

## Review Article

# Management of Pain in the Emergency Department

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Since pain is a primary impetus for patient presentation to the Emergency Department (ED), its treatment should be a priority for acute care providers. Historically, the ED has been marked by shortcomings in both the evaluation and amelioration of pain. Over the past decade, improvements in the science of pain assessment and management have combined to facilitate care improvements in the ED. The purpose of this review is to address selected topics within the realm of ED pain management. Commencing with general principles and definitions, the review continues with an assessment of areas of controversy and advancing knowledge in acute pain care. Some barriers to optimal pain care are discussed, and potential mechanisms to overcome these barriers are offered. While the review is not intended as a resource for specific pain conditions or drug information, selected agents and approaches are mentioned with respect to evolving evidence and areas for future research.

## 1. Introduction

*“Pain is, with very few, if indeed any exceptions, morally and physically a mighty and unqualified evil. And, surely, any means by which its abolition could possibly be accomplished, with security and safety, deserves to be joyfully and gratefully welcomed by medical science” [1], Sir James Young Simpson, administerer of the first obstetrical anesthesia.*

Addressing patient’s pain is one of the most important contributions ED providers can make. The frequency with which pain is the impetus for an ED visit, the significance of pain relief to individual patients (and family), and the relative ease with which pain can often be ameliorated render analgesia a prime—and achievable—target for optimization of a patient’s ED care. In considering pain care in the ED, some general principles should be kept in mind; these are reviewed in the initial part of this discussion. The next subject to consider is the question of whether there is need for discussion on pain care in the ED. The case for focus on pain management is bolstered by results of an assessment of the *status quo* of ED analgesia practices. Rather than simply identifying areas in which ED practitioners are performing suboptimally,

the discussion will also include recommendations for overcoming barriers to appropriate pain care. Specific analgesic approaches will be addressed, with attention to various patient populations in which analgesia care is historically poor or controversial.

The goal of this review is not to be a comprehensive discussion of all matters related to ED pain assessment and care; the subject is simply too broad (a PubMed search using the terms “ED analgesia” and “acute analgesia” returns thousands of articles). Rather, through a mechanism of highlighting areas of particular clinical interest and relevance, it is hoped that the review can achieve its aim of focusing attention on ED analgesia and furthering the goal of reducing patients’ pain.

The necessarily focused nature of this discussion means that some important information will not be discussed. Drug dosages, analgesic times of onset and duration, and other pharmacologic information is quickly and easily retrievable from a variety of other sources. With a few exceptions for illustrative examples, specific disease and injury analgesia approaches are not mentioned. For this type and level of information, there are entire texts addressing ED-specific approaches to analgesia [2]. The critically important topic of prehospital analgesia, addressed in previous reviews [3], largely falls outside of the scope of this discussion. The goal

of this discussion is to share selected opinions and related evidence pertinent to pain care in the ED. Rather than being a final resource for those seeking information regarding ED analgesia, the discussion hopes to provide a “jumping-off point” to facilitate education, debate, clinical research, and conversation about advancing acute pain care.

It may be useful for ED practitioners to be familiar with some basic terminology from the pain care arena. Some terms below will be familiar to acute care providers, but others may be new and can facilitate both patient care (e.g., understanding the varying treatments for neuropathic versus inflammatory pain) and conversations with pain care specialists. Terms that may be encountered during discussions of acute pain care include the following.

- (i) *Hyperalgesia*: the state where a painful stimulus causes more pain than normally expected.
- (ii) *Inflammatory pain*: is caused by tissue injury related to heat, hypoxia, inflammation, or trauma; this injury leads to peripheral stimulation of nociceptors (pain receptors) of nonmyelinated C fibers.
- (iii) *Narcotic*: derived from the Greek word for stupor; this term has mostly legal context (e.g., marijuana is a narcotic) and is no longer useful as a medical term.
- (iv) *Neuralgic pain*: is similar to neuropathic pain but does not involve nerve damage.
- (v) *Neuropathic pain*: occurs when there is direct activation of either sensory nerves or sensory ganglia by nerve injury or disease.
- (vi) *Opiates*: are opium-derived drugs and their semisynthetic congeners; morphine (after Morpheus, the Greek god of dreams) is one of many alkaloids isolated from opium and codeine is another opium-derived alkaloid.
- (vii) *Opioid*: is a more inclusive term and is generally preferred to “opiate”; it applies to all agonists and antagonists with morphine-like activity and also applies to naturally occurring and synthetic opioid peptides.
- (viii) *Opium*: is derived from Greek name for juice and refers to the juice of the poppy, *Papaver somniferum*.
- (ix) *Wind-up*: a phenomenon of recruitment and increased analgesia requirements.

## 2. General Principles Underlying ED Pain Care

Pain and analgesia represent such a broad subject area that there are doubtless dozens of potentially important tenets guiding care. Some general principles that have been found useful in the author’s experience are presented in this section.

**2.1. Pain Is Often the Primary Complaint and Impetus for ED Presentation.** In most cases the average EM specialist is primarily concerned with differential diagnosis, ruling out life-threatening disease and providing stabilizing emergency interventions. For the patient, though, the priorities are more

likely to include pain management. Many decades ago, editorialists pointed out that pain relief is not only one of the patient’s priorities, but that it can be *the* major reason for up to (and possibly more than) half of ED visits [4]. There is little reason to believe that the patients’ focus on pain relief has substantially altered in the 3+ decades since the point was initially made. In fact, the argument can be made that in 2013 patients’ focus on pain relief is now being used as a basis for both internal and external adjudication as to how well an ED is doing (e.g., as assessed by regulatory bodies) [5]. The point is if pain relief is a primary reason patients present to the ED, pain relief should be one of the primary foci of emergency care provision.

**2.2. Many Things That Happen to Patients in the ED Add to Their Pain.** ED procedures that may hardly prompt a second thought from care providers can cause pain. Even something as ubiquitous and seemingly trivial as venipuncture has been demonstrated to cause pain that is can be perceived by patients (especially children) as significant [6]. Other procedures, ranging from arterial puncture to intravenous access and placement of indwelling tubes in the stomach or bladder, have been known for decades to be potential causes of significant pain in the ED population [7]. The ED physician is not admonished against performing these necessary procedures; the point is rather that the pain caused by the ED work-up and stabilization should be taken into account when analgesia care is considered. Sometimes a little explanation as to the reasons for causing pain can go a long way.

**2.3. Improved Analgesia Facilitates Patient Care.** It is undoubtedly the case that severe pain can create barriers to obtaining an adequate history and physical exam, and also that removal of these barriers by pain relief can facilitate better patient care [3, 8]. The risks of analgesia should always be kept in mind, but a fair risk/benefit assessment should include the potential upside to making patients more comfortable.

