widely used benzodiazepine that is usually administered intravenously (Thakker & Shanbag, 2013). There are a number of studies available that evaluate the efficacy of rectal diazepam in the treatment of seizures; however, research on the use of intranasal diazepam is sparse, especially in comparison with traditional administration routes. Only one study was found that compared intravenous or rectal diazepam with intranasal diazepam. Inokuchi and colleagues (2015) conducted a retrospective cohort study comparing the efficacy of intranasal diazepam with intravenous diazepam in 19 elderly patients with seizures and a history of stroke, and concluded intranasal diazepam was administered about nine times faster than intravenous diazepam (1 vs. 9.5 minutes from arrival to medication delivery, $p = 0.001$) and resulted in a reduction in time from seizure onset to cessation of seizure activity of three minutes (IN administration) compared to 9.5 minutes in the intravenous diazepam group ($p = 0.03$). This small study provides some initial evidence that intranasal diazepam is faster to administer and appears to be a safe and effective method for delivering diazepam for adult seizure patients (Inokuchi et al., 2015).

Two additional studies were analyzed that evaluated the dosing feasibility, pharmacokinetics, and adverse effects of IN diazepam. Sperling et al. (2014) completed a small, multicenter, open-label study of adult epilepsy patients who were in epilepsy monitoring units to determine their candidacy for surgery or for adjustment of antiepileptic medications. A total of 31 patients were enrolled that required treatment for seizures. These patients received a single, weight-based dose of IN diazepam and had drug assays drawn at baseline, 10, 15, 30, and 45 minutes, followed by draws at 1, 1.5, 2, 4, 6, 9, and 12 hours. Study findings indicated that IN diazepam can be safely administered in therapeutic concentrations during the convulsive and postictal phase of tonic-clonic seizures (Sperling et al., 2014). Agarwal, Kriel, Brundage, Ivaturi, and Cloyd (2013) completed a study evaluating the bioavailability and pharmacokinetics of IN diazepam in 24 healthy adult volunteers. This randomized, three-way crossover, open-label study compared commercially available parenteral diazepam (5 mg) with two intranasal formulations (10 mg) and found that both intranasal formulations were well-tolerated and had high levels of bioavailability. Agarwal et al. (2013) concluded that the development of an effective intranasal diazepam formulation is feasible. Preliminary evidence suggests that diazepam can be safely and effectively delivered via the intranasal route; however, further research is needed to strengthen the evidence for the use of IN diazepam in the emergency setting.

Midazolam: Midazolam is the first water-soluble benzodiazepine with a rapid onset of action and a relatively short duration, and tends to accumulate less than other benzodiazepines (Thakker & Shanbag, 2013). Thakker and colleagues (2013) completed a randomized controlled trial designed to compare the safety and efficacy of 0.2 mg/kg IN midazolam with 0.3 mg IV diazepam for the treatment of acute seizures in children. They found no statistically significant differences ($p > 0.05$) between IN midazolam and IV diazepam. In a randomized controlled trial seeking to determine if using an atomizer to aerosolize midazolam (IN or buccal) would decrease distress during pediatric laceration repairs, 169 children were assigned to either 0.5 mg/kg oral midazolam or 0.3 mg/kg midazolam given intranasally or buccally (Klein, Brown, Kobayashi, Osincup, & Seidel, 2011). The IN route demonstrated a quicker sedation onset, a greater proportion of subjects achieving adequate sedation, and a higher parental satisfaction despite a greater proportion of subjects having difficulty accepting the medication and a greater issue with irritation. Adverse events were similar between all three groups. Intranasal administration of atomized midazolam appears to be a reliable and effective drug delivery method (Klein et al., 2011) and has been shown to be safe and effective for the management of acute seizure activity in children (Humphries & Eiland, 2013; Thakker & Shanbag, 2013).

Lorazepam: Lorazepam is a benzodiazepine commonly used for the treatment of seizure disorders and anxiety, yet there are limited studies comparing IN lorazepam with other anticonvulsants. In a randomized, open-label study designed to compare the efficacy and adverse effects of IN vs. IV lorazepam, 141 children, aged 6–14, received either 0.1 mg/kg (0.05 mL/kg) IN or IV lorazepam (Arya, Gulati, Kabra, Sahu, & Kalra, 2011). The primary outcome measure was the cessation of clinically visible seizure activity within 10 minutes of receiving the initial lorazepam dose. There was no statistically or clinically significant difference between seizure remission as evidenced by 1–36 min (median 3 min) for IV lorazepam and 1–25 min (median 3 min) for IN lorazepam. These results demonstrate IN lorazepam is not inferior to IV lorazepam and support the assumption that IN lorazepam appears to be safe and efficacious for the control of seizures in children. More research is needed to determine the safety and efficacy of IN lorazepam.

NARCOTIC ANTAGONIST

Naloxone: Naloxone is an opioid antagonist that reverses the acute effects of opioids and has been shown to be an effective initial treatment of heroin overdoses in the community (Kerr, Dietze, & Kelly, 2008). Merlin and colleagues (2010) performed a retrospective chart review of 343 patients experiencing an opioid overdose in the prehospital setting. They demonstrated IN naloxone was as effective at reversing the effects of the opioid overdose as the intravenous route. Kerr et al. (2009) completed an RCT of 172 patients with a possible opioid overdose in the prehospital setting. Intranasal naloxone successfully reversed heroin overdoses 82% of the time with no statistically different mean response times (IN 8.0 minutes, IM 7.9 minutes). Kerr and colleagues (2009) emphasize these results demonstrate the IN naloxone route has a similar effectiveness to the IM naloxone route and is an effective treatment for heroin overdoses in the prehospital setting.

Description of Decision Options/Interventions and the Level of Recommendation

Conclusion and recommendations regarding the use of intranasal medication administration during the period of emergency care.

Level A recommendations: High
1. IN fentanyl can be safely and effectively used in the emergency setting to treat moderate to severe pain in adults and children aged 1–18 (Cole, Shepherd, & Young, 2009; Holdgate, Cao, & Lo, 2010; Karlsen et al., 2014; Kress et al., 2009; Murphy et al., 2016; Murphy et al., 2014).
Level B recommendations: Moderate
1. IN ketamine may be a safe and effective intervention for managing pain in the emergency setting (Andolfatto et al., 2013; Graudins et al., 2015; Yeaman et al., 2014; Yeaman et al., 2013). 2. IN midazolam, when atomized (Klein et al., 2011), has been shown to be safe and effective for the management of acute seizure activity in children (Humphries & Eiland, 2013; Thakker & Shanbag, 2013). 3. IN naloxone can be administered as a safe and effective agent for reversing the acute effects of opioids (Kerr et al., 2008; Merlin et al., 2010).
Level C recommendations: Weak
1. IN diazepam may be a safe and effective method for treating acute seizures in adult patients (Arya et al., 2011; Inokuchi et al., 2015). 2. IN glucagon is non-inferior to IM glucagon in clinical safety and efficacy for treating acute hypoglycemia (Boido et al. 2015; Rickels et al., 2016). 3. IN ketorolac may be safely and effectively used for treatment of short-term acute pain in adults and adolescent patients (Drover et al., 2012). 4. IN lorazepam may be safe and efficacious for the control of seizures in children (Arya et al., 2011). 5. IN morphine provides pain reduction and is safe and well-tolerated in adult patients (Christensen et al., 2008; Stoker et al., 2008)
Insufficient Evidence
1. There is insufficient evidence to recommend IN hydromorphone in the emergency setting (Wermeling et al., 2010). 2. There is insufficient evidence to recommend IN sufentanil in the emergency setting (Stephen et al., 2012 and Steenbilk et al., 2012). 3. There is insufficient evidence to recommend a commercially available device or method for intranasal medication administration. Expert opinion indicates using a mucosal atomization device may be more effective than the dripping method (Thomas et al., 2015).

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Appendix 1: Evidence Table

Reference	Research Purpose Questions/Hypothesis	Design Sample/Setting	Variables/Measures Analysis	Findings/Implications	Quality of Evidence	Level of Evidence
Afridi, S. K., Giffin, N. J., Kaube, H., & Goadsby, P. J. (2013). A randomized controlled trial of intranasal ketamine in migraine with prolonged aura. *Neurology*, *80*(7), 642–647. doi:10.1212/WNL.0b013e3182824e66	To test if Ketamine would affect the aura in patients with migraine headaches.	Double-blinded, randomized parallel-group controlled study 18 subjects Clinic	Duration and severity of aura. Composite severity scale. Primary endpoint was a reduction in either the length or severity of aura.	The median difference in duration of attacks was three hours (2–46, N = 9) shorter with ketamine. Ketamine can be used in clinically appropriate settings in outpatients. "Intranasal ketamine 25 mg is a safe and effective treatment for prolonged aura that is useful for patients and provides support for glutamatergic hypotheses around migraine and its relationship to cortical spreading depression (CSD)."	II	II
Andolfatto, G., Willman, E., Joo, D., Miller, P., Wong, W. B., Koehn, M., … Moadebi, S. (2013). Intranasal ketamine for analgesia in the emergency department: A prospective observational series. *Academic Emergency Medicine*, *20*(10), 1050–1054. doi:10.1111/acem.12229	To examine the feasibility, effectiveness, and adverse effect profile of intranasal ketamine for analgesia in the ED.	Prospective, descriptive study Convenience sample N = 40 Community teaching hospital Enrolled patients > 6 years old with VAS of 50 or higher. Q 5 minutes for 30 minutes then Q 10 minutes for 30 minutes – VAS	100 mm Visual Analogue Scale (VAS) Side effects rating scale for dissociative anesthetics (SERSDA), Nasal irritation 1–10 scale Pain relief satisfaction 1–10	Reductions in VAS scores were statistically significant at all time points ($p < 0.001$). Adverse events were transitory .	II	IV
Arya, R., Gulati, S., Kabra, M., Sahu, J. K., & Kalra, V. (2011). Intranasal versus intravenous lorazepam for control of acute seizures in children: A randomized open-label study. *Epilepsia*, *54*(4), 788–793. doi:10.1111/j.1528-1167.2010.02949.x	To compare the efficacy of IN lorazepam with IV lorazepam in children aged 6–14 who presented with acute seizures.	Randomized open label non-inferiority study 141 subjects Teaching hospital	Primary outcome measure: cessation of all visible seizure activity within 10 minutes. Secondary outcome: persistent cessation of seizure activity to one hour, time to IV start, time to cessation of seizures, adverse effects.	IN lorazepam is comparable in efficacy to IV lorazepam. Cessation of seizures in 10 minutes was 80% for IV lorazepam and 83% in IN lorazepam ($p = 0.635$). One hour cessation of seizures was 58.57% for IV lorazepam and 61.97% for IN lorazepam ($p = 0.680$). Study was underpowered for adverse effect determination.	I	II

