The Evolving Landscape of Acute Pain Management in the Era of the Opioid Crisis

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Abstract

Purpose of Review The purpose of the study is to evaluate and analyze the role of both opioid and non-opioid analgesics in the emergency department (ED).

Recent Findings Studies have shown that the implementation of opioid-prescribing policies in the ED has the potential to reduce the opioid addiction burden. Clinical studies point to inconsistencies in providers’ approach to pain treatment. In this review, we discuss specific aspects of opioid utilization and explore alternative non-opioid approaches to pain management.

Summary Pain is the most common reason patients present to the ED. As such, emergency medicine (EM) providers must be well versed in treating pain. EM providers must be comfortable using a wide variety of analgesic medications. Opioid analgesics, while effective for some indications, are associated with significant adverse effects and abuse potential. EM providers should utilize opioid analgesics in a safe and rational manner in an effort to combat the opioid epidemic and to avoid therapeutic misadventures. EM providers should be aware of all of their therapeutic options, e.g., opioid and non-opioid, in order to provide effective analgesia for their patients, while avoiding adverse effects and minimizing the potential for misuse.

Keywords Opioid · Prescriptions · Non-opioid pain medications · NSAIDS

Introduction

There is a clear correlation between the rise in number of opioid prescriptions written and rise in the number of hospital visits and deaths resulting from opioid abuse and overdose. According to the Centers for Disease Control and Prevention (CDC), drug overdose deaths attributed to prescription opioids quadrupled between 1999 and 2014 [1]. It may be no coincidence that the number of prescriptions written for opioids has also quadrupled in that 15-year time period, despite the fact that Americans have not been reporting an increase in

the amount of pain they are experiencing [1, 2]. This burden is felt in the emergency department (ED), where 1000 people are treated for prescription opioid misuse everyday [3]. EM providers face many barriers to appropriate pain management, including lack of universal opioid-prescribing guidelines, lack of formalized residency training surrounding pain management, and limited evidence supporting both opioid and non-opioid pain protocols [4, 5].

The opioid epidemic is of particular relevance to providers in the ED, where pain is the most common reason why patients present [4]. Between 2001 and 2010, the percentage of ED visits that resulted in an opioid being used increased from 20.8 to 31%. In contrast, there was a more modest increase in pain-related ED visits (47.1 to 51.1%) [6], while simultaneously, the use of non-opioid pain relievers remained relatively unchanged [6]. The ED was cited as the main source for prescription opioids in 10% of patients, who diverted opioids [7, 8]. Of the opioids prescribed, studies have suggested that 10% are associated with indicators of inappropriate prescribing, and approximately 40% are misused, most commonly by taking more than prescribed [8, 9]. Indicators of inappropriate prescribing practices include overlapping opioid prescriptions, high daily dosages, and prescriptions for long-acting opioids for acute pain [9].
More recent trends reveal that emergency physicians have actually experienced the largest drop in opioid-prescribing rates compared to all other specialties [10]. In fact, half of all opioid prescriptions dispensed nationwide can be attributed to primary care specialties, with physical medicine and rehabilitation specialists being responsible for the greatest increase in opioid-prescribing rates since 2007 [10].

The roots of the opioid epidemic are multifactorial. One contributing factor is well-meaning providers attempting to alleviate the massive pain burden in the USA. According to the Institute of Medicine’s report on Relieving Pain in America, over 116 million Americans suffer from chronic pain, with management costing upwards of $635 billion per year [5]. Efforts over the years have focused on relieving this burden. Since the 1990s, pharmaceutical companies have been promoting opioids for non-cancer pain, while the American Academy of Pain Medicine promoted the long-term use of opioids for non-cancer pain control with little risk of dependence [4]. In 2001, the Joint Commission on Accreditation of Healthcare Organizations strongly advocated for patients’ right to appropriate pain management, thereby introducing pain as the fifth vital sign [11]. More recently, the Institute of Medicine has called for early and effective pain management to be the moral responsibility and the duty of the healthcare professional [5, 12].