**2.4. Pain Should Be Addressed within a Reasonable Amount of Time.** Whether or not pain is treated—and there are relatively few cases in which nontreatment is truly appropriate—ED providers should acknowledge the patient’s pain and discuss the plan for treatment. Even if the plan is for no treatment, it is preferable for patients to hear the explanation from physicians as to why they are not receiving analgesia. The particular time frame that constitutes “reasonable” will obviously vary; it is different for a renal colic patient versus one who has a mild ankle sprain. Available evidence does give as a rough guide an estimate that pain needs to be addressed within 20–25 minutes of initial healthcare provider evaluation in the ED [9, 10].

**2.5. Pain Relief Has Medical Benefits.** In addition to the intrinsic value of improving patient comfort, relief of pain brings with it a variety of physiologic advantages. Some of these advantages are fairly obvious and easily understood. Reduction of pain-related tachycardia, for example, would be expected to have substantial salutary effects in patients

with acute coronary syndrome. Amelioration of pain-related tachycardia would also be of significant benefit in the setting of aortic dissection.

Other benefits of pain relief are less obvious, but not necessarily less important. For example, patients with improved pain relief have improved tidal volumes in the setting of sickle cell crisis with acute chest syndrome [11]. Decisions about whether to provide analgesia should be informed by consideration of all of the potential physiologic benefits—as well as the risks—of reducing pain.

*2.6. Medications That Have Not Worked at Home Are Not Likely to Work in the ED.* Patients are often frustrated when they go to an ED for pain relief and are given the same medications they have been taking at home. It is quite true that in some situations, the right initial ED analgesic will be an over-the-counter (OTC) agent such as a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen. However, it is also quite true that when these OTC medications have failed, it makes little sense to lose the time entailed in a retrial in the ED.

The principle of not administering the same medication that has failed already is just common sense, but experience suggests it is nonetheless worth mentioning. It is important for ED providers to ask what has failed prior to ED presentation so that a more informed decision can be made regarding the analgesia approach in the ED.

As a postscript on the concept of “not trying what’s already failed,” it is worth pointing out that if a particular approach *has not* been tried prior to the ED, then it may be reasonable—even if it is just an over-the-counter (OTC) PO drug. The clinician should keep in mind that the opioids bring with their increased potency increased side effects that include both nuisance side effects such as nausea and more serious sequelae such as respiratory depression. If an OTC agent has not been tried at home, then in some cases it may be a reasonable starting point in the ED.

*2.7. Consider Targeted Analgesia.* In preparing a handbook on ED analgesia [2], the author of this review confirmed that for many chief complaints and suspected diagnoses in acute care, the right initial approach is quite often a “generalized pain medication” such as an NSAID or opioid. It is true that nonspecific analgesics (e.g., NSAIDs, acetaminophen, opioids) are incredibly useful in the ED. However, all of these agents have side effects and there may be situations in which more targeted analgesia is best. For example, migraine can be treated with a variety of approaches (e.g., triptans, antiemetics, and parenteral valproate), neuralgic conditions may be best treated with agents such as carbamazepine or gabapentin, steroids provide some degree of relief from pharyngitis pain, and calcitonin can improve pain from osteoporotic compression fractures [12–17]. Clinicians should not go to undue lengths to avoid use of “broadly active” analgesics, but there should always be consideration as to whether there might be a specific therapy available, that can either replace or reduce the need for agents such as opioids.

While this review focuses on systemic pharmacologic approaches, one “targeted analgesia” approach that deserves special mention is the use of regional nerve blocks. For some conditions in which pain can be severe, injection therapy can be quite helpful. A few examples are illustrative.

Dental conditions are, based upon many years’ experience of the author, particularly likely to raise the specter of “drug-seeking behavior.” The savvy ED clinical should keep in mind that a long-acting local anesthetic block can achieve better pain relief than PO opioids, and the block can likely get a patient through the night for a morning dental followup. Regional blocks of the teeth can also be helpful in special situations such as pregnant patients [18].

Even when drug-seeking behavior is not an issue, regional blocks can be ideal approaches to pain management in the ED. Elderly hip fracture patients often have pronounced risk of side effects from opioids. Fortunately, these commonly encountered patients are usually good candidates for effective analgesia from ultrasound-guided nerve blocks [19, 20].

*2.8. When Pain Is Severe, Intravenous (IV) Analgesia Is Usually Preferable.* The route of drug administration is one of the more situational decisions within the realm of pain care. However, consideration of the pertinent issues (e.g., ease of IV access, patient preference) should be executed with understanding that the long-known “default” preference when pain is severe is for IV analgesia [21].

Oral (PO) pain medications have often been tried at home and take a long time for effect. The intramuscular (IM) route is often the easiest, but IM pain medication administration can be characterized by injection pain (especially if multiple injections are required), uncertainty with respect to onset times, and difficulty with titration. Although there is less ED experience with newer routes such as intranasal (IN) or oral transmucosal (OTM), these approaches do have promise [22]. Rectal (PR) analgesia has been known for many years to be potentially useful in treating painful conditions in which nausea is prominent (e.g., migraine) [23], but the PR route’s comfort, convenience, and acceptability limitations preclude widespread use.

The key with regard to analgesia administration route is not necessarily, “always use IV.” Rather, the bottom line is “the more severe the pain, the more likely IV is the right route.” For those cases in which the IV route’s disadvantages (in terms of time, patient discomfort, or resource utilization) seem to outweigh its benefits, alternative approaches may be best [22, 24].

*2.9. Pain Care Is an Ongoing Process in the ED.* It has been known for decades that the initial treatment of acute pain is all too often followed by substantial delay in reassessment and repeat therapy [25]. In fact, the constant and ongoing nature of this problem has been identified as a limitation of some of the newer (otherwise preferable) analgesic agents such as fentanyl: the opioid’s short duration of action can translate into analgesia’s wearing off before repeat treatment [26].

Ignorance of the principle of ongoing pain treatment also risks “wind-up” and increased analgesia requirements.

One of the guiding principles underlying the importance of ongoing pain assessment is that pain is easier to prevent than treat. This means that lower overall doses of analgesia tend to be needed if pain is treated early and (appropriately) often, as compared to waiting for pain to become severe again after an initial analgesic administration, before repeat drug therapy is given. The need to reassess and retreat pain can seem time consuming but proper pain care actually saves time overall. Furthermore, optimal control of pain over the entirety of the ED visit contributes to overall quality of both ED care and its perception by patients (and in some cases, by regulatory bodies).