Appendix 1: Evidence Table

Reference	Research Purpose Questions/Hypothesis	Design Sample/Setting	Variables/Measures Analysis	Findings/Implications	Quality of Evidence	Level of Evidence
Boido, A., Ceriani, V., & Pontiroli, A. E. (2015). Glucagon for hypoglycemic episodes in insulin-treated diabetic patients: A systematic review and meta-analysis with a comparison of glucagon with dextrose and of different glucagon formulations. *Acta Diabetologica*, *52*(2), 405–412. doi:10.1007/s00592-014-0665-0	Evaluate research on the effectiveness of glucagon alone, comparison of glucagon and dextrose, and comparison of IN glucagon with injectable route of administration.	Systematic review and meta-analysis Sample: Three groups of studies, group 2 and 3 only used controlled studies	16 studies included for the three study areas: 1) efficacy of glucagon, 2) comparison of glucagon and dextrose, and 3) comparison of IN glucagon with injectable glucagon. Used PRISMA guidelines with established criteria and assessment of publication bias. Odds ratio with 95% CI used for intervention effect; Wald test, meta regression.	IN glucagon has comparable efficacy to injected glucagon for the treatment of hypoglycemia.	I	I
Borland, M., Milsom, S., & Esson, A. (2011). Equivalency of two concentrations of fentanyl administered by the intranasal route for acute analgesia in children in a paediatric emergency department: A randomized controlled trial. *Emergency Medicine Australasia*, *23*(2), 202–208. doi:10.1111/j.1742-6723.2011.01391.x	What are the comparative effects of a standard concentration IN fentanyl to the highly concentrated IN fentanyl? If equivalency is proven, then the standard solution can be recommended for intranasal use.	Double-blinded randomized clinical trial	N = 189 Pre- and Post-analgesia pain scores (0, 10, 20, 30 min post initial IN fentanyl dose)	Each agent (SIN fentanyl 50 ug/mL or HIN fentanyl 300 ug/mL) demonstrated a statistically and clinically significant decrease in pain scores over the study time. The SIN fentanyl group had significantly more additional analgesia. Side effects were minimal over the time of the study.	II	II
Brown, C., Moodie, J., Bisley, E., & Bynum, L. (2009). Intranasal ketorolac for postoperative pain: A phase 3, double-blind, randomized study. *Pain Medicine*, *10*(6), 1106–1114. doi:10.1111/j.1526-4637.2009.00647.x	To evaluate the analgesic efficacy and tolerability of IN ketorolac.	Double-blinded randomized clinical trial N = 300	Global evaluation of pain [(0) (poor) to 4 (excellent)] scale, mean morphine sulfate usage, quality of analgesia ratings. Powered to 90%. Multiple statistical methods, including ANOVA, two-group t-test, chi-square, and Wilcoxon rank sum.	IN ketorolac was well-tolerated and associated with a rapid onset of analgesia. There was a decreased use of morphine in the ketorolac group. Administration of IN ketorolac is well-tolerated.	I	II

Appendix 1: Evidence Table

Reference	Research Purpose Questions/Hypothesis	Design Sample/Setting	Variables/Measures Analysis	Findings/Implications	Quality of Evidence	Level of Evidence
Christensen, K. S., Coen, A. E., Mermelstein, F. H., Hamilton, D. A., McNicol, E., Babul, N., & Carr, D. B. (2008). The analgesic efficacy and safety of a novel intranasal morphine formulation (morphine plus chitosan), immediate release oral morphine, intravenous morphine, and placebo in a postsurgical dental pain model. *Anasthesia and Analgesia*, *107*(6), 2018–2024. doi:10:1213/ane.0b013e318187b952	To assess the efficacy and safety of a single dose of IN morphine with chitosan relative to placebo for treatment of moderate-to-severe pain after third molar extraction.	Two-center, single-dose, randomized, double-blind, active-comparator and placebo-controlled parallel-group	Vital signs, pulse oeimetry 100 mm VAS and categorical pain scale, pain intensity and pain relief assessed at 5, 10, 15, 20, 30, and 45 min and 1, 1.5, 2, 3, 4, 5, and 6 hours after drug administration. Power analysis calculated at a 5% significance level (2-sided).	IN 7.5 mg morphine separated from placebo at 45 min and 1 hour. IN 15 mg separated from placebo as early as 5 minutes and remained superior at all subsequent time points except 3 hours. IN morphine 15 mg presented an efficacy profile similar to that of IV morphine 7.5 mg. Study medications were well tolerated. IN morphine 15 mg and IV morphine 7.5 mg had earlier onset of action than IN morphine 7.5 mg or oral morphine 60 mg. IN morphine 15 mg provided similar onset, level of analgesia, and duration of effect as IV morphine 7.5 mg. IN morphine may offer a convenient, rapid- onset, noninvasive alternative to IV morphine.	II	I
Cole, J., Shepherd, M., & Young, P. (2009). Intranasal fentanyl in 1-3-year-olds: A prospective study of the effectiveness of intranasal fentanyl as acute analgesia. *Emergency Medicine Australasia*, *21*(5), 395–400. doi:10.1111/j.1742-6723.2009.01216.x	To determine the effectiveness if IN fentanyl as analgesia in children aged 1–3 years with acute moderate to severe pain presenting to the ED.	Prospective, intervention study Convenience sample, N = 46 Two pediatric EDs in New Zealand	FLACC scale, heart rate, respiration, oxygen saturation, and AVPU	Median FLACC score before IN fentanyl administration was 8 (IQR 5–10) and decreased to 2 (IQR 0–4) at 10 min post IN fentanyl and 0 (IQR 0–2) at 30 minutes. Following IN fentanyl administration, heart rate, respiratory rate, and oxygen saturations did not decrease below the agree-related normal range for any child.	II	IV
Drover, D. R., Hammer, G. B., & Anderson, B. J. (2012). The pharmacokinetics of ketorolac after single postoperative intranasal administration in adolescent patients. *Anesthesia & Analgesia*, *114*(6), 1270–1276. doi:10.1213/ANE.0b013e31824f92c2	Determine pharmokinetics of a single dose of IN ketorolac in adolescents.	Open label clinical trial Convenience sample = 20 post-op patients age 12–17 Post-operative hospital setting	Participants received a single dose of IN ketorolac (either 15 mg or 30 mg, depending on weight) and had blood samples drawn at baseline, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours after dose	IN ketorolac resulted in rapid increase in plasma concentration with minimal adverse effects. IN ketorolac was well tolerated by this study cohort.	II	IV

Appendix 1: Evidence Table

Reference	Research Purpose Questions/Hypothesis	Design Sample/Setting	Variables/Measures Analysis	Findings/Implications	Quality of Evidence	Level of Evidence
Graudins, A., Meek, R., Egerton-Warburton, D., Oakley, E., & Seith, R. (2015). The PICH-FORK (pain in children fentanyl or ketamine) trial: A randomized controlled trial comparing intra-nasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries. Annals of *Emergency Medicine*, *65*(3), 248–254. doi:10.1016/j.annemergmed.2014.09.024	Comparison of the analgesic effectiveness of intranasal fentanyl and ketamine in children.	Double-blind, randomized, intention to treat Convenience sample, N = 73 Pediatric ED, mixed ED, New Zealand and Australia	Pain rating for age 3–6 was Faces Pain Scale-Revised; 7 years and older used a standard 100 mm line. Subjective description of pain was accessed by asking whether pain was "a lot less," "a little less," "the same," "a little more," or "a lot more." Degree of sedation was accessed by attending medical staff, patient, parent, or guardian. The physician used the University of Michigan Sedation Scale. Others were asked to subjectively describe the degree of sedation as "too sedated," "sedated enough," "un-changed," "not sedated enough."	Similar pain reduction was observed with either agent in this RCT. Ketamine had more adverse effects, but none serious.	I	II
Hansen, M. S., Mathiesen, O., Trautner, S., & Dahl, J. B. (2012). Intranasal fentanyl in the treatment of acute pain—a systematic review. *Acta Anaesthesiologica Scandinavica*, *56*(4), 407–419. doi:10.1111/j.1399-6576.2011.02613.x	To evaluate current evidence related to IN fentanyl use for pain management in the ED and prehospital settings.	Systematic review	Measures: evaluate the current evidencefor the use of IN fentanyl as an analgesic in the emergency department (ED) and prehospital settings. Statistics: N/A, only qualitative review of studies; no meta-analysis.	Findings: Eight studies investigated intra-nasal fentanyl in the ED and four studies in the prehospital setting. In the ED, analgesic non-inferiority and superiority were demonstrated when comparing IN fentanyl with intravenous (IV) and intramuscular morphine, respectively. Due to a rather low scientific quality of studies performed in these settings, it is not currently possible to recommend intranasal fentanyl as routine care.	II	I

