



REVIEW ARTICLE

Pediatrics

# Managing acute pain in children presenting to the emergency department without opioids

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## Abstract

Pediatric pain is challenging to assess and manage. Frequently underestimated in children, untreated pain may have consequences including increased fear, anxiety, and psychological issues. With the current opioid crisis, emergency physicians must be knowledgeable in both pharmacologic and non-pharmacologic approaches to address pain and anxiety in children that lead to enhanced patient cooperation and family satisfaction. This document focuses pain management and distress mitigation strategies for the brief diagnostic and therapeutic procedures commonly performed.

## KEYWORDS

analgesia, emergency department, non-pharmacologic, pain management, pediatrics, policy

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## 1 | INTRODUCTION

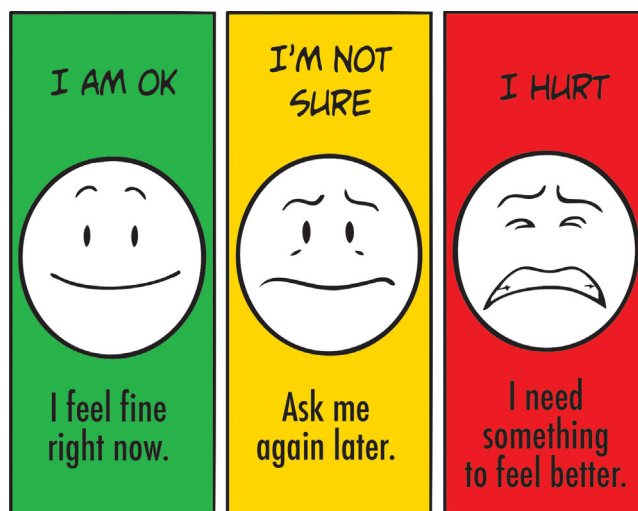
Pain is the most common reason for patient presentation to the emergency department, yet it is often underestimated and managed inadequately in children.<sup>1-3</sup> Untreated pain has been shown to have significant consequences in both the short and long term.<sup>4</sup> A patient- and family-centered approach that includes attention to pain and distress has been tied to improved patient experience while facilitating successful procedure and diagnostic testing completion in the emergency department (ED).<sup>5</sup> As such, all emergency physicians, nurses, physician assistants (PAs), and advanced practice registered nurses (APRNs) should be familiar with various modalities and strategies to minimize pain and distress in children. As many pediatric ED prescribers are steering away from opioid medications as first-line agents in pain relief, the goal of this paper is to discuss the growing armamentarium of approaches for pain and anxiety management.

### 1.1 | Prehospital

Much education has been done across the continuum of care, but especially in the prehospital setting to advocate for early pediatric pain assessment and management. These efforts have been supported by the National Association of Emergency Medical Services Physicians, the joint NHTSA, and Emergency Medical Services for Children Evidence-based Guideline for Prehospital Analgesia in Trauma.<sup>6</sup> Despite this work, the recognition, assessment, and treatment of prehospital pain remains suboptimal and can serve as a focus for quality improvement activities.<sup>7</sup> In a large study of the National Emergency Services Information System database, pain was listed as a primary reason of transport in nearly 30% of patients. Yet children (<15 years) receive pain medication less often than adults.<sup>8</sup> Additionally, 2 metrics for pain were named in National Emergency Medical Services Quality Alliance measures for 2019: to assess pain in injured patients and evaluate the pain management effectiveness.<sup>9</sup> Those measures can provide a nice starting point for understanding where prehospital agencies stand in regard to their pain management practice. Similarly, undertreatment of pain at home before presentation to the ED has been widely reported as well with approximately only half of children receiving pain medication before arrival in the ED. In one study, 54% received ibuprofen, 26% received acetaminophen, and 8% received other medications.<sup>10</sup>

### 1.2 | Approach to pediatric acute pain

Pain assessment should occur early, whether in the field or on arrival to the ED, and reassessment throughout the ED encounter is necessary to ensure appropriate management. A combination approach of physical, psychological, and pharmacological strategies can work more effectively than a single strategy alone.<sup>11-13</sup> An attempt to mitigate the busy, at times loud and chaotic, ED physical environment will assist in minimizing the pain and distress in the child. If possible, a dedicated pediatric area that provides a child-friendly environment with color-