**2.10. Pain Care Is an Ongoing Process after ED Discharge.** Decades ago, investigation of the problem of unscheduled return ED visits (“bouncebacks”) revealed a finding that inadequate postdischarge pain care was often responsible [27]. More recent studies (as well as nearly every ED physician’s experience) suggest that the problem of inadequate postdischarge analgesia, while not as bad as in years past, continues to be an area in which improvements can be made [28].

Pain does not always stop when patients leave the ED, and physicians should keep in mind as a general guide that when potent analgesia (e.g., opioids) is necessary in the ED (as for a fracture), it will likely be necessary for at least a few days—and often more—after discharge [29]. The issue of opioid addiction is too important and too complex for detailed treatment in this review which intends to focus on assessment and treatment of pain, rather than the means to prevent treating pain with opioids. That said, clinicians would be wise to follow the advice given many years ago by experts [30] who (correctly) foresaw risks of denying warranted analgesia in patients due to inappropriately applied concerns for addiction.

**2.11. Keep It Simple.** Polypharmacy brings a number of disadvantages to pain care. Side effects may be compounded when more than one analgesic is administered. Additionally, varying pharmacokinetics of coadministered drugs can render titration very difficult. Finally, if pain relief does occur after multiple agents have been given, it is difficult to know the degree to which a particular drug helped.

One mistake that is commonly made is to move to a “rescue agent” when the initial drug has been insufficiently dosed. Perhaps because of the frequency with which opioids are used for acute pain in the ED, this class of drug is often being used when there is premature declaration of treatment failure—followed by replacement of the initial opioid with yet another drug that works on the same receptors. Using the example of morphine, the literature (combined with clinical experience) provides a ready explanation. It is well known that many (if not most) ED patients will not achieve full pain relief with initial morphine doses up to 0.15 mg/kg [31]. Therefore it makes little sense to give an adult 8–10 mg of morphine and then switch to a different agent because of “treatment failure.” Clinicians are often advised to become familiar with a particular

drug from each class (e.g., opioids). Part of becoming familiar with a drug is learning what the expected effective dose might be. For morphine it may be twice the usually insufficient 0.15 mg/kg dose, while for hydromorphone it may be a straight forward dose of 2 mg [32]. Whatever the selected drug, clinicians should give the first-choice drug a fair trial before moving to a rescue therapy.

As always, there are exceptions to the rule of keeping it simple. Perhaps the best example would be use of NSAIDs or even ketamine as “opioid-sparing” agents (i.e., to allow for a lower overall dose of opioids) [33]. These exceptions are important, but they are indeed exceptions to the rule that keeping it simple is usually the best approach.

On a related note, clinicians should keep in mind that the available evidence argues against a requirement for coadministered prophylactic antiemetics with ED opioid analgesia [34]. For patients who are already nauseated (e.g., renal colic cases), antiemetics make sense, but ED practitioners are counseled to consider risks and benefits of antiemetics and consider reserving these agents for symptomatic treatment (rather than always give them as prophylaxis).

**2.12. Pain Cannot Be Treated If It Cannot Be Assessed.** For a subject that has garnered such broad research and even regulatory body attention, pain assessment has been (and continues to be) underemphasized in actual clinical practice. Whether using a numeric rating scale (NRS), visual analog scale (VAS), or one of the seemingly infinite variety of alternative methods for gauging patients’ pain, the most important principle is that clinicians should *somehow* assess their patients’ pain levels.

Determining the levels of pain patients are having is acknowledged to be occasionally challenging. Children or patients with altered mental status (e.g., patients with dementia) are among the groups for whom pain assessment can be tricky. Special scales have been developed and validated for patients in whom communication can be difficult, and physicians in the ED should have a plan for assessing pain in a variety of patient types [35, 36].

Fortunately, data show that for most acute care patients, a simple “zero-to-10 scale” allows for acceptably reliable assessment of pain levels [37]. Evidence suggests that patients *do* want to give a pain number, rather than simply relate whether they want analgesia [38]. This is probably for the best, since the linkage between pain severity and indication for treatment can be confounded by a variety of patient and disease factors. Increasing emphasis placed on pain assessment (and treatment) by regulatory authorities (such as the Joint Commission and Centers for Medicare & Medicaid Services) is spurring novel pain assessment mechanisms—such as patient-held tablet computers networked to the ED nurses’ station [39].

Patients, families, nurses, and physicians feel better about pain care when pain levels are assessed [3, 38–41]. Regardless of one’s preferred approach, some assessment method should be used and supplemented with regular pain reassessments (the schedule of pain reassessment should be driven by patients’ pain severity) [40].

### 3. Inadequate Pain Care in the ED: Problems and Potential Solutions

The coining of the term “ED oligoanalgesia” in 1989 [42] launched a steady, if perhaps suboptimally rapid, rise in the level of attention to the subject of inadequate pain care in acute medical practice. While there are signs that the problem’s magnitude and pervasiveness may be a bit inflated [43, 44], ongoing study does raise a specter of delayed or inadequate ED analgesia that has not been fully eliminated [1, 10, 21, 25, 45–72]. One of the many representative studies demonstrates that analgesia provision rates are poor, pain assessment and reassessment are infrequent, and ED providers are failing to follow the pain care guidelines of their own national societies [10]. It does seem clear that there is room for some improvement in pain care in the acute clinical setting.

The purpose of this review does not include repetition of the litany of allegations—some true, some exaggerated, some debunked—of inadequate, biased, or otherwise poor pain care by ED providers. Rather, this section will address some of the specific situations in which pain care has been impacted by patient or ED situations, with the goal of improving pain care for all.

Pain care obviously needs to be provided equally to all patient populations, regardless of race, ethnicity, gender, or age. There can sometimes be barriers to this equality—language being a prime example—but the overriding goal should be for all patients to get the same quality of pain care (as they should of course receive the same quality overall care). The literature suggesting, and refuting, claims of differential and preferential pain treatment is sufficiently robust to warrant a separate review. There are clearly data on both sides of the issue, and the likely state of the art is that in some places, differential pain treatment is unfortunately present but in others it is not [70, 71]. The adage “treat the patient as if they were your family member” is probably the best guide to clinical decision making in this respect. Some specific situations are next mentioned, in order to highlight their potential as areas for improved pain care.

*3.1. Pay Special Attention to Pain Care at the Extremes of Age.* The extremes of age provide special challenges to pain care. Pediatric patients and geriatric patients have little in common physiologically, but they share a propensity towards undermedication for pain [19, 72–77]. There is some evidence that the undertreatment of pain in those at the extremes of age is improving [78], but the rule for acute care clinicians should be to pay particular attention to pain assessment and care in these patients.

For pediatric patients, assessment can be a primary cause for data that show less than 10% of patients with long-bone fractures receive adequate analgesia within their first hour in the ED [72]. Special scales that have been well described in the literature can be used for validated pain assessment (and thus enable appropriate analgesia provision) [79–82]. The lack of IV access can also be problematic. Alternate analgesia routes such as nasal medication administration are often helpful in

younger patients, in whom obtaining IV access can be both time consuming and painful [83].