Appendix 1: Evidence Table

Reference	Research Purpose Questions/Hypothesis	Design Sample/Setting	Variables/Measures Analysis	Findings/Implications	Quality of Evidence	Level of Evidence
Holdgate, A., Cao, A., & Lo, K. M. (2010). The implementation of intranasal fentanyl for children in a mixed adult and pediatric emergency department reduces time to analgesic administration. *Academic Emergency Medicine*, *17*(2), 214–217. doi:10.1111/j.1553-2712.2009.00636.x	To determine whether the introduction of IN fentanyl for children with acute pain would reduce the time to analgesia administration in a mixed adult and pediatric ED.	Retrospective chart review	181 children were identified as having received IV MS or IN fentanyl; children who received IV morphine in the 7 months (January to July 2007) prior to the introduction of IN fentanyl were identified. Following implementation of the protocol, all children who received either IV morphine or IN fentanyl in the subsequent 7 months (August 2007 to February 2008) were identified.	A higher proportion of children received opioid analgesia in the post-implementation period compared with the pre-implementation period (1.6% [95% confidence interval (CI) = .07% to 1.2%] vs. 0.9% [95% CL = 1.4% to 1.9%], $p < 0.001$). There was no change in the proportion of children presenting with either fractures or burns over the 14 months (3.3% [95% CL = 2.9% to 3.7%] vs. 3.8% [CI = 3.3% to 4.3%], $p = 0.1$). In the post-implementation phase, patients with burns were almost exclusively initially treated with fentanyl, and patients with fractures were more frequently treated with fentanyl than morphine, whereas morphine was still the primary opioid agent of choice for those with abdominal pain.	I	III
Inokuchi, R., Ohashi-Fukuda, N., Nakamura, K., Wada, T., Gunshin, M., Kitsuta, Y., … Yahagi, N. (2015). Comparison of intranasal and intravenous diazepam on status epilepticus in stroke patients. *Medicine (Baltimore), 94*(7), e555. doi:10.1097/MD.0000000000000555	To evaluate whether IN diazepam is an effective alternative to IV diazepam in status epilepticus.	Longitudinal retrospective cohort study 19 adult elderly patients with previous stroke history: 9 with IN diazepam and 10 with IV diazepam ED in Tokyo, Japan	Measures: Time from arrival at the ED and termination of the seizure, time from diazepam administration to seizure termination, time from arrival at the hospital to medical intervention, and the total dose of diazepam delivered by each route. Adverse events were also recorded. Statistics: Wilcoxon–Mann–Whitney test. Pearson's chi-square test was used for categorical data. Statistical significance was defined as a two-tailed p value < 0.05.	Intranasal diazepam was administered about nine times faster than intravenous diazepam (1 vs. 9.5 minutes, $p = 0.001$), resulting in about three-fold reduction in the time to termination of seizure activity after arrival at the hospital (3 minutes compared with 9.5 minutes in the intravenous group, $p = 0.030$). No adverse effects of intranasal diazepam were evident from the medical records. Intranasal diazepam administration is safer, easier, and quicker than intravenous administration.	II	IV

Appendix 1: Evidence Table

Reference	Research Purpose Questions/Hypothesis	Design Sample/Setting	Variables/Measures Analysis	Findings/Implications	Quality of Evidence	Level of Evidence
Jia, J. E., Chen, J. Y., Hu, X., & Li, W. X. (2013). A randomised study of intranasal dexmedetomidine and oral ketamine for premedication in children. *Anaesthesia*, *68*(9), 944–949. doi:10.1111/anae.12312	A study of the effects of intranasal dexmedetomidine combined with oral ketamine for premedication in children.	Randomized clinical trial N = 150 patients	All groups used IN dexmedetomidine + another agent; randomly assigned to four groups Emotional state score, sedation scale	There were no significant differences in sedation scores between the groups 10 and 20 min following premedication; IN dexmedetomidine in a dose of 2 mcg/kg combined with oral ketamine in a dose of 3 mg/kg when administered as a premedication in children appears to be the optimal combination. It achieved satisfactory pre-operative sedation, allowed calm separation of patients from their parents, resulted in acceptance of intravenous cannulation, and did not cause excessive postoperative nausea, vomiting, or psychological disturbance.	I	II
Karlsen, A. P. H., Pederson, D. M. B., Trautner, S., Dahl, J. B., & Hansen, M. S. (2014). Safety of intranasal fentanyl in the out-of-hospital setting: A prospective observational study. *Annals of Emergency Medicine*, *63*(6), 699–703. doi:10.1016/j.annemergmed.2013.10.025	To assess the safety profile and apparent analgesic effect of intranasal fentanyl in the out-of-hospital setting.	Prospective, observational N = 903 Convenience sample > 8 years old (or weight > 30 kg) with orthopedic or abdominal conditions and ACS refractory to Nitro. Setting: Out-of-hospital, Zealand region of Denmark	11-point NRS pain scale, BP, HR, RR, GCS before/after each dose; Presence of adverse effects (hypotension, respiratory depression, decreased GCS, nausea, dizziness, fatigue); Wilcoxon signed-rank test.	Safety: 39 potential adverse effects in 36 patients, none serious. No reversal agent use. No respiratory depression. 10 hypotensive, but only one with clinical symptoms; GCS reductions were transient. Efficacy: Mean reduction in pain by 3 points with 79% demonstrating a clinically relevant reduction (≥ 2) in pain. Participants with an initial NRS of 5 or less experienced a lesser absolute but similar pain reduction. Conclusion: Out-of-hospital administration of intranasal fentanyl in doses of 50 and 100 mcg was safe and well-tolerated and appeared effective in a wide variety of patients.	II	III
Kerr, D., Kelly, A. M., Dietze, P., Jolley, D., & Barger, B. (2009). Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. *Addiction*, *104*(12), 2067–2074. doi:10.1111/j.1360-0443.2009.02724.x	To determine the effectiveness of concentrated (2 mg/mL) IN. naloxone vs. intramuscular (IM) naloxone for suspected opioid overdose.	Prospective, randomized, unblinded clinical trial N = 172 Convenience sample	Response within 10 minutes of naloxone administration (response defined as RR ≥ 10 and/or GCS ≥ 13). Adverse events grouped into three groups: drug-related, administration-related, study-related. Statistical analysis: descriptive analyses (proportion, mean, median, effect size with 95% CI), OR with 95% CI, hazard ratio (HR) and chi-square analysis, logistic/Cox regression for multivariate analysis with age/gender/concomitant alcohol/drug use.	Response within 10 min: 72.3% IN vs. 77.5% IM. Rescue naloxone for inadequate response: 18.1% IN vs. 4.5% IM (OR 4.8, p = 0.01). Hospitalization/minor adverse events similar (28.9/25.8, 19.3/19.1). Mean response time (min) = 8.0 IN vs. 7.9 IM (OR 0.84, p = 0.29). Conclusion: Naloxone administration is effective and safe in the IN route; not more effective than IM route. Low adverse event rate for both IN and IM administration routes.	I	II