**FIGURE 1** The stop-light pain scale. With permission © 2014 Booster Shot Media, Inc. and Amy L Drendel, DO [www.StoplightPainScale.com](http://www.StoplightPainScale.com)

ful walls or ambient lighting, cartoon paintings, or wall displays, and activities (books, toys, or bubble games and activities) can minimize fear induced by the foreign setting, which may lead to less perceived pain.<sup>11-16</sup> Most procedures performed in the ED are painful, and care should be taken to use a multimodal strategy to provide high-quality care through analgesia management. Preparation goes a long way in setting the stage for the procedure, with use of comfort positioning when possible.<sup>17</sup> Classic interventions such as non-nutritive sucking with pacifier use, swaddling, rocking, or holding children can lower distress.<sup>18</sup> Family presence should be encouraged when preferred by the caregiver.<sup>19</sup>

Several well-validated scales exist for children beginning at age 3 to self-report their pain, and work is ongoing to include easy to interpret scales such as the stop-light pain scale (Figure 1).<sup>20</sup> Interventions should be targeted to the unique age and developmental stage of the child. Preparation provides an opportunity to reduce perceived pain and distress in children. Videos are available on how to integrate techniques into practice.<sup>21</sup> Strategies to ensure the least painful or traumatic approach is employed at the earliest time and when available with awareness for additional follow-up steps if needed. For example, when an intravenous line and/or blood draw are required, as much as possible all tests should be obtained in that initial attempt such that the intravenous line need not be repeatedly manipulated. Similarly, the health care team should plan ahead of time if painful or distressful procedures occur in succession to create a management plan that maximizes management for both procedures (for example, head imaging with planned subsequent lumbar puncture).

### 1.3 | Pharmacologic pain management

#### 1.3.1 | Non-opioid pain medications

A variety of non-opioid pain medications can be regularly used in the pediatric patient: non-steroidal anti-inflammatory drugs (NSAIDs),

**TABLE 1** Pharmacologic pain management

Medication	Route	Dose	Maximum dose	Comment
Acetaminophen	PO	15 mg/kg every 4 h	1000 mg	Not to exceed 75 mg/kg/day or 3750 mg/day
	PR	20 mg/kg every 6 h	650 mg	
	IV	15 mg/kg every 6 h	1000 mg	Not to exceed 75 mg/kg/day or 3,750 mg/day
Ibuprofen	PO	10 mg/kg every 6 h	800 mg	Not to exceed 40 mg/kg/day or 2400 mg/day Not recommended in infants < 6 months
	IV	10 mg/kg every 6 h	400 mg	Not to exceed 40 mg/kg/day or 2400 mg/day Not recommended in infants < 6 months
Ketorolac	IV	0.5 mg/kg every 6 h	15 mg	Not to exceed 5 days
Naproxen	PO	5-7 mg/kg	500 mg	Max 1000 mg/day, children > 2 years
Ketamine	IV	0.05-15 mg/kg/h	0.5 mg/kg/h	Reduced dose in renal impairment
	IN	1 mg/kg	100 mg	
Adjuncts	Route	Dose	Onset	Comments
Buzzy	Topical	0.5-1 mL/dose	Immediate	>3 years, Use on intact skin
Vapocoolant spray	Topical		Immediate	Max 5 mg/kg or 7 mg/kg with a vasoconstrictor
Surcrose	PO		2 mins	(epinephrine)
Buffered lidocaine	SQ		1 min	
Zingo	SQ		< 3 mins	Use on intact skin
J-tip lidocaine	SQ		1 min	Use on intact skin
LET gel	Topical		> 30 min	Use on intact skin
LMX 4% cream	Topical		30 mins	
Ametop cream	Topical		30 mins	
EMLA cream	Topical		> 60 mins	

Abbreviations: EMLA, Eutectic Mixture of Local Anesthetics; IN, intranasal; IV, intravenous; LET, lidocaine-epinephrine-tetracaine; PO, per os; PR, per rectum; SQ, subcutaneous

acetaminophen, subdissociative (analgesic) doses of ketamine, muscle relaxers, gamma-aminobutyric acid agonists, and nerve blockade<sup>22</sup> (Table 1). Often times, rigorous randomized control trials are not available regarding children; thus clinicians are faced with the decision of withholding potentially beneficial medications because they are not labeled for a specific age group or administering a drug based on largely adult data.