Some authors have decried the undermedication of pain in older adults as “the most apparent underuse of medication in emergency medicine” [68]. In older adults, pain assessment is occasionally the problem (e.g., when there is dementia) but again there are validated scales that allow reliable characterization of pain levels [36, 76]. In the older adults, the usual issue is less one of assessment than one of concern for side effects; older patients are simply more likely than younger patients to suffer untoward side effects of many popular ED analgesics such as opioids. A balancing of the risks and benefits of analgesia in older patients is wise, and inclusion of this balancing need in conversations with patients and families is recommended. The challenge of geriatric analgesia can often be overcome through use of opioid-sparing analgesic regimens or employment of specific therapies (e.g., regional nerve blocks for hip fractures) [19, 20].

*3.2. Do Not Let Pain Care Be Neglected When the ED Gets Busy.* Overcrowding in the ED is a pervasive problem, with pervasive ramifications. One of the many downstream issues from an ED with too many patients is diminished attention to proper pain care. This has been suspected for years and definitively demonstrated as long ago as 2008 [69]. Since the problem of ED overcrowding is not likely to be solved anytime soon, ED clinicians should “automate” the process of pain assessment and care as much as is safely possible, so that this important part of patient care is not neglected when census is high.

The meaning of the dictum to “automate pain care” can vary depending on a given ED’s situation. The ideal would be for pain levels to be automatically assessed, in a manner that follows assessment of other vital signs (e.g., automatic blood pressure monitoring). Current technology does not allow this, but there are solutions that may vary depending on an ED’s particular situation and patient population. In one ED, patients are given hand-held tablet computers that allow them to report their pain levels, indicate whether they want analgesia, and select the time interval to their next pain assessment; the practice is called “semiautomated” pain assessment because patients still have to provide input, but the input is transmitted and displayed on a central nursing station monitor with other vital signs [39].

*3.3. Execute Due Diligence, but Give Patients the Benefit of the Doubt.* The concept of “drug-seeking behavior” has already been mentioned as one which extends far beyond the scope of anything other than a focused review. Comprehensive discussions of the issue are easily found both in the general medical literature which reflects great strides in understanding of the anatomy, physiology, and psychology of addictive behaviors [84–86]. Clinicians should take advantage of local and regional tools (e.g., state-approved web resources that track narcotics abusers) that facilitate due diligence in determining whether a given patient is not a truly viable candidate for opioids. Furthermore, the focused history and examination

should include—although not overly focus on—items that can indicate inconsistencies or falsifications associated with inappropriate drug-seeking behavior.

The ED physician is often in a difficult position. Most physicians believe they are good judges of character, but the data show that physicians are subject to human limitations in their reading of their patients. For instance, evidence clearly demonstrates that even when inappropriate drug-seeking behavior is *not* a consideration, physicians are unable to predict how much pain their patients are having [87–93]. Admitting that physicians cannot read patient's minds is no weakness, but an inherent inability to be 100% certain that a patient's need for analgesia is "real" has to be incorporated into daily practice. Physicians must make judgment calls every day, on nearly every patient; pain management is but one such judgment call. Physicians are counseled to carefully consider their comfort levels with the balancing act between "losing" to drug seekers and denying analgesia to patients who are genuinely in need. There is no rigidly correct answer, but as a general guide it is best to give patients the benefit of the doubt.

**3.4. Assessment of Pain Is a Necessary, but Not Sufficient, Component in Pain Care.** Because of understandable complexities entailing who should receive what pain medication and when it should be delivered, there has been focus on pain care's initial step: pain assessment. Nursing and regulatory body guidelines (e.g., the Joint Commission) have promulgated recommendations for initial and ongoing pain assessment. These moves are laudable and have doubtlessly resulted in important advances in pain care, but pain assessment was never intended to be the endpoint of focus. Unfortunately, one result of the standardization of pain assessment is that the assaying of pain levels has in some cases surpassed the addressing of the pain being rated. It is not uncommon to encounter a clinical record in acute care, in which there are regular entries of pain levels of "9" or "10" on a 10-point scale, with no accompanying treatment or explanation for nontreatment. Like any other vital sign, pain level should be monitored with the aim of addressing ("correcting" where possible) any abnormalities. If there is a high pain level, then the clinician needs to either treat the patient or acknowledge the reason for nontreatment; such acknowledgment should occur both in conversations with the patient (or family) and also in the medical record. Failure to address severe pain that is documented in the physician's own medical record is a *res ipsa loquitur* of a most dangerous kind: it is easily understandable by, and potentially sends a most damaging message to, even the least sophisticated reviewer of the physician's care.

#### 4. Selected Nonopioid Pharmacologic Approaches in the ED

The variety of analgesic agents available to the ED practitioner is continually broadening. There are dozens, even scores, of drugs that can be used depending on the clinical circumstances. A detailed pharmacology discussion of even half of the available agents is beyond the scope of this review, which

has as its intent the focus on selected topics of particular interest. Certain drugs are mentioned in this review, with the intent of highlighting either unique or new applications of these agents (e.g., the IV formulation of acetaminophen).

Readers are encouraged to use standard medication reference resources for the most up-to-date information on drug dosages, side effects, and related information. One resource, prepared by emergency medicine experts worldwide and edited by this review's author focuses on the ED applications of analgesics: *Emergency Department Analgesia: An evidence-based guide* [2]. This text provides information—for every drug mentioned in this review and for many others—on ED uses, dosages (initial dose, repeat dose, and dosing adjustments), precautions, and applications in pregnancy and pediatrics.

**4.1. Acetaminophen.** As a *p*-aminophenol derivative providing analgesia generally comparable to that of aspirin, acetaminophen is characterized by additional benefits of antipyresis. The drug has little anti-inflammatory activity (it is a weak inhibitor of cyclooxygenase in the presence of peroxides found at inflammatory sites). Acetaminophen is therefore not nearly as useful as NSAIDs for many ED conditions in which inflammation plays a role.

Traditionally administered via the PO or PR route, acetaminophen is now available as an IV analgesic. While there is little ED experience with this route, early evidence from the inpatient setting suggests IV administration of acetaminophen is useful in situations in which patients are best kept *nil per os* (NPO), mild-moderate analgesia is needed, and opioid-sparing effects are desired [94–99].

Given the well-known safety profile of acetaminophen in general, the use of the IV formulation seems to be a particularly interesting avenue for ongoing research in the ED. Caution must be taken, with regard to the potential for overdose due to drug calculation/formulation errors (for the IV approach) and in cases in which patients have ingested acetaminophen-containing OTC agents prior to ED presentation [100]. However, the use of a few doses of acetaminophen is likely to be characterized by lower overall risk than alternative agents of similar strength (e.g., NSAIDs).