Appendix 1: Evidence Table

Reference	Research Purpose Questions/Hypothesis	Design Sample/Setting	Variables/Measures Analysis	Findings/Implications	Quality of Evidence	Level of Evidence
Klein, E. J., Brown, J. C., Kobayashi, A., Osincup, D., & Seidel, K. (2011). A randomized clinical trial comparing oral, aerosolized intranasal, and aerosolized buccal midazolam. *Annals of Emergency Medicine*, *58*(4), 323–329. doi:10.1016/j.annemergmed.2011.05.016	To determine whether aerosolized intranasal or buccal midazolam reduces distress of pediatric laceration repair compared to oral midazolam. Secondary: comparison of activity scores, sedation adequacy, sedation onset, satisfaction, and adverse events.	Randomized clinical trial N = 169 (primary), 177 (secondary) Children 0.5–7 years old needed procedural sedation for laceration repair Setting: Seattle Children's Hospital ED, urban, 40K visits	CHEOPS (Children's Hospital of Eastern Ontario Pain Scale) scored via recorded video by nurse evaluators blinded to treatment group and study purpose Statistical analysis: Wilcoxon rank-sum test with p-values doubled as a Bonferroni correction ($p < 0.05$ statistically significant)	Buccal statistically significant less distress than oral ($p = 0.04$, difference -2, 95% CI -4, 0). Intranasal non-significant trend ($p = 0.08$, difference -1, 95% CI -3, 1). Intranasal demonstrated faster onset, greater proportion receiving adequate sedation, greater proportion with optimal activity scores, and a higher rate of parents choosing the regimen again for future cases. Intranasal did have a higher rate of irritation and lower proportion of patients who accepted the medication easily. Adverse event rates were similar between the two groups. Conclusion: Aerosolized buccal and intranasal midazolam are effective alternatives to oral midazolam for sedation for laceration repair.	II	II
Kress, H. G., Orońska, A., Kaczmarek, Z., Kaasa, S., Colberg, T., & Nolte, T. (2009). Efficacy and tolerability of intranasal fentanyl spray 50 to 200 ug for breakthrough pain in patients with cancer: A phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. *Clinical Therapeutics*, *31*(6), 1177–1191. doi:10.1016/j.clinthera.2009.05.022	To investigate the efficacy and long-term tolerability of intranasal fentanyl spray (INFS) 50 to 200 mcg in the treatment of breakthrough pain in opioid-tolerant patients with cancer.	Phase III, double-blind, randomized, placebo-controlled, crossover trial N = 111 Adult inpatient/outpatient with cancer, age at least 18, with life expectancy of at least three months. Study eligible experienced at least three severe breakthrough pain episodes per week, max of four per day, each with duration exceeding 15 minutes and requiring treatment with an analgesic agent.	11-point NRS pain scale, relief within 10 minutes of administration, adverse events; two-tailed tests, F-test	Pain intensity difference at 10 minutes (PID-10) scores were statistically significantly higher (double) in intranasal fentanyl spray group vs. placebo (mean scores 2.36 vs. 1.10); Adverse effect rate was 19.8% with most prevalent adverse effects being nausea (4.5%) — no serious adverse effects were considered to be related to the study drugs.	I	II
Merlin, M. A., Saybolt, M., Kapitanyan, R., Alter, S. M., Jeges, J., Liu, J., … Pryor, P. W. (2010). Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. *The American Journal of Emergency Medicine*, *28*(3), 296–303. doi:10.1016/j.ajem.2008.12.009	Investigate whether IN naloxone was non-inferior compared to IV naloxone in increasing respiratory rates (RRs) and mental status in patients presenting with suspected opioid overdose in the prehospital setting.	Retrospective chart review N = 38 (IN group), 55 (IV group) Confirmed opioid overdoses treated with naloxone IN or IV	GCS and unassisted RR following naloxone administration; Wilcoxon signed-rank test	Final values for RR ($P = 0.001$) and GCS ($p = 0.01$) were significantly higher in both the IN and IV groups. Median change in RR was 6 for IV group and 4 for IN group ($p = 0.08$). Median change in GCS was 4 for IV group and 3 for IN group ($p = 0.19$). Conclusion: IN naloxone was as effective as IV naloxone at reversing CNS depression caused by opioids.	I	IV

Appendix 1: Evidence Table

Reference	Research Purpose Questions/Hypothesis	Design Sample/Setting	Variables/Measures Analysis	Findings/Implications	Quality of Evidence	Level of Evidence
Mudd, S. (2011). Intranasal fentanyl for pain management in children: A systematic review of the literature. *Journal of Pediatric Health Care*, *25*(5), 316–322. doi:10.1016/j.pedhc.2010.04.011	To review the available research on intranasally administered fentanyl (INF) to help evaluate its role in safe and effective pain relief for children in a variety of clinical settings.	Systematic review N = 12 studies reviewed PubMed, ISI, Scopus, Popline, CINAHL, and Embase. Included meta-analyses, randomized controlled trials, comparative studies, multicenter studies related to pediatric INF	Johns Hopkins Hospital/Johns Hopkins University evidence rating scale	All of the reviewed studies showed similar or improved pain scores when compared with other opioids and administration methods. No severe adverse outcomes were reported.	II	I
Murphy, A., O'Sullivan, R., Wakai, A., Grant, T. S., Barrett, M. J., Cronin, J., … Kandamany, N. (2014). Intranasal fentanyl for the management of acute pain in children. *Cochrane Database of Systematic Reviews*, *10*, article number CD009942. doi:10.1002/14651858.CD009942.pub2	To identify and evaluate all RCTs and quasi-randomized trials to assess the effects of intranasal fentanyl (INF) versus alternative analgesic interventions in children with acute pain.	Cochrane review 3 studies (N = 313)	Cochrane review process	IN fentanyl produced a greater reduction in pain scores at 10 minutes compared with IM morphine. No statistically significant differences in pain scores were noted when IN fentanyl was compared with IV morphine and high concentration IN fentanyl. When IN fentanyl was compared with IV morphine, both produced a statistically significant reduction in pain scores up to 20 minutes post analgesia. When standard concentration IN fentanyl was compared with high concentration IN fentanyl, a statistically and clinically significant reduction in pain scores over the study time was observed.	I	I
Murphy, A. P., Hughes, M., Mccoy, S., Crispino, G., Wakai, A., & O'Sullivan, R. (2016). Intranasal fentanyl for the prehospital management of acute pain in children. *European Journal of Emergency Medicine*, *00*(00), 1–5. doi:10.1097/MEJ.0000000000000389	To determine whether INF provides a clinically effective and safe analgesia for children with acute severe pain in the prehospital setting.	Prospective, cross-sectional descriptive observational study Convenience, N = 94, NRS 7–10	Primary outcome measure was to determine if 1.5 mcg/kg (50 mcg/mL concentration) delivered by mucosal atomizer produced an effective reduction in pain at 10 min after administration. Secondary was documenting adverse effects. Mean, SD, IQR, Wilcoxon signed-rank test for paired groups.	83% achieved a clinically and statistically significant reduction in pain intensity at 10 min after administration. Medial initial pain was 10 (IQR 8–10) and after 10 min median pain was 5 (IRQ 2–7), $p < 0.001$).	II	VI
Pavis, H., Wilcock, A., Edgecombe, J., Carr, D., Manderson, C., Church, A., & Fisher, A. (2002). Pilot study of nasal morphine-chitosan for the relief of breakthrough pain in patients with cancer. *Journal of Pain and Symptom Management*, *24*(6), 598–602. doi:10.1016/S0885-3924(02)00522-5	To investigate the tolerability and efficacy of a novel morphine-chitosan formulation.	Pilot study, descriptive Convenience, N = 14 Inpatients at a specialist palliative care unit with cancer related pain	Pain intensity (0–4) scale, pain relief -4 to 4 (4 = complete pain relief, -4 = pain has become maximal. Pts received one or two doses of 5 mg (3 patients), 10 mg (3 patients), 15 mg (2 patients), 20 mg (4 patients), 30 mg (1 patient) or 80 mg (1 patient).	Satisfaction: excellent = 1, very good = 6, good = 11, and fair = 2. Efficacy: Improvements in pain intensity and relief were reported at 5 minutes and reached a maximum after 45 minutes.	II	III

Appendix 1: Evidence Table

Reference	Research Purpose Questions/Hypothesis	Design Sample/Setting	Variables/Measures Analysis	Findings/Implications	Quality of Evidence	Level of Evidence
Prommer, E., & Thompson, L. (2011). Intranasal fentanyl for pain control: Current status with a focus on patient considerations. *Patient Preference and Adherence*, *5*, 157–164	To examine the role of the nasal route of opioid administration and examine the evidence base for the use of fentanyl intranasally.	Literature review		The IN route of opioid administration shows great promise as an alternative to the traditional routes of administration. It provides a low burden to patients, is suitable for pain management for a variety of analgesic issues ranging from postoperative pain to cancer-related breakthrough pain and is applicable to both adult and pediatric patients. Can be self-administered with a rapid onset of action.	I	V
Rickels, M. R., Ruedy, K. J., Foster, N. C., Piche, C. A., Dulude, H., Sherr, J. L., … Beck, R. W. (2016). Intranasal glucagon for treatment of insulin-induced hypoglycemia in adults with type 1 diabetes: A randomized crossover noninferiority study. *Diabetes Care*, *39*(2), 264–270. doi:10.2337/dc15-1498	Compare needle-free IN glucagon with IM glucagon for the treatment of hypoglycemia.	Randomized crossover noninferiority study 75 adults aged 18–64 with type I diabetes Eight diabetic clinics in the United States	Primary outcome measure is an increase in plasma glucose level to > 70 mg/dl within 30 minutes after administration of glucagon. Participants were randomized to receive 3 mg IN glucagon or 1 mg IM glucagon in visit one and then crossover in the second session. Hypoglycemia was induced in clinic prior to medication administration. Serial blood samples were drawn at 5, 10, 20, 25, 30, 40, 60, and 90 minutes. Powered at 80%.	IN glucagon was highly effective in treating hypoglycemia in type I diabetics. Outcome measure was met in all but one of the IN patients. Symptoms of hypoglycemia using the Edinburgh Hypoglycemia Scale were greater in the IN group for the first 45 minutes but similar after that point. 25% of IN patients experienced transient facial discomfort.	I	II
Robertson, T. M., Hendey, G. W., Stroh, G., & Shalit, M. (2009). Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. *Prehospital Emergency Care*, *13*(4), 512–515. doi:10.1080/10903120903144866	To compare prehospital time intervals from patient contact and medication administration to clinical response for patients who received IN naloxone or IV naloxone for suspected narcotic overdose.	Retrospective review of records; non-experimental Sample: 154 Setting: EMS system	Primary outcome measures were time from patient contact to clinical response and time from medication administration to clinical response. Secondary measures included number of doses administered and rescue doses given by alternative route. Statistical analysis for between-group comparison using t-tests and chi-square tests.	Time from dose administration to clinical response (increase in RR and GCS > 6) was longer in the IN group ($p = 0.02$), but time from patient contact to clinical response was not statistically significantly different ($p = 0.3$).	II	IV