NSAIDs are the most commonly used analgesic medications that work via their inhibitory actions on the COX-2 enzyme.<sup>15</sup> COX-2 facilitates the production of proinflammatory prostaglandins; therefore, prostaglandin production is inhibited to obtain analgesia.<sup>15</sup> Widely used examples of NSAIDs in children include ibuprofen, diclofenac, and naproxen. Other COX-2 inhibitors, such as indomethacin, meloxicam, and celecoxib, are used more commonly in inflammatory and rheumatologic disorders than for acute pain. Although acetaminophen/paracetamol demonstrates similar inhibitory activity to NSAIDs, it does not have the same anti-inflammatory properties.<sup>22</sup> Both NSAIDs and acetaminophen have been shown to have non-inferior analgesic effects when compared to opioids for acute extremity pain. Similar findings have been demonstrated when NSAIDs were compared to opioids for management of post-fracture pain in children.<sup>23</sup> A 2016 review demonstrated that the analgesic effects of NSAIDs were equivalently efficacious as opioids when treating musculoskeletal pain.<sup>24</sup> In addition, studies have demonstrated that NSAIDs not only have non-inferior analgesic effects but result in

better functional outcomes and fewer adverse side effects than opioid analgesics.<sup>24-27</sup> When an intravenous administration is required, ketorolac has demonstrated equivalent efficacy in reducing moderate to severe pain as intravenous opioids.<sup>28</sup>

Nitrous oxide (N<sub>2</sub>O) is an odorless, colorless gas with potent analgesic, anxiolytic, and amnestic properties. Approximately 30% to 50% concentrations can be used for mild to moderate pain and escalate to a 70% concentration in severe pain.<sup>29-31</sup> Benefits include fast onset within 30 seconds with peak effect in 5 minutes and rapid return to baseline, as well as minimal effects on respiration.<sup>29-31</sup> However, there is a risk of hypoxemia, so N<sub>2</sub>O should be given with a minimum of 30% of O<sub>2</sub> and once N<sub>2</sub>O is stopped the patient should be placed on non-rebreather mask for at least 5 minutes. Contraindications for N<sub>2</sub>O use include pneumothorax, bowel obstructions, recent eye surgery, and occluded middle ear, as N<sub>2</sub>O causes gas-filled structures to expand when inhaled.<sup>29-31</sup> Another contraindication includes increased intracranial pressure (ICP) or patients with head injury, as N<sub>2</sub>O increases cerebral blood flow and as a result further increases ICP. In addition, there is a relative contraindication in patients with cardiac history and/or decreased ejection fraction as N<sub>2</sub>O decreases cardiac output, heart rate, and contractility; albeit N<sub>2</sub>O can also increase sympathomimetic effects by releasing endogenous catecholamines.<sup>29-31</sup> Side effects include nausea, vomiting, dizziness, headache, and euphoria after use.<sup>32</sup> Although contraindications and risk of hypoxemia exist, the safety of N<sub>2</sub>O has been repeatedly

demonstrated for acute pain control to assist with painful procedures and for anxiolysis in the pediatric ED.<sup>33</sup> A large cohort study has shown that mild adverse events increase when N<sub>2</sub>O is administered for longer than 15 minutes.<sup>31</sup>

Dexmedetomidine, an alpha-2-adrenergic receptor agonist, produces analgesia by dampening the centrally activated sympathetic response. Its use has expanded from sedation to a promising analgesic adjunct. One of its many advantages as a procedure alternative is that it can be effectively delivered through a variety of routes, including intravenously, intranasally, and buccally. It also has fewer respiratory side effects, namely apnea.<sup>34</sup> Concomitant dexmedetomidine use has been shown to reduce opioid (oxycodone) consumption, decrease opioid side effect profile, and improve patient satisfaction in the postoperative setting.<sup>35</sup>

Ketamine, a drug widely used as a sedative, has been shown to be an effective analgesic in both adult and pediatrics when administered at sub-dissociative doses. Ketamine acts to block the effects of glutamate, an excitatory neurotransmitter in the central nervous system, by inhibiting N-methyl-D-aspartate receptors.<sup>36</sup> Benefits to using ketamine over opioid medications include decreased risk of airway compromise, lack of addictive properties, and a short half-life when given intravenously.<sup>36</sup>