Efforts must be made to combat opioid misuse in the ED, focusing on interventions such as rational use of opioid analgesics, expanded use of opioid alternatives, and initiation of addiction treatment. According to the Drug Abuse Warning Network, although ED visits linked to non-medical use of prescription opioids doubled between 2004 and 2009, the rate leveled off between 2009 and 2011 [3]. This plateau could be related to the increase in number of patients seeking outpatient treatment for opioid use disorders, as well as the increase in buprenorphine prescriptions during this same time period [3]. Other factors include the implementation of prescribing guidelines and widespread use of Prescription Drug Monitoring Programs (PDMPs). Programs targeted at initiating addiction treatment in the ED have shown promising results. Researchers at Yale found that an ED-initiated buprenorphine treatment program significantly increased addiction treatment services and reduced non-medical opioid use in enrollees [13].

Studies have shown that the implementation of opioid-prescribing policies in the ED has the potential to reduce the opioid addiction burden as well. A group of researchers from Virginia Mason Medical Center in Seattle found that the implementation of an ED policy for prescribing opioids is associated with a significant reduction in total opioid prescriptions [14•]. However, a review conducted by Beaudoin et al. evaluating the impact of opioid-prescribing policies on patient outcomes discovered that while implementing such policies may reduce overdose, there is little evidence to suggest they reduce opioid misuse [15]. This paper will review specific aspects of the opioid utilization related to emergency medicine and explore alternative non-opioid approaches to pain management.

### Analgesic Options in the Acute Setting

#### Opioids

**Morphine**

Morphine is one of the most commonly prescribed opioids in the ED. It is considered the gold standard in treating pain. In addition to severe pain, morphine is also part of the standard treatment in the management of both myocardial infarction and acute pulmonary edema.

For analgesia, a starting dose of 0.1 mg/kg given intravenously is often recommended with subsequent doses of 0.05 mg/kg given every 5 min until pain relief is achieved [16]. Obesity does not influence a patient’s response to this dosing; thus, patients who are obese do not require higher doses of morphine [17]. Providers should expect that the initial dose of 0.1 mg/kg might not provide adequate analgesia. A study by Bijur et al. found that 67% of patients who received this dose reported less than a 50% reduction in their pain after 30 min [18]. Another study found that 47% of patients in the ED did not achieve adequate pain reduction after 1 h when receiving 0.1 mg/kg [19]. In searching for the optimal dose of IV morphine, Lvovschi et al. found that 99% of ED patients received adequate analgesia with a mean dose of 0.15 ± 0.09 mg/kg given in three boluses [20].

Morphine can also be given as patient controlled analgesia (PCA). Typically, patients are given a 2-mg bolus followed by a 1-mg patient-activated dose. The lockout period is usually 6 to 8 min. Birnbaum et al. studied the effectiveness of morphine PCA in acute abdominal pain patients in the ED. They found that patients who received morphine PCA had greater satisfaction and greater pain relief at 120 min than those who received the standard physician-managed analgesia [21].

Adverse effects of morphine include respiratory depression, hypotension, nausea, vomiting, and pruritus. Fear of these side effects often leads physicians to underutilize morphine. However, multiple studies have demonstrated that morphine is safe when proper prescribing protocol is respected [22–24]. One study found that using morphine during ST segment myocardial infarction did not lead to an increase of in hospital complications nor 1-year mortality [25]. All of the metabolites of morphine are renally excreted and morphine.

6-Glucuronide is an active analgesic metabolite [26]. Several case reports have reported nausea and sedation in patients with impaired renal function receiving morphine [27, 28]. Dose adjustment and monitoring is recommended when using morphine in patients with renal impairment. Related to its lower abuse liability compared to other opioids,
Hydromorphone

Hydromorphone is a semisynthetic derivative of morphine. Studies have shown it can be used for many conditions, ranging from renal colic to sickle cell crisis [30, 31]. A starting dose of 0.015 mg/kg every 5 min to achieve pain relief is recommended for hydromorphone [1]. Another popular dosing strategy in the ED is known as the “1+1 titration method” where patients receive a loading dose of 1 mg IV followed by an additional 1 mg 15 min later if requested by the patient. Chang et al. studied the efficacy of the 1+1 titration method in treating acute pain. They found that the 1+1 titration method leads to adequate analgesia in 96% of patients after 1 h [32]. A subsequent study, also by Chang et al., showed that this patient controlled method was just as effective and safe as the standard physician-driven method of treating pain [33]. Chang et al. also studied whether a single dose of 2 mg of hydromorphone IV was more effective for treating acute pain. While their study showed a dramatic reduction in pain scores, 32% of patients had their O2 saturations drop below 95%. While none of the patients required naloxone, the authors concluded that the “finding suggests that 2 mg IV hydromorphone is too much opioid to be given routinely to patients in pain as a single initial dose” [34]. A retrospective study that compared patients receiving hydromorphone PCA vs morphine PCA found that more patients receiving morphine PCA required rescue pain medication due to inadequate analgesia [35]. Of note, the metabolites of hydromorphone are renally excreted [36]. As such, it should be dosed cautiously in patients with renal impairment (Table 2).