Appendix 1: Evidence Table

Reference	Research Purpose Questions/Hypothesis	Design Sample/Setting	Variables/Measures Analysis	Findings/Implications	Quality of Evidence	Level of Evidence
Saunders, M., Adelgais, K., & Nelson, D. (2010). Use of intranasal fentanyl for the relief of pediatric orthopedic trauma pain. *Academic Emergency Medicine*, *17*(11), 1155–1161. doi:10.1111/j.1553-2712.2010.00905.x	To evaluate the use of a single 2 mcg/kg dose of intranasal fentanyl as analgesia for painful orthopedic injuries in children presenting to a pediatric ED.	Prospective, nonblinded, interventional trial N = 81 Convenience sample of patients 3 to 18 years of age with isolated orthopedic injuries and pain level of 3 or more on WBS and 40 mm on VAS Urban, tertiary care, Level I pediatric trauma center	Pain scores, satisfaction, time of onset, vital signs, adverse outcomes	IN fentanyl at a dose of 2 mcg/kg provides effective analgesia for pediatric ED patients with painful orthopedic trauma within 10 minutes that was sustained for 30 minutes for the majority of patients.	I	III
Seith, R. W., Theophilos, T., & Babl, F. E. (2012). Intranasal fentanyl and high-concentration inhaled nitrous oxide for procedural sedation: A prospective observational pilot study of adverse events and depth of sedation. *Academic Emergency Medicine*, *19*(1), 31–36. doi:10.1111/j.1553-2712.2011.01241.x	To characterize the depth of sedation and incidence of adverse events associated with the combined use of N_2O and IN fentanyl for pediatric PSA in the ED.	Prospective, observational, pilot study	University of Michigan Sedation Scale, Consensus Panel on Sedation Research of Pediatric Emergency Research Canada, Pediatric Emergency Care Applied Research Network. Chi-square, t-tests, Wilcoxon rank- sum tests, $p < 0.01$.	No serious adverse events; 22% vomiting. There was a significant increase in the depth of sedation when INF is used in combination with N_2O compared to N_2O alone.	II	III
Thakker, A., & Shanbag, P. (2013). A randomized controlled trial of intranasal-midazolam versus intravenous-diazepam for acute childhood seizures. *Journal of Neurology*, *260*(2), 470–474. doi:10.1007/s00415-012-6659-3	The objective of this study is to compare the safety and efficacy of midazolam given intranasally with diazepam given intravenously in the treatment of acute childhood seizures.	Randomized clinical trial 50 children age 1–12 years with acute seizures lasting at least 10 minutes in a pediatric general ED in India One year duration	The main outcome measures were interval between arrival at hospital and starting treatment, and interval between arrival at hospital and cessation of seizures. The two groups were compared by the independent sample t-test or Fisher's exact test.	The mean interval between arrival at hospital and starting treatment was significantly shorter in the midazolam group [3.37 min (SD 2.46)] as compared to the diazepam group [14.13 min (SD 3.39)]. The mean interval between cessation of seizures and arrival at hospital was significantly shorter in the midazolam group [6.67 min (SD 3.12)] as compared to the diazepam group [17.18 min (SD 5.09)]. The mean interval between control of seizures and administration of the drug was shorter in the diazepam group [2.67 min (SD 2.31)] as compared to the midazolam group [3.01 min (SD 2.79)]. Midazolam was as safe and effective as diazepam. Both drugs were equally effective.	II	I

Appendix 1: Evidence Table

Reference	Research Purpose Questions/Hypothesis	Design Sample/Setting	Variables/Measures Analysis	Findings/Implications	Quality of Evidence	Level of Evidence
Thomas, A., Miller, J. L., Couloures, K., & Johnson, P. N. (2015). Non-intravenous sedatives and analgesics for procedural sedation for imaging procedures in pediatric patients. *The Journal of Pediatric Pharmacology and Therapeutics*, *20*(6), 418–430. doi:10.5863/1551-6776-20.6.418	Describe the method of delivery, dosage regimen, and outcomes of sedatives administered by extravascular route for children undergoing imaging procedures.	Systematic review	Sample: 20 studies included with a total of 1,412 patients from age 0–19 Multiple databases searched	Examined studies published from 1946 to March 2015. No statistical analysis because of variation in doses and type of study analysis used in included studies. Review criteria and assessment of bias discussed. Findings: Oral midazolam most common in studies. IN ketamine, fentanyl, or midazolam were included in 7 studies.	I	I
Veldhorst-Janssen, N. M., Fiddelers, A. A., van der Kuy, P. H., Neef, C., & Marcus, M. A. (2009). A review of the clinical pharmacokinetics of opioids, benzodiazepines, and antimigraine drugs delivered intranasally. *Clinical Therapeutics*, *31*(12), 2954–2987. doi:10.1016/j.clinthera.2009.12.015	To compare the pharmacokinetic properties of three cerebroactive drug classes that might be suitable for intranasal delivery: opioids, benzodiazepines, and antimigraine drugs.	Systematic review Search of Medline, PubMed, CINAHL, Embase, and Cochrane database from 1964–April 2009. A total of 45 English language studies were included.		Intranasal medication administration is suitable for rapid medication delivery of opioids, benzodiazepines, and antimigraine medications.. Pharmokinetics vary based on route of administration and types of medications used.	II	I
Wermeling, D. P., Clinch, T., Rudy, A. C., Dreitlein, D., Suner, S., & Lacouture, P. G. (2010). A multicenter, open-label, exploratory dose-ranging trial of intranasal hydromorphone for managing acute pain from traumatic injury. *The Journal of Pain*, *11*(1), 24–31. doi:10.1016/j.jpain.2009.05.002	To explore the tolerability and efficacy of an escalating dose-range of IN hydromorphone HCL in moderate to severe pain from traumatic injury.	Prospective, multicenter, open-label, escalating dose-range trial Convenience sample N = 113	Baseline pain intensity. Pain intensity and relief at 10, 20, 30, 45, 60, 75, 90, 120, 180, and hourly up to 6 hours or until rescue medication administered. Descriptive, ANOVA, Fischer's exact for categorical data.	Mean decrease in pain intensity from baseline to 30 minutes was -3.1 to -3.8 (SD 2.2–3.0) or 39% to 44% reduction for the 4, 6, 8, and 10 mg doses. Most patients received initial pain relief within 10–15 minutes, a 30% reduction in pain intensity by 30 minutes, and 50% or greater pain intensity reduction at 60 minutes.	II	III

Appendix 1: Evidence Table

Reference	Research Purpose Questions/Hypothesis	Design Sample/Setting	Variables/Measures Analysis	Findings/Implications	Quality of Evidence	Level of Evidence
Yeaman, F., Meek, R., Egerton-Warburton, D., Rosengarten, P., & Graudins, A. (2014) Sub-dissociative-dose intranasal ketamine for moderate to severe pain in adult emergency department patients. *Emergency Medicine Australia, 26,* 237-242. doi:10.1111/1742-6723.12173	The study aims to examine the effectiveness of sub-dissociative IN ketamine as a primary analgesic agent for adult patients in the ED.	This is a prospective, observational study of adult ED patients presenting with severe pain (≥ 6 on 11-point scale at triage). N = 72 Setting: Australian ED	Paper case report forms were completed by the treating ED doctor. Data were analyzed using Stata version 8.0 statistical package (Stata Corporation, College Station, TX, USA). Baseline variables (sex, age, and pain etiology) are described as number and percentage or median with interquartile range, as appropriate. Pain severity is reported as median with interquartile range and compared using the Mann–Whitney U-test. Categorical descriptions of change are reported as number and percentage with 95% confidence intervals (CI), and compared using the chi-square test or Fisher's exact test. Levels of satisfaction, sedation, and AEs are descriptive.	Of the 72 patients available for analysis, median age was 34.5 years and 64% were men. Median initial VAS rating was 76 mm (interquartile range [IQR]: 65–82). Median total dose of IN ketamine for all patients was 0.98 mg/kg (IQR: 0.75–1.15, range: 0.59–1.57). Median reduction in VAS rating at 30 min was 24 mm (IQR: 2–45). Forty (56%, 95% CI: 44.0–66.7) reported VAS reduction ≥ 20 mm, these patients having had a total median ketamine dose of 0.94 mg/kg (IQR: 0.72–1.04). IN ketamine at a dose of about 1 mg/kg was an effective analgesic agent in 56% of study patients. The place of IN ketamine in analgesic guidelines for adults requires further investigation.	I	IV
Yeaman, F., Oakley, E., Meek, R., & Graudins, A. (2013). Sub-dissociative dose intranasal ketamine for limb injury pain in children in the emergency department: A pilot study. *Emergency Medicine Australasia*, 25(2), 161–167. doi:10.1111/1742-6723.12059	To conduct a pilot study examining the effectiveness of intranasal (IN) ketamine as an analgesic for children in the ED.	An observational study on a convenience sample of paediatric ED patients aged 3–13 years with moderate to severe (6/10) pain from isolated limb injury N = 30 Australian ED	Pain severity for each time point is presented as median with IQR, as is the amount of change to each time point. Number and percentage for each level of sedation on the UMSS at each time are described, as are all other adverse events. Number and percentage reporting satisfaction with the medication and those requiring additional analgesia are also described.	Eighteen (64%) received only one dose of IN ketamine (mean dose 0.84 mg/kg), whereas 10 (36%) required a second dose at 15 min (mean for second dose 0.54 mg/kg). The total mean dose for all patients was 1.0 mg/kg (95% CI: 0.92–1.14). The median pain rating decreased from 74.5 mm (IQR 60–85) to 30 mm (IQR 12–51.5) at 30 min ($p < 0.001$, Mann–Whitney). For the 24 children who contributed data at 60 min, the median pain rating was 25 mm (IQR 4–44). Twenty (83%) subjects were satisfied with their analgesia. Eight (33%) were given additional opioid analgesia and the 28 reported adverse events were all transient and mild.	I	IV