The "bottom line" for acetaminophen is that it is quite useful as a mild-moderate analgesic agent, especially in patients with NSAID contraindications or in those with fever. Like any drug, there are concerns (e.g., use in patients with severe liver or renal disease), but acetaminophen is one of the safer agents available in the ED. Early mention of the potential for IV acetaminophen use in the ED tends to be favorable (even comparable to morphine in one study of extremity pain) [101, 102], but this is an area ripe for development of further ED understanding and evidence. Other areas of potential interest for ED assessment of acetaminophen utility include further investigation of the suggested synergistic effect between acetaminophen and NSAIDs [103].

**4.2. NSAIDs.** NSAIDs provide analgesia through a variety of mechanisms, but most importantly through their inhibition of cyclooxygenase (COX) in both its constitutive

(COX-1) and inducible (COX-2) isoforms. COX-1 is constitutively expressed and generates prostanoids involved in platelet aggregation and maintenance of gastrointestinal (GI) mucosal integrity. COX-2 generates prostaglandins that mediate inflammation and pain. By this admittedly simplistic view, COX-2 inhibition is thought to mediate analgesia, and COX-1 inhibition to mediate most side effects. Aspirin irreversibly acetylates COX, while other NSAIDs compete with arachidonic acid at COX active sites. Entire textbooks could be (and have been) written about the NSAIDs. For the purposes of this review, some key points are selected for emphasis.

First, when NSAIDs are given in equipotent doses, there is little if any difference in analgesic efficacy. This includes the IV versus PO routes of administration; there are advantages of parenteral NSAIDs, but improved analgesic efficacy is not among them. Results on the analgesic efficacy front are both consistent and long known; the first studies demonstrating equal analgesia between PO ibuprofen and parenteral ketorolac are now two decades old [104, 105].

Second, as NSAIDs tend to be used in actual clinical practice (i.e., not necessarily always prescribed at equianalgesic levels), there are differences in side effects of the various agents [106]. Thus, it is important for clinicians to consider the GI (and other) side effects of NSAIDs, and consider how these risks may be mitigated (e.g., through combination use with a cytoprotective agent such as misoprostol). The side effects of the agents with COX-2 specificity receptor are in fact different from the side effects of nonselective NSAIDs but the picture is not simple. For example, there are COX-2 receptors within the kidneys, so although they are “GI-sparing” in their nature, COX-2 agents can risk nephropathy [107, 108]. Furthermore, COX-2 agents still incur risks (e.g., interfering with cardioprotection) [109, 110]. In the end analysis, the ED clinician is advised to become familiar with NSAID side effects and carefully consider the risks and benefits of therapy on an individualized basis. For the young patient with an ankle sprain, it is not likely that a few days of any NSAID will pose much risk. The case can be different, though, for longer-duration prescriptions or higher-risk patients such as the elderly (or those with borderline renal function or other comorbidities). As is the case with any agent, the prescription decision should be informed by a variety of patient and disease factors. The longer the prescription duration, and the more comorbidities present, the higher the NSAID risk (and the more likely an unfavorable risk : benefit ratio).

Third, when an NSAID does not appear to be working, one reasonable approach is to switch to an NSAID of a different class. This is not because a particular NSAID is “stronger” than another in the population as a whole, but rather because of the epigenetics of drug therapy and the possibility that for an individual, a heteroaryl acetic acid derivative (e.g., ketorolac) may succeed where an arylpropionic acid derivative (e.g., ibuprofen) failed.

Fourth, when considering an NSAID, clinicians should consider that—true to their name—NSAIDs are best for inflammatory pain such as that mediated by prostaglandins. Examples of such pain for which NSAIDs are known to be particularly useful include renal colic [111–113] and menstrual

cramps [114, 115]. NSAIDs are far less likely to be effective for pain that is noninflammatory (e.g., neuropathic pain, or pain from leg swelling related to chronic edema).

In conclusion, for all of their major side effect risks (which number too many to be listed in this review) it must be acknowledged that NSAIDs have their place firmly established in the ED. They tend to have few “nuisance” side effects such as nausea or allergy. Furthermore, use of NSAIDs has been shown to have useful opioid-sparing effects in a variety of clinical situations ranging from sickle cell vaso-occlusive crisis to renal colic [111, 116–118]. Some of the more serious or controversial side effects of ED NSAID use deserve attention in prospective trials. For example, how dangerous are short-course NSAIDs for fracture patients, in terms of nonunion risk [119]? What are the true rates of GI or clinically relevant platelet function or renal side effects in short courses of ED-prescribed NSAIDs? Since NSAIDs are a major part of ED pain control and ED physician-prescribed pain control, these questions would appear a worthy area of investigation for future clinician-scientists.

**4.3. Ketamine.** Ketamine is possibly the most complicated, and yet potentially one of the most useful, of ED analgesics. As a true dissociative phencyclidine-like anesthetic, in full dissociative doses (e.g., at least 1.5–2.0 mg/kg IV), ketamine causes a trance-like cataleptic state characterized by open eyes (and nystagmus) with preservation of airway reflexes. The drug can be given PO, IV, IM, or even PR; onset and duration vary widely with administration route although there are few important differences in side effect profiles between varying administration routes [120].

In subdissociative doses (i.e., doses lower than those required for its full anesthetic effect) to provide analgesia, ketamine has been shown to be useful either as a single agent or for its opioid-sparing effect [121]. While ketamine’s use in the ED is largely within the realm of procedural sedation (a topic outside this review’s scope) [122, 123], some attention to its potential role as an analgesic is warranted.

Ketamine has been the subject of a broad array of physiologically appropriate, if sometimes exaggerated, concerns. Hypersalivation, vomiting, laryngospasm, and unpleasant emergence reactions are among the major nonhemodynamic issues that should be considered when ketamine is used in any dose (risk of side effects does not appear to be dose dependent) [120, 124–131]. Hemodynamically, ketamine’s sympathomimetic effects are well known to be associated with increases in heart rate and blood pressure, but the latest data indicate that there is little reason for concern about the more important issue of hemodynamic stimulation’s adverse impact on intracranial pressure [132, 133].