Studies have demonstrated subdissociative doses of ketamine to be an effective analgesic for back pain, headache, extremity, or musculoskeletal pain, acute abdominal pain, and renal colic.<sup>36–38</sup> When compared to morphine, ketamine has been found to be comparable in pain control with fewer adverse effects.<sup>37</sup> Many adult studies have demonstrated ketamine was better than fentanyl for the relief of moderate to severe pain.<sup>38–41</sup> Ketamine given as either a push or drip has been shown to be non-inferior to opioids in managing acute pain crisis in sickle cell patients as well.<sup>42,43</sup> In addition, 2 systematic reviews and meta-analyses demonstrated ketamine as non-inferior to opioid medications for acute pain management in the ED with similar analgesic effect and safety profiles.<sup>41,44</sup> Consensus guidelines from the American Society of Regional Anesthesia and Pain Medicine, American Academy of Pain Medicine, and American Society of Anesthesiologists recommend subanesthetic intravenous ketamine bolus doses of up to 0.35 mg/kg and infusions up to 1 mg/kg/h as opioid adjuncts for perioperative analgesia.<sup>37</sup> In the ED setting for pain management, we recommend starting an infusion at 0.05–0.15 mg/kg and titrate to a max of 0.5 mg/kg/h.

### 1.3.2 | Topical anesthetics

Topical local anesthetics are effective for local pain control over the skin for procedures such as intravenous access, venipuncture, lumbar puncture, laceration repair, or incision and drainage of abscess involve injectable or topical anesthetics. Topical anesthetics are very helpful for both open and closed soft tissue complaints, including laceration repairs, peripheral intravenous placement, abscess drainage, and wound management. The American Academy of Pediatrics recommends pain control for venipuncture “whenever possible.”<sup>13</sup> These

medications are useful adjuncts and at times alternatives to oral, intravenous, and intranasal (IN) medications. The most commonly used in the pediatric emergency setting are the topical lidocaine derivatives. For lacerations, a mixture of lidocaine-epinephrine-tetracaine (LET) has been found to be highly effective, often obviating the need for the uncomfortable injection of local anesthetics. A key component to these anesthetics is the allowance of time, as they can often require a minimum of a few minutes and up to 30 minutes to take effect.<sup>45</sup> There are other mixtures of topical analgesics containing lidocaine in a cream base, which provides dermal anesthesia. It is effective for pain control in older children for simple procedures such as peripheral intravenous starts.<sup>46</sup> Quality improvement initiatives have proven successful in improving pain management through the application of topical adjuncts.<sup>47</sup>

Examples of these topical and injectable adjuncts include lidocaine, Eutectic Mixture of Local Anesthetics (EMLA; Astra-Zeneca, Wilmington, DE), and LMX-4 (Eloquest Healthcare, Ferndale, MI). LMX-4 is a 4% lidocaine preparation that is delivered in liposomes for rapid absorption. It works effectively in 30 minutes and is equivalent to EMLA for venipuncture pain.<sup>48</sup> In 1 study, LMX-4 improved cannulation success on the first attempt (74% vs. 55%) when compared with placebo and lowered time of insertion as well as pain scores.<sup>49</sup> LMX-4 has also been shown to improve abscess incision and drainage.<sup>50</sup> Tetracaine compounds (e.g., Ametop Gel, Smith & Nephew Healthcare, Hull, UK; Synera, Galen US, Inc; Endo Pharmaceuticals, Malvern, PA) have also been proven successful, yet is not approved for use on broken skin.<sup>51</sup> Pressurized subcutaneous lidocaine has been used in a variety of needle-free devices to deliver lidocaine or buffered lidocaine under the skin via a jet of compressed carbon dioxide.<sup>52,53</sup> Examples of commercially available devices are the J-Tip® (National Medical Products, Irvine, CA) and lidocaine hydrochloride powder (Zingo, Anesiva, Inc. San Francisco, CA).<sup>54</sup> For the lidocaine powder, one can apply the device to the site planned for intravenous or venipuncture 1–3 minutes before needle insertion and perform the procedure within 10 minutes after administration.

Vapocoolants are another class of medications that may be applied for intravenous placement site<sup>55,56</sup> and have been successful. The container should be held 3–7 inches from the target area with the spray directed downward to the target area for 4 to 10 seconds. Studies have found the J-tip less painful for intravenous cannulation than EMLA cream or vapocoolant spray.<sup>57</sup>

### 1.3.3 | Local nerve blocks

Local nerve blocks such as radial, ulnar, and tibial nerve blocks are routinely used effectively with ultrasound guidance for laceration repairs, hand injuries, and nail bed injuries.<sup>58,59</sup> Digital blocks and field blocks are common and straightforward to perform in the pediatric emergency setting. They are helpful for laceration repair and reduction of simple fractures or finger joint dislocations. Hematoma blocks are also a safe and effective for orthopedic long bone injuries requiring reductions.<sup>60</sup> In pediatrics, hematoma and Bier blocks are most