GRADING THE QUALITY OF THE EVIDENCE

I. Acceptable Quality: No concerns
II. Limitations in Quality: Minor flaws or inconsistencies in the evidence
III. Major Limitations in Quality: Many flaws and inconsistencies in the evidence
IV. Not Acceptable: Major flaws in the evidence

GRADING THE LEVELS OF THE EVIDENCE (MELNYK & FINEOUT-OVERHOLT, 2015)

I. Evidence from a systematic review or meta-analysis of all relevant, randomized, controlled trials or evidence-based clinical practice guidelines based on systematic reviews of RCTs
II. Evidence obtained from at least one properly designed, randomized, controlled trial
III. Evidence obtained from well-designed controlled trials without randomization
IV. Evidence obtained from well-designed case control and cohort studies
V. Evidence from systematic reviews of descriptive and qualitative studies
VI. Evidence from a single descriptive or qualitative study
VII. Evidence from opinion of authorities and/or reports of expert committees

Appendix 2: Other Resources Table

Reference	Research Purpose	Conclusions
Agarwal, S. K., Kriel, R. L., Brundage, R. C., Ivaturi, V. D., & Cloyd, J. C. (2013). A pilot study assessing the bioavailability and pharmacokinetics of diazepam after intranasal and intravenous administration in healthy volunteers. *Epilepsy Research*, *105*(3), 362–367. doi:10.1016/j.epilepsy res.2013.02.018	Purpose: To compare the pharmokinetics (PK) and bioavailability of two novel intranasal diazepams with intravenous diazepam in healthy adult patients.	Safety and tolerability findings indicate both formulations of the IN diazepam were well tolerated with minimal adverse effects. Development of a diazepam solution for IN administration is feasible.
Bausewein, C., & Simon, S. T. (2014). Inhaled nebulized and intranasal opioids for the relief of breathlessness. *Current Opinion in Supportive and Palliative Care*, *8*(3), 208–212. doi:10.1097/SPC.0000000000000071	To describe recent studies evaluating the effectiveness of inhaled nebulized and intranasal application of opioids for patients suffering from refractory breathlessness.	There is not enough evidence to support the use of inhaled application of opioids for the relief of breathlessness.
Bitter, C., Suter-Zimmermann, K., & Surber, C. (2011). Nasal drug delivery in humans. *Current Problems in Dermatology*, *40*, 20–35. doi:10.1159/000321044	To discuss the feasibility and potential of intranasal administration.	Intranasal drug administration is noninvasive, essentially painless, and particularly suited for children. Intranasal drug delivery offers a rapid onset of therapeutic effects (local or systemic).
Bullingham, R., & Juan, A. (2012). Comparison of intranasal ketorolac tromethamine pharmacokinetics in younger and older adults. *Drugs & Aging*, *29*(11), 899–904. doi:10.1007/s40266-012-0023-2	Compare the pharmacokinetics of a single intranasal dose of ketorolac tromethamine 31.5 mg in adults aged younger than 65 and older than 65.	After single-dose administration of 31.5 mg intranasal ketorolac tromethamine, adult subjects greater than 65 years of age showed a small mean increase (10%) in plasma ketorolac, a modest increase in mean and MRT (36%), and a corresponding modest increase (28%) in mean AUC with respect to younger subjects. The similarity of ketorolac plasma concentrations between intranasal ketorolac tromethamine 31.5 mg and IM ketorolac tromethamine 30 mg, and the fact that the dose response curve between 15 and 30 mg for IM ketorolac tromethamine is flat, together with consideration of increased toxicity in older individuals, suggest that a smaller dose be given in older individuals.
Corrigan, M., Wilson, S. S., & Hampton, J. (2015). Safety and efficacy of intranasally administered medications in the emergency department and prehospital settings. *American Journal of Health-System Pharmacy*, *72*(18), 1544–1554. doi:10.2146/ajhp140630	Discuss the use of IN medication administration in emergency settings.	Based on a review of the literature (not systematic review), fentanyl, sufentanil, ketamine, hydromorphone, midazolam, haloperidol, naloxone, glucagon, and, in some cases, flumazenil may be a safe, effective, and well-tolerated alternative to intramuscular or intravenous administration in the prehospital and ED settings.
Crellin, D., Ling, R. X., & Babl, F. E. (2010). Does the standard intravenous solution of fentanyl (50 microg/mL) administered intranasally have analgesic efficacy? *Emergency Medicine Australasia*, *22*(1), 62–67. doi:10.1111/j/1742-6723.2010.01257.x	Is the standard solution of fentanyl (50 mcg/mL) efficacious in providing analgesia in children with upper limb injuries?	The early reduction of pain scores from a median of 7 to 5 at 5 min post fentanyl administration implies therapeutic levels of fentanyl were achieved early even at a more dilute concentration.
Del Pizzo, J., & Callahan, J. M. (2014). Intranasal medications in pediatric emergency medicine. *Pediatric Emergency Care*, *30*(7), 496–501. doi:10.1097/PEC.0000000000000171	Reviews the use of intranasal medications in the emergency care of children.	Intranasal medication administration is useful in the prehospital setting and emergency department. Medications for sedation, analgesia, and the treatment of migraines, opioid overdose, and seizures have all been shown to be effective in children when administered intranasally.
Doe-Simkins, M., Walley, A. Y., Epstein, A., & Moyer, P. (2009). Saved by the nose: Bystander-administered intranasal naloxone hydrochloride for opioid overdose. *American Journal of Public Health*, *99*(5), 788–91. doi:10.2105/AJPH.2008.146647	Report of an overdose prevention program training non-medical personnel to recognize opioid overdose and administer intranasal naloxone.	The PICOT question relates to emergency patients across the lifespan in regards to IN medication administration; however, this study does not compare any other route of administration. It supports that IN naloxone successfully reverses opioid OD during emergency care.
Finn, M., & Harris, D. (2010). Intranasal fentanyl for analgesia in the paediatric emergency department. *Emergency Medicine Journal*, *27*(4), 300–301. doi:10.1136/emj.2008.070474	To investigate if IN fentanyl is an acceptable and safe alternative drug to diamorphine in the management of severe pain in children.	IN fentanyl was found to be both effective and safe (zero numerator statistic 95% CI 0.00 to 0.03 based upon Louis' rule of 3). Average parent/carer satisfaction scores of 9.1/10 (6–9.7), average time to discharge for patients not admitted was 3.1 h (2.6–3.4)

Appendix 2: Other Resources Table

Reference	Research Purpose	Conclusions
Fortuna, A., Alves, G., Serralheiro, A., Sousa, J., & Falcão, A. (2014). Intranasal delivery of systemic-acting drugs: Small-molecules and biomacromolecules. *European Journal of Pharmaceutics and Biopharmaceutics*, *88*(1), 8–27. doi:10.1016/j.ejpb.2014.03.004	To provide an anatomical, histological, and mechanistic overview of drug systemic absorption after nasal administration and the relevant aspects of the therapeutic interest and limitations of intranasal systemic delivery.	Discusses the advantages of IN medication administration for use in acute or chronic pain management, crisis situations such as angina pectoris, motion sickness, smoking cessation, and erectile dysfunction.
Garlapati, R. R., Lee, H. P., Chong, F. H., & Wang, D. Y. (2009). Indicators for the correct usage of intranasal medications: A computational fluid dynamics study. *The Laryngoscope*, *119*(10), 1975–1982. doi:10.1002/lary.20660	Review pharmacological properties of IN ketorolac and discuss clinical efficacy and tolerability in the short-term management of pain (adults).	This computational study provides qualitative and quantitative information on the improvement of drug penetration in patients with inferior turbinate hypertrophy that will contribute to the improvement of the clinical efficacy of these drugs. It is advisable to have an inspiratory flow to improve drug penetration. This simulation study relates to the PICOT question as it discusses several factors that impact the efficacy of IN medications, which include head position, and the need to have apnea or inspiratory flow during administration of IN medication.
Garnock-Jones, K. P. (2012). Intranasal ketorolac: For short-term pain management. *Clinical Drug Investigation, 32*(6), 361–371. doi:10.2165/11209240-000000000-00000	Review pharmacological properties of IN ketorolac and discuss clinical efficacy and tolerability in the short-term management of pain (adults).	IN ketorolac is indicated for short-term (< 5 days) pain management for adults in the United States who require moderate to severe pain management.
Goadsby, P. J., & Yates, R. (2006). Zolmitriptan intranasal: a review of the pharmacokinetics and clinical efficacy. *Headache*, *46*(1), 138–149. doi:10.1111/j.1526-4610.2006.00301.x	Review the influence of route of administration on clinical profile. Explore pharmacokinetic properties of zolmitriptan nasal spray. Review the distribution and elimination of zolmitriptan and pharmacokinetic reliability. Review the efficacy studies using placebo, oral zolmitriptan or zolmitriptan nasal spray. Review the efficacy and long-term tolerability studies.	Based on the reviewed studies, zolmitriptan 5 mg nasal spray offers a rapid onset of effect, achieved long before t1/2 (plasma 1/2 life) is reached, with high and consistent efficacy and excellent tolerability. By comparison, the oral formulation depends on absorption from the upper gastrointestinal tract. This suggests that, compared with the equivalent oral dose, an IN dose will give earlier and more sustained efficacy from deferred absorption of parent drug and generation of the active metabolite from the fraction of the dose that is swallowed. This has direct relevance to emergency patients across the lifespan who present with migraines.
Grassin-Delyle, S., Buenestado, A., Naline, E., Faisy, C., Blouquit-Laye, S., Couderc, L. J., … Devillier, P. (2012). Intranasal drug delivery: An efficient and non-invasive route for systemic administration: Focus on opiods. *Pharmacology & Therapeutics*, *134*(3), 366–379. doi:10.1016/j.pharmthera.2012.03.003	To outline the relevant aspects of the therapeutic interest and limits of intranasal delivery of drugs. Focus on opioids.	Provides information on morphine, oxycodone, remifentanil, hydromorphone, alfentanil, naloxone, butorphanol, methadone, sufentanil, fentanyl, and buprenorphine.
Hadley, G., Maconochie, I., & Jackson, A. (2010). A survey of intranasal medication use in the paediatric emergency setting in England and Wales. *Emergency Medicine Journal*, *27*(7), 553–554. doi:10.1136/emj.2009.072538	A survey was conducted looking at the use of intranasal medication in the pediatric population in Accident and EDs in Wales and England.	More than one half of all units surveyed used intranasal medication, primarily diamorphine. Directly related to the PICOT question.
Humphries, L. K., & Eiland, L. S. (2013). Treatment of acute seizures: Is intranasal midazolam a viable option? *Journal of Pediatric Pharmacological Therapy*, *18*(2), 79–87. doi:10.5863/1551-6776-18.2.79	Discusses the use of IN midazolam in the treatment of acute seizures.	Intranasal midazolam was found to be efficacious and reasonably safe for treatment of acute seizures in the pediatric population. Various studies have demonstrated a shorter time to seizure cessation with intranasal midazolam versus rectal diazepam in children in the community, prehospital, and ED settings.