To simplify a fairly complicated pharmacologic picture, the following recommendations can be made based upon the literature addressing ketamine use for both procedural sedation and low-dose analgesia. First, while a coadministered benzodiazepine is not strictly required in all patients (it appears to be unnecessary for emergence reaction prevention in young children), the addition of a benzodiazepine such as midazolam is not harmful and may have additional benefits

(e.g., as antiemetics) besides prophylaxis against emergence [124, 131, 134, 135]. Second, while data are variable [131, 136], the best (and most recent) prospective trial evidence suggests it is worthwhile to coadminister an antisialagogue such as atropine [123]. Third, although postketamine vomiting usually occurs well after ED discharge (and thus well after there is significant risk for aspiration), the occurrence of this “nuisance” side effect may be reduced by postprocedure utilization of an antiemetic such as ondansetron at home (atropine and metoclopramide do not appear to work well for this indication) [137].

Emerging data on dissociative ketamine use for pain management are fascinating and tend to be positive. For cancer pain, palliative care, and acute conditions such as burns ketamine has been demonstrated to be both effective and well tolerated in settings outside of the ED [138–140]. Ketamine’s support of blood pressure lends to its emerging utility in the prehospital and austere care settings, where its analgesic efficacy is touted as synergistic with, or even comparable to, that of morphine [141–143]. ED use of ketamine analgesia is newer, and the data are more limited but are positive [144, 145]. Perhaps one of the most important early indicators of a role for ketamine in ED analgesia is the overall approval of both patients and physicians after the agent has been used for pain relief [146].

Like any other analgesic, ketamine should be used only after familiarization with its properties, dosing regimens, and recommendations as to coadministered agents. With this *caveat* in mind, the use of subanesthetic dosing of ketamine is both a promising clinical research area and a promising clinical care arena, as ED practitioners look to extend their analgesic armamentarium.

**4.4. Nitrous Oxide ( $N_2O$ ).** As an inhaled, rapid-onset short-acting analgesic in doses used in acute care (generally 50 : 50 with oxygen but sometimes at higher concentrations for cities at higher altitudes),  $N_2O$  has been in effective use in the prehospital and ED settings for many decades [147–149]. Its onset and offset times of roughly 3–5 minutes contribute to  $N_2O$ ’s potential utility in the acute care environment. The gas has been reported useful for analgesia for acute conditions ranging from procedures to acute intensely painful conditions in which traditional analgesia is difficult (e.g., burns, fractures, and envenomations) [150–152].

Decades of safe use in non-ED settings (e.g., dental offices) contribute to a widespread awareness of nitrous oxide’s low risk, and in fact there have been few reports of problems in ED (or prehospital) patients receiving the inhalational agent. One area of attention and contraindication is the patient with pneumothorax or pulmonary blebs (due to the risk of gas accumulation) [153]. Vomiting occurs uncommonly (about 5% rate) even in “high-dose” (70 : 30)  $N_2O$  administration [154]; nausea without vomiting occurred only once in a recent prospective trial of 50 : 50  $N_2O$  use in the ED [155]. The risk of nausea/vomiting appears to be increased with use of higher concentrations of  $N_2O$  or with combination therapy of  $N_2O$  and an opioid such as fentanyl [156].

The summation of the decades of experience with  $N_2O$  is that it is both safe and fairly effective—perhaps comparable to low-dose fentanyl—when used with the traditional self-administration apparatus (i.e., patients hold the mask to their mouths and when they are fully dosed, drop the mask and cease  $N_2O$  delivery) [157]. So why is the agent used with relative infrequency? The reasons are probably related to its efficacy—which is good but not 100% [158–160] and thus may prompt need for a coadministered agent—as well as the requirement for specialized training and equipment (for both delivery and “scrubbing” to clear this potentially teratogenic gas from the healthcare setting) [161–163].

Based upon the recent literature,  $N_2O$  may be poised for something of a comeback in the acute care setting [80, 155, 156, 164–167]. The agent is well known, self-administered, safe, and at least moderately effective. It avoids the need for IV access and has a very low risk of concerning side effects. It is excreted unchanged by the lungs so there are no issues with renal or hepatic disease. When the training, technical and related physical barriers (e.g., external venting) to  $N_2O$  use in the ED can be overcome, it makes sense for an ED to incorporate capability for administration of this inhaled agent for analgesia (the subject of this review) and also as an adjunct for procedural sedation. (This review’s author’s hospital is in the process of building a new ED, and  $N_2O$  capability is being added into the facility.) Future areas of investigation into the ED application of  $N_2O$  include the real costs (i.e., inclusive of all components necessary for  $N_2O$  delivery), the assessment of varying  $N_2O$  : oxygen ratios (50 : 50 to 70 : 30), and the throughput gains that may be attendant to avoiding IV placement and using a rapid-onset, rapid-offset analgesic.

**4.5. Nonopioid Analgesia—Summary.** For patients in whom ED treatment with “broadly effective analgesia” is judged necessary (i.e., there is a disease-specific pain treatment), nonopioid approaches may offer improved overall safety and efficacy as compared to the more potent analgesics discussed in the next section. Rather than immediately moving to opioids—which work well but which have their own issues—the ED physician should consider whether nonopioid approaches may be appropriate. The agents discussed in the preceding section are mentioned not as a comprehensive listing, nor are the agents discussed in comprehensive detail. Rather, the information is presented to give the reader a sense of some of the proven and emerging options in nonopioid analgesia. For both patient care and clinical research purposes, there is much to be gained from attention to the nonopioid analgesic options available to acute care.

## 5. Selected Opioid Approaches to ED Analgesia

The opioids tend to be the benchmark against which other ED analgesics are compared, both in clinicians’ minds and in the setting of ongoing clinical research. As noted earlier, there are some definitions to keep in mind when considering the various opioids. Additionally, some brief discussion of the

major receptor types is helpful as a guide to understanding some interopoid differences.

Opioids provide analgesia through receptor-mediated blockade of neurotransmitter release and pain transmission. The clinical relevance of receptor types is found in tracking the effects and side effects of agonists and antagonists. There are general classes of opioid receptors ( $\mu$ ,  $\kappa$ ,  $\delta$ , and  $\sigma$ ) with many subtypes (not discussed in this review). Most of the ED-used opioids, with the exception of agonist-antagonist agents (e.g., buprenorphine), are relatively selective at the  $\mu$  receptor; the  $\mu$  receptor mediates analgesia and also euphoria, respiratory depression, miosis, and constipation. The  $\kappa$  receptor mediates some analgesia and sedation and is responsible for GI motility and dysphoria side effects. The  $\delta$  receptor function is less fully understood; it appears to mediate spinal analgesia and antinociception for thermal stimuli. The  $\sigma$  receptor is attracting attention as a target for monotherapy for neuropathic pain [168]. As opioid doses increase,  $\mu$ -selectivity decreases and effects from the other receptors become clinically prominent. As a final note on receptors, splice variants of the  $\mu$  and  $\kappa$  receptors can account for incomplete crosstolerance between various opioids; when one opioid dose is “maxed out” switching to another may well bring additional analgesic effect [169–171].