**TABLE 2** List of non-pharmacological strategies for pain management

Behavioral strategies	Cognitive strategies	Complementary strategies
Behavioral distraction	Breathing exercises	Medical play
Desensitization	Cognitive (mental) distraction	Therapeutic art
Medical staff coaching	Comforting/reassurance	Therapeutic play
Modeling	Coping self-statements	Therapeutic uses of music
Parent coaching	Hypnosis	
Parent training	Imagery	
Positive reinforcement	Memory change	
Rehearsal	Progressive muscle relaxation	
	Providing information/preparation	
	Relaxation training	
	Suggestion	
	Thought stopping	
	Virtual reality	

effectively administered with adjuncts such as N<sub>2</sub>O owing to the anxiety-provoking nature of the procedure in younger children.<sup>61</sup>

When injected lidocaine is required, care should be taken to ensure liquid is at room temperature before administration and buffer the acidity of the lidocaine with sodium bicarbonate. Use the smallest gauge needle to inject intradermally (ie, 27 gauge) 1/2 cm below the proposed insertion site. Aspirate the plunger of the syringe to verify that the vein has not been entered. Instill buffered lidocaine 0.1 mL at a constant rate to form a small wheal. Wait at least 1 minute before attempting the insertion/puncture. Perform needlestick with the needle entering the skin within the wheal.

## 1.4 | Non-pharmacologic pain management

### 1.4.1 | Cold and vibration devices

The external application of cold and vibration devices has been used by dentists over the past century to provide counterstimulation of the lip to reduce pain from local anesthesia injection. The mechanism of action is to provide a mild noxious stimulus (eg, combination cold and vibration) at one site to inhibit pain response at a more distal site. The vibration can block the afferent pain-receptive fibers by non-noxious fibers, further blocking pain transmission. Several commercially available vibration devices have been developed to assist by this mechanism.<sup>62</sup> Buzzy (MMJ Labs, Atlanta, GA), a bee shaped device that delivers a combination of vibration (body) and cold (wings), has been studied and shown to be an effective way to provide local anesthesia to the skin before a painful procedure.<sup>63</sup>

### 1.4.2 | Cognitive behavioral strategies

Cognitive and behavioral strategies refer to techniques that alter the perception of painful experience in patients. When appropriate, most pain in children should be first addressed with distraction techniques, such as the use of guided imagery, music, videos, interactive games, and singing. A non-exhaustive overview of these strategies is listed in

Table 2.<sup>64</sup> Although some of these techniques do not require much training from parents or staff (eg, use of toy as a distraction tool, playing movies, or songs), others (eg, medical play, guided imagery) require the guidance of trained personnel such as certified child life specialists. The goals of these interventions are to decrease fear, reduce distress and pain, and give children a sense of control.<sup>65</sup>

Most of the published clinical trials on cognitive and behavioral strategies conducted in the ED setting used some form of distraction.<sup>66-77</sup> The most commonly reported procedures were venipuncture and laceration repair. All except 2<sup>66,77</sup> of these studies reported some degree of improved observed pain/distress (by parents or observers) or self-reported pain with intervention. Three additional studies reported that the presence of certified child life specialists generally led to less pain or distress in children undergoing venipuncture or laceration repair in the ED, though it may be hard to separate the effect of the personnel from the interventions they performed.<sup>78-80</sup> A Cochrane Review of a randomized clinical trials involving children 2-19 years found evidence supporting the efficacy of distraction, hypnosis, combined cognitive behavioral therapy, and breathing interventions for reducing children's needle-related pain, distress, or both.<sup>81</sup>

## 1.5 | Special populations

### 1.5.1 | Neonates

Neonates represent a particularly important population that often has painful procedures performed as a result of evaluations for infection and other medical needs. Historically, pain management in neonates was given little attention, but it is clear both that neonates feel pain and that improper pain management and even prior painful procedures have potential long-term consequences for the patient.<sup>82-86</sup> Multiple options exist for non-opioid pain management of neonates during potentially painful procedures. In addition to local anesthesia, oral sucrose as well as skin-to-skin care have shown evidence of a reduction in pain.<sup>83,87,88</sup>