Fentanyl

Fentanyl is the most potent opioid, e.g., 80–100 times as potent than morphine, and routinely is used in the ED. It is also one of the fastest acting opioids; it has a time of onset of 1–2 min and typically lasts around 30 min [37]. This rapid onset is very useful when quick pain relief is needed, such as in the setting of trauma. Additionally, fentanyl has a very short half-life, which makes it ideal for situations where serial exams are needed, also because it is structurally different so may be useful in patients with morphine allergies.

Fentanyl is typically dosed at 1 μg/kg when providing analgesia [21]. However, for trauma patients, Curtis et al. showed significant improvements in analgesia with a dose of 25–50 μg for patients over 40 kg and 10–25 μg for patients less than 40 kg [38]. Fentanyl has a very favorable safety profile; a retrospective chart review of over 2000 patients showed that fentanyl only affected vital signs in less than 1% of patients [39]. However, fentanyl can cause chest wall rigidity when doses of greater than 15 μg/kg are administered. This complication is rare and can be reversed with naloxone, although higher doses may be required [40].

Interestingly, in addition to the IV route, intranasal and buccal tablet forms of fentanyl have also been shown in very limited studies to be effective in providing analgesia. Intranasal fentanyl has primarily been studied in the pediatric population. Saunders et al. showed that a single intranasal dose of 2 μg/kg of fentanyl provided effective analgesia for pediatric patients with orthopedic trauma [41]. Transbuccal fentanyl has been evaluated for orthopedic pain for adult patients in the ED. The FAIRTOP trial compared pain response in patients receiving transbuccal fentanyl versus oxycodone/acetaminophen. They found that those receiving transbuccal fentanyl had significantly faster onset of analgesia without an increased risk of adverse effects [42] (Table 3).

Non-opioids

Acetaminophen

Acetaminophen is a common over-the-counter analgesic that can be used for pain relief in the ED. It has a central anti-pyretic effect; thus, acetaminophen is useful when a fever needs to be reduced. While acetaminophen is a good analgesic for mild to moderate pain, it does not have anti-inflammatory properties. Systemic reviews have shown that acetaminophen is less effective at relieving pain than non-steroidal anti-inflammatory drugs (NSAIDs), including conditions such as osteoarthritis and back pain [43–45]. Acetaminophen is generally well tolerated; however, overdose can cause severe hepatotoxicity.

Table 1 Morphine

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patanwala et al. [17]</td>
<td>Prospective observational</td>
<td>50</td>
<td>Patient weight was not associated with degree of analgesic response</td>
</tr>
<tr>
<td>Lvovschi et al. [20]</td>
<td>Observational prospective cohort</td>
<td>162</td>
<td>99% of ED patients received adequate analgesia with a mean dose of 0.15 ± 0.09 mg/kg given in 3 boluses</td>
</tr>
<tr>
<td>Birnbaum et al. [21]</td>
<td>Randomized controlled trial</td>
<td>211</td>
<td>Abdominal pain patients had greater analgesia with morphine PCA compared to physician-managed analgesia</td>
</tr>
<tr>
<td>Puymirat et al. [25]</td>
<td>Prospective observational</td>
<td>2438</td>
<td>Morphine was not associated with increased 1 year mortality in STEMI patients</td>
</tr>
</tbody>
</table>
Thus, acetaminophen should be used sparingly in patients in whom liver disease is suspected (i.e., alcoholics). Recently, intravenous acetaminophen has been studied for its analgesic properties. Craig et al. compared intravenous acetaminophen against intravenous morphine for pain control in patients with acute limb injuries in the ED. They found no significant differences in analgesia between the two groups but there were significantly higher adverse reactions in the morphine group [47]. Eismaillan et al. had similar findings when comparing intravenous acetaminophen to intravenous morphine in rib fracture patients [48]. Other studies have shown that intravenous acetaminophen reduces the need for rescue pain medications [49, 50] (Table 4).