The area of opioid pharmacology is incredibly broad. Out of this breadth of information, some selected topics and agents will be discussed in this section. There are many areas of intense interest and promising research; the following highlights are but a few with particular relevance to the ED.

**5.1. Morphine.** Morphine is historically the “base comparison” opioid, and with good reason [172]. The drug has been around for as long as any other opioid and has excellent safety and efficacy when used appropriately. Despite theoretical and practical concerns about histamine release and hypotension, the use of morphine (including higher-risk patients such as cardiac and trauma cases) has not been associated with dangerous hypotension even in the relatively less controlled setting of prehospital care [173–176]. Some of the more interesting recent investigations of morphine in the acute care setting suggest that it may be combined with ketamine for increased efficacy (with minimization of hemodynamic risks) [143]. Of course, morphine use in the ED setting is quite well characterized and broadly understood to be quite safe when administered by a number of methods (including patient-controlled analgesia pumps) for an array of medical and surgical conditions [177–179]. The literature describing morphine use is so broad that just a few aspects of particular interest are selected for discussion here. Two topics of interest include new dosing and administration approaches.

In terms of IV dosing, it appears that rigid adherence to weight-based dosing is unnecessary. Data demonstrate that there is little difference in analgesic effect within the dosing ranges most likely used in most EDs (from 0.1 to 0.15 mg/kg IV) [180]. Other studies have also found that obese patients do not require extra morphine and that, indeed, weight-based dosing is not truly necessary [173, 181]. The “standard” initial dose of morphine of 0.1 mg/kg (about 7 mg in an adult) has

been found to provide inadequate analgesia (i.e., less than 50% decrease in pain) in 2/3rds of ED patients [182]. With regard to adult dosing, therefore, the recommendation is to start with a minimum of approximately 7 mg (0.1 mg/kg) when there is concern for side effects risk (being prepared to rebolus for inadequate analgesia), and use roughly 10 mg (0.15 mg/kg) otherwise.

With respect to alternate dosing routes, the advantages of IV over IM injection analgesia have been previously discussed. Morphine can of course be given IM, but clinicians will have to deal with the previously mentioned issues of potentially delayed onset and titration difficulties. One unusual administration route for morphine that has been reported successful previously, but which has been studied little if any in the ED, is the inhaled route. Described many decades ago in intubated patients, nebulized morphine appears to have a bioavailability ranging from 9 to 35% [183]. Largely used for dyspnea, particularly in cancer and palliative care patients, nebulized morphine has also been found effective in situations of acute pain and difficult IV access (e.g., acute chest crisis in sickle cell patients) [184]. In chest trauma patients, nebulized morphine was reported to provide analgesia roughly equal to that attained with IV morphine by patient-controlled analgesia (PCA), but with less sedation [185]. The jury is still out on the overall analgesic efficacy of nebulized morphine [186], with some ED data indicating poor pain relief as compared to the IV route for morphine [187]. However, for patients with difficult IV access and perhaps moderate (but not severe) pain, nebulized morphine seems an interesting avenue for clinical investigation.

**5.2. Hydromorphone.** Hydromorphone administered at an IV dose of 0.015 mg/kg has been found to provide roughly equal analgesia to that attained with 0.1 mg/kg morphine [188]. The agent does seem to be gaining popularity for use in the ED, for reasons that are both evidence based and anecdotal. The evidence basis for hydromorphone use in the ED is long standing and broad, for indications ranging from renal colic [189] to sickle cell crisis [190]. As for the anecdotal reasons for hydromorphone’s growing popularity, some physicians (including this author) have found that hydromorphone use can be a route around inappropriately overcautious nurses who (despite requests to the contrary) split 0.1 mg/kg morphine orders into nearhomeopathic doses administered over 15–30 minutes “for safety.” These same nurses are fine giving the (roughly equianalgesic) bolus of a milligram of hydromorphone, presumably because “it is just 1 mg (hydromorphone) instead of 7 mg (morphine).”

While 2 mg hydromorphone was found effective in one study in ED patients, the authors reported that the finding of hypoxemia (oxygen desaturation below 95%) in 1/3rd of cases rendered the dose unsafe for routine use [191]. Instead, the most prudent recommendation appears to be to use the “1 + 1” technique: 1 mg hydromorphone IV, followed by a repeat dose 15 minutes later if pain relief is insufficient; this approach was found as safe as, and more effective than, “standard care” (i.e., whatever analgesia was provided to patients not randomized

to the 1 + 1 protocol) [192]. Further study is needed to confirm with certainty the utility of the 1 + 1 approach for dosing hydromorphone, but the safety and general efficacy of this dosing regimen appear appropriate for its consideration in EDs working on improving and simplifying pain care.

**5.3. Fentanyl.** Fentanyl, the most potent opioid that is routinely used in most ED and prehospital settings, is no new drug. Its introduction into common ED use (in the United States, at least) was probably based more on use for procedural sedation or rapid sequence intubation rather than isolated analgesia, but ED physicians have been familiar with the agent for many decades [193, 194]. Over the years, IV fentanyl has been demonstrated safe and effective for a breadth of conditions in acute care [25, 26, 195–197]. Data support the idea that, while appropriately dosed morphine and fentanyl should have roughly equal analgesic effects, fentanyl has a significantly faster onset time [198]. In terms of “what’s new” with fentanyl, areas of recent focus tend to fall within the category of administration route.

Perhaps the newest approach to fentanyl administration is via the nasal passages (IN). Differing formulations for IN fentanyl have been developed [199], but the overall efficacy results are similar: IN fentanyl data are incomplete but the approach has promise for a variety of patient types [200–202]. It appears possible that, while the analgesic efficacy may not match that of IV morphine, the ease of administration may render IN fentanyl (one commonly used dose is 1.5 mcg/kg via atomizer) a viable option in some situations [203]. While there are some preliminary data on IN fentanyl use, the state of the art for this approach is that it is prime subject matter for clinical research rather than widespread adoption [204].

Another novel approach for fentanyl administration is the nebulization of 4 mcg/kg. One study of pediatric fracture patients found that this administration route for fentanyl provided analgesic efficacy equivalent to that attained with IV morphine (0.1 mg/kg) [205].

Fentanyl can also be administered orally. The “lollipop” method of fentanyl delivery was described many years ago [206] but has not really caught on in the ED setting—perhaps due to psychological barriers against equating an opioid with candy, but more likely due to high rates of vomiting (approaching 50% in one study) [207]. Oral transmucosal fentanyl has been demonstrated a potentially useful adjunct (to nitrous oxide) for fracture reductions in the ED [165]. A more simplified delivery mechanism for oral transmucosal fentanyl uses a transbuccal tablet formation of 200 mcg or 400 mcg; this approach is not associated with vomiting in early ED studies [24]. This transbuccal tablet preparation, which can be delivered in the absence of IV access and which allows for rapid early analgesia for moderate pain, is a promising area for additional ED-based investigation [208].