Appendix 2: Other Resources Table

Reference	Research Purpose	Conclusions
Illum, L., Watts, P., Fisher, A. N., Hinchcliffe, M., Norbury, H., Jabbal-Gill, I., … Davis, S. S. (2002). Intranasal delivery of morphine. *The Journal of Pharmacology and Experimental Therapeutics*, *301*(1), 391–400. doi:10.1124/jpet.301.1.391	Review article describing the development of novel nasal morphine formulations incorporating chitosan.	It is possible for a nasal morphine formulation containing chitosan to obtain a rapid and therapeutically relevant peak plasma level of morphine. Pilot studies in patients with cancer have shown the efficacy of the nasal morphine formulation as a means of improving the treatment of breakthrough pain. The nasal morphine formulation containing chitosan has been shown to be well tolerated and well accepted by both volunteer subjects and patients with cancer. Both plasma and metabolite profiles of chitosan-morphine formulation were similar to IV administration of morphine.
Kälviäinen, R. (2015). Intranasal therapies for acute seizures. *Epilepsy & Behavior*, *49*, 303–306. doi:10.1016/j-yebeh.2015.04.027	To investigate the recent advances in IN treatment of prolonged seizures and seizure clusters.	Although time to seizure cessation varies from study to study, intranasal midazolam is efficacious not only when administered by emergency department personnel but also by paramedics and caregivers in out-of-hospital and home settings.
Kapoor, M., Winter, T., Lis, L., Georg, G. I., & Siegel, R. A. (2014). Rapid delivery of diazepam from supersaturated solutions prepared using prodrug/enzyme mixtures: Toward intranasal treatment of seizure emergencies. *The AAPS Journal*, *16*(3), 577–585. doi:10.1208/s12248-014-9596-5	To investigate if the AVF/A.O protease system is useful for the rapid delivery of DZP across cell monolayers.	Rapid delivery of diazepam (DZP) can be obtained by using supersaturated solutions.
Kerr, D., Dietze, P., & Kelly, A-M (2008). Intranasal naloxone for the treatment of suspected heroin overdose. *Addiction. 103*, 379-386. doi: 10.1111/j.1360-0443-2007.02097.x	Conducted a literature review to assess the effectiveness, safety, and usefulness of IN Naloxone for the treatment of heroin overdoses.	Naloxone administration is safe and effective when administered intranasally, but not more effective than the inter-muscular route in patients with heroin overdoses. Both IN and IM naloxone have low adverse event rates.
McAleer, S. D., Majid, O., Venables, E., Polack, T., & Sheikh, M. S. (2007). Pharmacokinetics and safety of ketorolac following single intranasal and intramuscular administration in healthy volunteers. J*ournal of Clinical Pharmacology*, *47*(1), 1318. doi:10.1177/0091270006294597	Determine pharmokinetics of IN ketorolac in healthy adult patients age 18–60.	IN and IM ketorolac doses resulted in comparable bioavailability. Ketorolac is rapidly and well absorbed via the IN route.
Mercadante, S., Prestia, G., Adile, C., & Casuccio, A. (2014). Intranasal fentanyl versus fentanyl pectin nasal spray for the management of breakthrough cancer pain in doses proportional to basal opioid regimen. *The Journal of Pain*, *15*(6), 602–607. doi:10.1016/j.jpain.2014.02.002	Assess the analgesic and adverse effects of two nasal preparations, intranasal fentanyl and fentanyl pectin nasal spray for breakthrough pain given in doses proportional to opioid basal regimen.	INFS and FPNS in doses proportional to basal opioid regimen are equally safe and effective for the management of breakthrough pain in cancer patients.
Moadebi, S., Kwan, F., Stackhouse, S., & Redekopp, L. (2013). The impact of interprofessional collaboration on nurses' satisfaction and comfort with intranasal fentanyl. *International Emergency Nursing*, *21*(1), 58–63. doi:10.1016/j.ienj.2012.02.004	Measure the impact of training conducted by the clinical pharmacist on ED nurses' level of comfort and satisfaction with intranasal fentanyl.	Most nurses felt very comfortable with intranasal fentanyl administration but there was increased comfort with IV morphine (83% versus 98%, $p < 0.05$).
Mundlia, J., Kumar, M., & Amardeep. (2015). Nasal drug delivery — an overview. *International Journal of Pharmaceutical Sciences and Research*, *6*(3), 951–959. doi:10.13040/IJPSR.0975-8232.6(3).951-60	To describe factors involved with nasal drug administration and discuss strategies that can be used to improve drug absorption using the IN route.	Clinical article — conclusions do not apply.
Normandin, P. A., Khorey, S. J., Donahue, M.A., Benotti, S. A., & Manning, B. A. (2016). Use of intranasal ketamine for the severely agitated or violent ED patient. *Journal of Emergency Nursing*, *41*(1), 61–63. doi:10.1016/j.jen.2015.09.017	Is intranasal ketamine safe to use with severely agitated, violent patients?	Clinical article — conclusions do not apply.