Furyk et al. compared intravenous acetaminophen to oral acetaminophen. They found that intravenous acetaminophen was not superior to oral acetaminophen [51]. This potentially limits the usefulness of intravenous acetaminophen as it is much more expensive than its oral formulation.

Non-steroidal Anti-inflammatory Drugs

All NSAIDs provide analgesia through inhibition of cyclooxygenase (COX) with some inhibiting both COX-1 and 2 while others are more selective for COX-2. COX-2 primarily mediates pain and inflammatory pathways; thus, all NSAIDs are effective for inflammatory pain. They are less useful for pain that is non-inflammatory (i.e., neuropathic pain). Studies have shown that there is no significant difference in analgesic quality between different NSAIDs [52, 53].

Although all NSAIDs have similar analgesic properties, they differ in adverse effects. In general, the most common adverse effect of NSAIDs is gastrointestinal injury mediated via the COX-1 pathways. Morbidity and mortality are common, including bleeding, dyspepsia, and/or gastric ulceration [54]. This is of particular concern for elderly patients. The risk of NSAID-induced GI adverse event nearly doubles with every decade of age after 55 and the majority of patients have painless bleeding [55]. Patients who are at high risk for gastric complications, such as the elderly, those with known gastrointestinal disease, or patients on glucocorticoids, have a relative contraindication to NSAIDs. However, each NSAID poses a different level of risk; for example, the relative risk of ibuprofen is 2.6 while the relative risk of ketorolac is 14.5 [56, 57]. There is also a risk of nephropathy with COX-2 inhibitors. COX-2 selective NSAIDs have been shown to decrease renal perfusion and lead to decreased sodium excretion [58, 59]. COX-2 inhibitors have also been shown to lead to an increased risk of serious adverse cardiac events [60]. Related to their unfavorable adverse effect profile, and the lack of superiority in analgesic ability compared to non-selective COX inhibitors, there is no advantage to use selective COX-2 inhibitors in the ED, unless the patient is at high risk for gastrointestinal bleeding.

NSAIDs have been shown to be very useful for a wide range of inflammatory conditions. For instance, ketorolac has been shown to significantly reduce pain associated with renal colic, and has similar analgesia in these patients as morphine [61]. When used in combination, NSAIDs and opioids have been shown to be superior to either drug alone and reduce the need for rescue analgesia [62]. NSAIDs have also been shown to be effective in the setting of acute low back pain and significantly improve daily function [63]. Adding opioids in this setting does not appear to be superior to NSAIDs alone [64].

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jasani et al.[30]</td>
<td>Randomized controlled trial</td>
<td>73</td>
<td>Hydromorphone provided better analgesia for patients with renal colic than meperidine</td>
</tr>
<tr>
<td>Tanabe et al.[31]</td>
<td>Prospective cohort</td>
<td>155</td>
<td>Hydromorphone provides adequate analgesia during sickle cell crisis</td>
</tr>
<tr>
<td>Chang et al.[32]</td>
<td>Randomized controlled trial</td>
<td>338</td>
<td>1+1 titration method was more effective than usual care</td>
</tr>
<tr>
<td>Chang et al.[34]</td>
<td>Randomized clinical trial</td>
<td>269</td>
<td>2 mg hydromorphone was efficacious but 32% of patients had O2 desaturation</td>
</tr>
<tr>
<td>DiGiusto et al.[35]</td>
<td>Retrospective cohort</td>
<td>514</td>
<td>Hydromorphone PCA had less side effects compared to morphine PCA</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curtis et al.[38]</td>
<td>Randomized controlled trial</td>
<td>243</td>
<td>Significant improvements in analgesia with a dose of 25–50 μg for patients over 40 kg and 10–25 μg for patients less than 40 kg</td>
</tr>
<tr>
<td>Thomas et al.[39]</td>
<td>Retrospective chart review</td>
<td>99</td>
<td>Fentanyl affected vital signs in less than 1% of patients</td>
</tr>
<tr>
<td>Saunders et al.[41]</td>
<td>Prospective interventional</td>
<td>81</td>
<td>Intranasal fentanyl at a dose of 2 μg/mg provided effective analgesia for pediatric patients with orthopedic trauma</td>
</tr>
<tr>
<td>Shear et al.[42]</td>
<td>Randomized controlled trial</td>
<td>60</td>
<td>Transbuccal fentanyl had significantly faster onset of analgesia without an increased risk of adverse effects compared to Percocet</td>
</tr>
</tbody>
</table>
Ketamine