**5.4. Other Opioids.** Inevitably, the availability of opioids with similarity to fentanyl has translated into consideration of these agents’ utility in acute care. For some agents, most notably sufentanil in a dose of roughly 0.5 mg/kg [209–211], alternate administration routes such as IN have been

favorably assessed. Sufentanil has also been found useful when administered via the IV route (0.15 mcg/kg, followed by 0.075 mcg/kg every 3 minutes) [212]. Another potent opioid reported useful in the acute care setting is alfentanil [213]. Although there is certainly nothing wrong with these opioids, there seems scant impetus to choose them over the more familiar agent fentanyl given the current state of the evidence.

**5.5. Special Issues with Opioids.** Analgesia in the setting of undifferentiated abdominal pain has long been an area for controversy; the idea is that “covering the physical findings” will worsen outcomes [8, 214]. Fortunately, there are sufficient data refuting this idea—an idea based upon historical cautions formulated due to problems with large opioid doses in the preradiology era—that the question has been answered to a reasonable degree of certainty [179, 215–226]. A variety of opioids (including the atypical agent tramadol) have been assessed, as administered a variety of ways ranging from IV bolus [227] to nebulized opioid [228] to patient-controlled analgesia [179], but the bottom line is that existing evidence does not support a practice of having patients suffer to preserve the physical examination [8].

Another area of potential controversy lies in the treatment of trauma patients. The problem is not so much one of diagnostic clouding by analgesics (although this is sometimes an issue), as it is the risking of physiologic compromise from opioids [229]. Concerns for respiratory and hemodynamic depression from analgesics are often bruited as rationale for withholding of trauma analgesia, but trauma analgesia can be safely improved and provided with educational programs that incorporate emphasis on judicious medication use [3, 25, 196, 230–233].

An additional question that often arises regarding analgesia is the desirability of continued use of meperidine. It has been written for years that meperidine should not be included in the initial treatment regimen for either adult or pediatric ED patients [234, 235]. Since even the historical “advantages” of meperidine (e.g., potential for less spasm of the sphincter of Oddi) have been debunked [236], the known pharmacological shortcomings of the drug (e.g., risk from normeperidine build-up) would seem to outweigh any particular reason for its first-line use in the ED.

The use of agonist-antagonist agents is a fascinating arena of pain care, and the subject does have implications for ED analgesia. Various opioid agonist-antagonists (e.g., buprenorphine, butorphanol, nalbuphine, and pentazocine) have been used for decades in the acute care setting, with results that are often positive but occasionally marked with problems such as dysphoria [237].

Buprenorphine is a useful example of agonist-antagonist use in the ED. It is a partial  $\mu$  agonist and a weak  $\kappa$  antagonist, with high affinity for the  $\mu$  receptor and a slow dissociation that results in long duration of effect and a potency about 25–40 times that of morphine [238]. There is a “ceiling effect” in that antagonist effects predominate at higher doses, thus imparting greater safety and lower addiction risk to buprenorphine [238]. While the agent is certainly useful and may even be theoretically preferred for various indications

(e.g., its salutary effects on spasm of the sphincter of Oddi renders it potentially preferable for biliary colic pain) [239], buprenorphine does not appear frequently in the ED analgesia literature. The agent has been occasionally used for treatment of withdrawal [240] and more recently posited as a useful antagonist for remifentanyl (administered during procedural sedation) in the ED [241]. At least one study [242] suggests that sublingual buprenorphine (in a dose of 0.4 mg) may be useful for fracture analgesia in the ED but the results are preliminary—buprenorphine was compared to an (inadequate) dose of 5 mg morphine IV. Further research may well focus on situations in which this use of buprenorphine is appropriate (e.g., lack of IV access in a fracture patient). The growing concerns about opioid abuse and misuse may also spur research into more use of the agonist-antagonist agents in the ED, but for now these agents are useful but not necessarily better than the pure agonist opioids in most situations.

One special agent, tramadol, deserves special attention because of some interesting aspects of its pharmacology. Tramadol has independent analgesic effects from opioid ( $\mu$ ,  $\delta$ , and  $\kappa$ ) and nonopioid mechanisms (inhibition of norepinephrine and serotonin uptake) [243, 244]. The opioid agonism means that opioid side effects can occur, but problems (including drug dependence) are uncommon [244, 245] and there are data indicating utility in acute pain [225, 246–248]. There are some issues, ranging from borderline efficacy in some “head-to-head” studies versus opioids [249, 250] to isolated reports of problems such as seizures in predisposed patients [251–253]. Research for the future may confirm suggestions of tramadol’s efficacy for pain traditionally poorly relieved by opioids, and with relative reduction in opioid-associated side effects [244, 245]. Additional clinical research in the ED setting could include use of tramadol in nonstandard delivery routes such as transbuccal [254]. While the pharmacology of tramadol is interesting, and there are likely some situational roles for the agent, the current evidence suggests that there is still truth to the conclusion that there is little evidence basis for the broad use of tramadol in the ED setting [251].

**5.6. Opioid Analgesia—Summary.** In terms of opioid safety, the ED practitioner benefits from working within a critical care environment where there is relatively close attention to patients. Untoward side effects can be prevented or treated early (e.g., with ondansetron) and physiologically dangerous sequelae can be detected quickly with modern equipment such as ETCO<sub>2</sub> monitoring. With rapid use of stimulation, airway repositioning, and pharmacologic intervention (i.e., naloxone), opioids may be used for effective analgesic with low risk to patient safety.

As was the case for the discussion on nonopioid analgesic agents, the above overview of opioids is not intended to be comprehensive in its listing of agents or in the information pertinent to the agents discussed. Instead, the selected items and highlights have been presented in order to convey some interesting and clinically useful points regarding use of these most potent analgesics in the acute care setting. The opioids

offer long-standing records of safety, efficacy, and ease of use. Their continued role in the ED will doubtless be of great comfort to patients even as further research identifies new administration routes, formulations, combinations, and uses for drugs of this class.

## 6. Summary

The preceding discussion, if admittedly selective, is hoped to provide a resource for those wishing to consider the fascinating clinical challenges of relieving ED patients’ pain. The opinions provided, while as evidence based as possible, reflect as much as anything else the lessons learned by one ED practitioner over decades of busy EM practice and efforts in ED analgesia research and education. If there is a “bottom line,” it is that ED physicians would be wise to keep in mind that, in addition to their priorities of diagnosis and life-saving therapy, improving patient’s pain and comfort is a laudable area for clinical effort and an endpoint in and of itself.

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