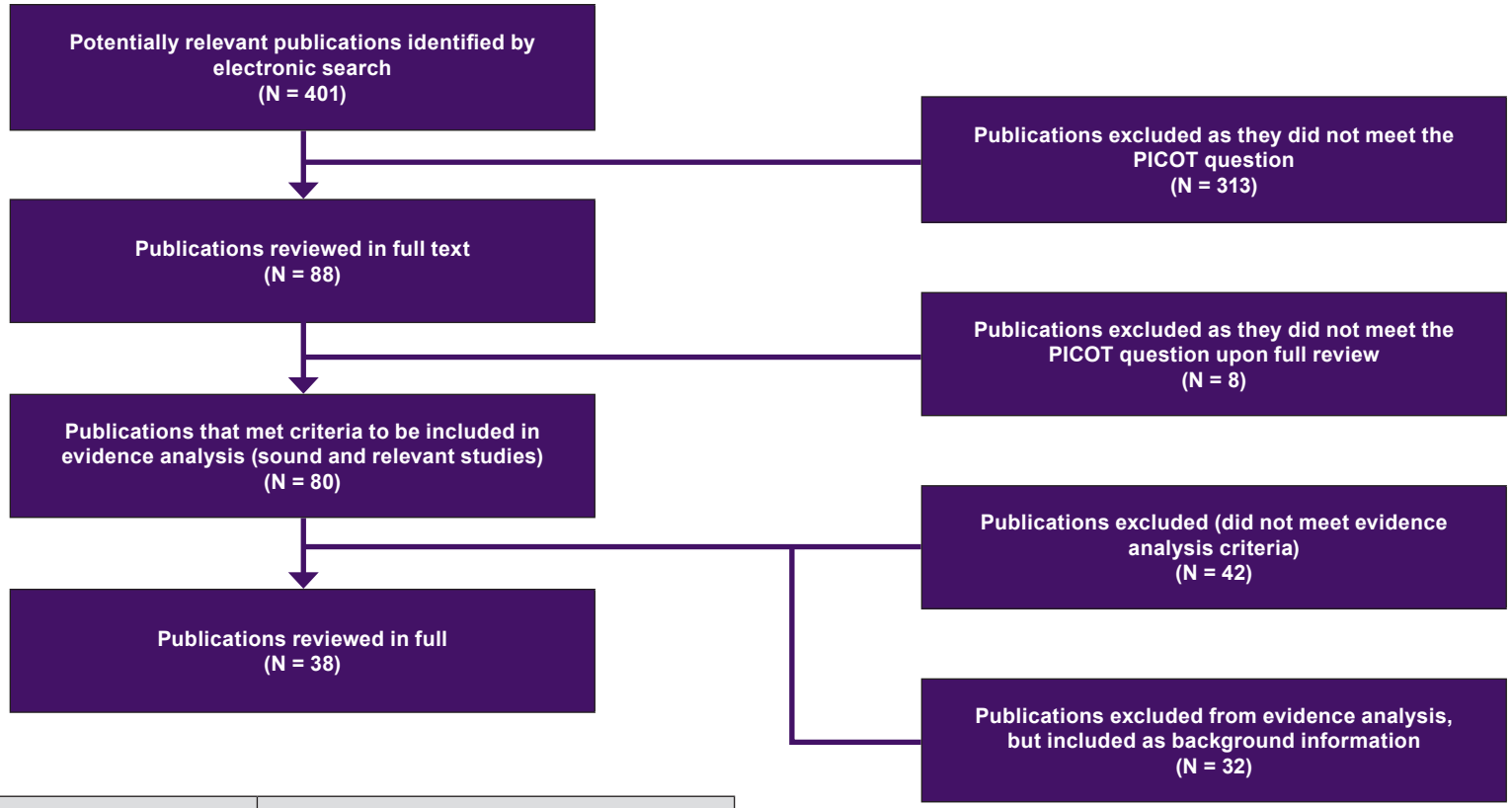
Appendix 2: Other Resources Table

Reference	Research Purpose	Conclusions
Pavis, H., Wilcock, A., Edgecombe, J., Carr, D., Manderson, C., Church, A., & Fisher, A. (2002). Pilot study of nasal morphine-chitosan for the relief of breakthrough pain in patients with cancer. *Journal of Pain and Symptom Management, 24*(6), 598–602. doi:10.1016/S0885-3924(02)00522-5	To investigate the tolerability and efficacy of a novel morphine-chitosan formulation. Sample: Convenience: N = 14. Setting: Inpatients at a specialist palliative care unit with cancer related pain.	Improvements in pain intensity and relief were reported at 5 minutes and reached a maximum after 45 minutes.
Pontiroli, A. E. (2015). Intranasal glucagon: A promising approach for treatment of severe hypoglycemia. *Journal of Diabetes Science and Technology*, *9*(1), 38–43. doi:10.1177/1932296814557518	Review of potential for IN glucagon as an approach for treating severe hypoglycemia.	Results of early studies are promising but more research is needed.
Robinson, A., & Wermeling, D. P. (2014). Intranasal naloxone administration for treatment of opioid overdose. *American Journal of Health-System Pharmacy*, *71*(24), 2129–2135. doi:10.2146/ajhp130798	Discusses the pharmacology, pharmacokinetic properties, and clinical efficacy of naloxone injection administered intranasally for the reversal of opioid overdose.	Clinical article — conclusions do not apply.
Sibley, T., Jacobsen, R., & Salomone, J. (2013). Successful administration of intranasal glucagon in the out-of-hospital environment. *Prehospital Emergency Care*, *17*(1), 98–102. doi:10.3109/10903127.2012.717171	Describes the use of intranasal (IN) glucagon in single hypoglycemic patient in the prehospital setting.	Appropriate increase in blood sugar.
Sperling, M. R., Haas, K. F., Krauss, G., Eddeine, H. S., Henney, H. R., Rabinowicz, A. L., … Carrazana, E. J. (2014). Dosing feasibility and tolerability of intranasal diazepam in adults with epilepsy. *Epilepsia*, *55*(10), 1544–1550. doi:10.1111/epi.12755	To determine the pharmokinetics (PK) of intranasal administration of diazepam in adults with epilepsy during or after a tonic-clonic seizure. Additionally, the study sought to evaluate drug tolerability in the adult population.	Safety and tolerability findings indicate the IN diazepam formulation can be administered with minimal treatment-related adverse events. The most common finding reported was headache, which was attributed to the seizure rather than the medication. Plasma diazepam concentrations were within the therapeutic range for patients who received dosing during or after a tonic-clonic seizure.
Steenblik, J., Goodman, M., Davis, V., Gee, C., Hopkins, C. L., Stephen, R., & Madsen, T. (2012). Intranasal sufentanil for the treatment of acute pain in a winter resort clinic. *The American Journal of Emergency Medicine*, *30*(9), 1817–1821. doi:10.1016/j.ajem.2012.02.019	Evaluate if IN sufentanil could provide rapid, noninvasive, effective pain relief to patients presenting with acute extremity injuries. Unblinded, nonrandomized, observational study. N = 40	Sufentanil was found to provide safe and effective pain relief of isolated extremity injuries.
Stephen, R., Lingenfelter, E., Broadwater-Hollifield, C., & Madsen, T. (2012). Intranasal sufentanil provides adequate analgesia for emergency department patients with extremity injuries. *Journal of Opioid Management*, *8*(4), 237–241. doi:10.5055/jom.2012.0121	A study was conducted to investigate the efficacy, dosing requirements, and safety of intranasal sufentanil in an adult ED population suffering moderate to severe pain due to an acute distal extremity injury. A secondary goal, was to evaluate patient, physician, and nursing satisfaction with intranasal opioid administration.	Sufentanil, administered intranasally at a dose of 0.5 mcg/kg, provided rapid, effective analgesia in ED patients presenting with acute extremity injuries. Patients, physicians, and nurses reported high average satisfaction with the treatment modality.
Tayebati, S. K., Nwankwo, I. E., & Amenta, F. (2013). Intranasal drug delivery to the central nervous system: Present status and future outlook. *Current Pharmaceutical Design*, *19*(3), 510–526. doi:10.2174/138161281306030510	To review existing CNS active drugs administered intranasally and to pay particular attention to efficient delivery of active principles to the brain.	Detailed information about the nose and nasal cavity anatomy, intranasal delivery, and advantages and disadvantages of IN medication delivery are provided.
Turner, C. L., Eggleston, G. W., Lunos, S., Johnson, N., Wiedmann, T. S., & Bowles, W. R. (2011). Sniffing out endodontic pain: Use of an intranasal analgesic in a randomized clinical trial. *Journal of Endodontics*, *37*(4), 439–444. doi:10.1016/j.joen.2010.12.010	The purpose of this study was to evaluate the efficacy of IN ketorolac for endodontic pain using a randomized, double-blind, placebo-controlled parallel design study.	These results suggest IN ketorolac may provide a novel and efficacious method for pain relief in endodontic pain patients.

Appendix 2: Other Resources Table

Reference	Research Purpose	Conclusions
Wermeling, D. P. (2009). Intranasal delivery of antiepileptic medications for treatment of seizures. *Neurotherapeutics*, *6*(2), 352–358. doi:10.1016/j.nurt.2009.01.002	This review summarizes factors to consider when choosing a benzodiazepine for IN administration, including formulation, pharmacology, and administration device.	Clinical article — conclusions do not apply.
Wolfe, T. R., & Braude, D. A. (2010). Intranasal medication delivery for children: A brief review and update. *Pediatrics*, 126(3), 532–537. doi:10.1542/peds.2010-0616	Only clinical trials of humans published in English were included. Only pediatric-focused articles were included in this review. Because this was intended as a brief topic review rather than a comprehensive literature review or meta-analysis, we included only articles that made unique and meaningful contributions, in the opinion of the authors.	Intranasal medication delivery is an effective method of delivering analgesia, anxiolysis, and anticonvulsants to pediatric patients. In the properly selected patient, nasal administration can reduce time to medication delivery and onset, reduce medical staff resource use, eliminate needle-stick exposure risk, and eliminate pain from the injection, thereby leading to improved patient and parent satisfaction. Pediatricians, pediatric emergency physicians, and emergency medical services medical directors should consider adopting this delivery method for medications and indications appropriate to their practice setting.
Zuckerman, M., Weisberg, S. N., & Boyer, E. W. (2014). Pitfalls of intranasal naloxone. *Prehospital Emergency Care*, 18(4), 550–554. doi:10.3109/10903127.2014.896961	Present a case of failed prehospital treatment of fentanyl-induced apnea with IN naloxone.	The use of IN naloxone may have delayed definitive IV naloxone therapy.

Appendix 3: Study Selection Flowchart and Inclusion/Exclusion Criteria



Inclusion Criteria	Exclusion Criteria
Studies published in English	Studies not published in English
Studies involving human subjects	Non-human studies
January 2005–April 2016*	Studies not in the time frame listed
Studies addressing the PICOT question	Studies not addressing the PICOT questions

The following databases were searched: PubMed, Google Scholar, CINAHL, Cochrane - British Medical Journal, Agency for Healthcare Research and Quality (AHRQ; www.ahrq.gov), and the National Guideline Clearinghouse (www.guidelines.gov)

Search terms included: "Intranasal medication administration," "emergency," "adult," "pediatric," "children," and "prehospital" using a variety of different search combinations. An additional search was conducted using a combination of "intranasal administration" and specific medications including "fentanyl," "morphine," "diazepam," "lorazepam," "sufentanil," "hydromorphone," "glucagon," "naloxone," "ketamine," "ketorolac," and "midazolam." The search time frame for specific medications only was extended to January 2000.