Ketamine is a phencyclidine-like anesthetic that, in full dissociative doses (1.5–2 mg/kg intravenous), causes a cataleptic state characterized by open eyes and preserved airway reflexes [65]. Classically, ketamine has been used in the ED for procedural sedation. However, there is emerging data that ketamine, in sub-dissociative doses, can provide analgesia as well.

Studies examining ketamine’s use as an analgesic are newer but tend to be positive. One study found that ketamine and morphine combined is superior to morphine alone for out of hospital trauma patients [66]. Other, small studies have shown that ketamine is effective and well tolerated among trauma patients [67, 68]. Another study by Motov et al. found that ketamine at a dose of 0.3 mg/kg intravenous provided equal analgesia to morphine in the ED [69]. However, that study was limited by a small sample size. In a correspondence piece in The American Journal of Emergency Medicine, Drs. Herring and Ahern stated that, in their experience, ketamine is useful for patients on opioids for chronic pain with new breakthrough pain [70]. However, to date, no studies have examined this issue.

In terms of adverse effects, hypersalivation, vomiting, and unpleasant emergence reactions are some of the most common non-hemodynamic complications associated with ketamine in induction doses, but very uncommon with sub-dissociative dose [71, 72]. Giving an antiemetic such as ondansetron, either in the ED or for the patient to take home and use as needed, can mitigate post-ketamine emesis [73]. Emergence reactions from ketamine are unpleasant and include nightmares and hallucinations. In a survey of ED physicians, fear of emergence reactions was the most common reason for not administering ketamine for analgesia [74]. However, concomitant administration of a benzodiazepine such as midazolam can provide prophylaxis against emergence reactions [75]. In terms of hemodynamics, ketamine has sympathomimetic effects, which leads to increases in heart rate and blood pressure. However, the latest data shows there is little concern for ketamine’s impact on intracranial pressure [76, 77] (Table 5).

Gabapentin

Gabapentin was initially developed as an anti-epileptic; however, in 2004, it was approved by the Food and Drug Administration to treat post-herpetic neuralgia. Since then, gabapentin has been shown to be effective in treating a number of neuropathic pain conditions including post-herpetic neuralgia, painful diabetic neuropathy, mixed neuropathic pain syndromes, phantom limb pain, Guillain-Barré syndrome, and spinal cord injury pain [81]. Gabapentin and similar agents that treat neuropathic pain are other analgesic options that can be utilized by emergency providers.

Historically, many presumed that gabapentin had no abuse potential. However, recent data suggests that this assumption may be incorrect. A study by Smith et al. found a 3000% increase in the rates of using gabapentin to “get high” from 2008 to 2014 in a cohort of over 500 prescription drug users in Central Appalachia [82]. Gabapentin is most often misused with other substances, especially opioids, alcohol, and benzodiazepines [83]. It is prescribed for a wide variety of medical conditions so it is relatively easy to legally acquire and is also
covered by many insurance plans. Emergency medicine providers need to be cognizant of gabapentin’s abuse potential when prescribing it in the ED.

Conclusions

Emergency medicine providers play a key role in pain management for many patients, often serving as the first point of contact between the patient and the health care system. Treating pain properly requires providers to balance the potential benefits against anticipated harms. Emergency medicine providers must recognize and utilize the wide array of medications they have access to in order to provide proper relief to their patients, while minimizing adverse effects and addiction potential.

Compliance with Ethical Standards

Conflict of Interest  Ali Pourmand, Gregory Jasani, Courtney Shay, and Maryann Mazer-Amirshahi declare no conflict of interest.

Human and Animal Rights and Informed Consent  This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

• Of importance
• Of major importance

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