Oral sucrose has been used in neonates undergoing a painful procedure. Studies have shown that oral sucrose combined with the action of

nonnutritive sucking has a mild analgesic effect. A recent review looking at the efficacy of oral sucrose showed pain reduction in a select group of procedures but not others.<sup>89</sup> Oral sucrose solutions in concentrations of 24% to 30% have been shown to be effective at decreasing pain for lumbar punctures, heel lance, venipuncture, and intramuscular injection. However, sucrose does not provide effective pain relief during circumcision. Sucrose is most effective for preterm infants and neonates younger than 2 months of age, although it may provide pain relief in 6-month-old infants for less invasive procedures. In addition, sucrose use and/or breastfeeding have been shown to have equal benefit to EMLA in the infant population on recent meta-analysis.<sup>46</sup> There is conflicting evidence for whether sucrose reduces pain for other minor painful procedures and further research is needed to investigate these more thoroughly. Considering all these options combined should be considered as appropriate for procedures such as intravenous starts, lumbar puncture, and bladder catheterization. In addition, when appropriate, opioids should be used in neonates as in older patients.<sup>90</sup>

### 1.6 | Children with intellectual disability

Children with intellectual disability present a particular challenge, both in terms of pain recognition to new physicians, nurses, PAs, and APRNs outside their medical home, and in their sometimes different response to various therapeutic modalities. Depending on the degree of cognitive impairment, traditional strategies of measuring pain can be less useful. Relying on parental reports on whether their child is uncomfortable is recommended, and parents will often identify the best practices to soothe their child and adapt to the particular medical situation.<sup>91</sup> In addition, clinicians must be attentive to what works and does not work for the individual child; some children with special needs will respond in a unique way to touch, sound, and light, so engaging both the patient when appropriate and the parent or guardian is vitally important.

### 1.7 | Chronic pain

Chronic pain has been noted to affect 15% to 35% of children<sup>92</sup> in the world and is defined as pain that is persistent or recurrent and either associated with a medical condition, such as sickle cell disease or arthritis, or the actual condition, such as functional abdominal pain or migraines.<sup>13</sup> Because of the variation in causes of chronic pain in children, treatment has to be varied with the goal of not only decreasing pain but improving functioning and quality of life.

Sickle cell patients are an underserved and frequently undertreated group subject to frequent cognitive bias on the part of the medical care team. Early administration of both opioid and non-opioid pain management such as NSAIDs affects both the perceived pain on the part of the patient as well as improving the rate of discharge from the ED.<sup>93-95</sup>

When a chronic condition causes acute pain, such as a vaso-occlusive crisis in sickle cell disease or a flare of arthritis, acute pain management with standard analgesics, NSAIDs, or acetaminophen is appropriate with the adjunct of opioid medications when needed. However, daily management involves a more scheduled approach that may

include NSAIDs, anticonvulsants, and antidepressants as well as other medications used for chronic pain.

### 1.8 | Other considerations

An important consideration when attempting to limit opioid usage in favor of other modalities is to remain sensitive to the issue of cognitive bias and disparities. It is clear that minorities and patients of lower socioeconomic status receive less opioid pain management. The reasons for this are unclear, although it is likely that implicit bias on the part of clinicians and health care systems play a role. Clinicians must ensure that all patients receive access to effective pain treatment options, and systems must be enacted to support this and work around any bias that continues to exist. As new modalities are pushed, it is important to be cautious that opioid use does not rise in disadvantaged populations.<sup>96-99</sup>

Multiple barriers exist to implementing alternatives to opioids. As in the adult population, opioids are often an easy first choice for severe pain management and the default option for most clinicians and health care systems. In the absence of protocols, it can be challenging to use multimodal treatment options in a busy ED. Moreover, significant gaps in pediatric preparedness exist, and many facilities see low volumes of children.<sup>100</sup> Resources such as child life specialists, multimedia distractions, and the like may be more limited to children's hospitals in the absence of adequate volumes and financial support. It may be particularly challenging for a facility that sees few pediatrics patients to manage the multiple modalities of pain management needed for pediatric patients. However, with the availability of smartphones giving access to information, music, and children's videos, pain and anxiety can be reduced simply by taking a few minutes to understand the age, developmental stage, and interests of pediatric patients.<sup>101</sup>

## 2 | CONCLUSION

Although the consideration of non-pharmacological and non-opioid pain management options should be used if feasible, clinicians should be careful to consider the underlying reason for the ED presentation. A patient with a traumatic injury is likely to be in pain and careful evaluation of vital signs, crying, or facial grimace can be helpful to direct escalation of pain management with careful reassessment to evaluate appropriate pain management versus evolving medical or surgical process. Appropriate recognition of pediatric pain and escalation of pain management, including opioids, should be used when appropriate.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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