Hindawi Publishing Corporation
ISRN Emergency Medicine
Volume 2013, Article ID 583132, 19 pages
http://dx.doi.org/10.1155/2013/583132

Review Article

Management of Pain in the Emergency Department

Stephen H. Thomas

Kaiser Foundation, University of Oklahoma, Department of Emergency Medicine, 4501 East, 41st Street, Suite 2E14, Tulsa, OK 74135, USA

Correspondence should be addressed to Stephen H. Thomas; stephen-thomas@ouhsc.edu

Received 3 April 2013; Accepted 23 April 2013

Academic Editors: O. Karcioglu, L. M. Lewis, and R. Pitetti

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 subdissociative 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 interopioid 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 (μ, κ, δ, and σ) 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 μ receptor; the μ receptor mediates analgesia and also euphoria, respiratory depression, miosis, and constipation. The κ receptor mediates some analgesia and sedation and is responsible for GI motility and dysphoria side effects. The δ receptor function is less fully understood; it appears to mediate spinal analgesia and antinociception for thermal stimuli. The σ receptor is attracting attention as a target for monotherapy for neuropathic pain [168]. As opioid doses increase, μ-selectivity decreases and effects from the other receptors become clinically prominent. As a final note on receptors, splice variants of the μ and κ 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 mug/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 μ agonist and a weak κ antagonist, with high affinity for the μ 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 remifentanil (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 (μ, δ, and κ) 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 $ETCO_2$ 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.

References

[1] J. Simpson, "Anesthesia," in *The Works of Sir J. Y. Simpson*, W. Simpson, Ed., Adam and Charles Black, Edinburgh, UK, 1871.

[2] S. Thomas, Ed., *Emergency Department Analgesia: An Evidence-Based Guide*, Cambridge University Press, Cambridge, UK, 1 edition, 2008.

[3] S. H. Thomas and S. Shewakramani, "Prehospital trauma analgesia," *Journal of Emergency Medicine*, vol. 35, no. 1, pp. 47–57, 2008.

[4] P. M. Paris, "No pain, no pain," *American Journal of Emergency Medicine*, vol. 7, no. 6, pp. 660–662, 1989.

[5] A. Wakai, R. O'Sullivan, P. Staunton, C. Walsh, F. Hickey, and P. K. Plunkett, "Development of key performance indicators for emergency departments in Ireland using an electronic modified-Delphi consensus approach," *European Journal of Emergency Medicine*, vol. 20, pp. 109–114, 2013.

[6] A. L. Baxter, P. H. Ewing, G. B. Young, A. Ware, N. Evans, and R. C. Manworren, "EMLA application exceeding two hours improves pediatric emergency department venipuncture success," *Advanced Emergency Nursing Journal*, vol. 35, pp. 67–75, 2013.

[7] A. J. Singer, P. B. Richman, A. Kowalska, and H. C. Thode Jr., "Comparison of patient and practitioner assessments of pain from commonly performed emergency department procedures," *Annals of Emergency Medicine*, vol. 33, no. 6, pp. 652–658, 1999.

[8] S. H. Thomas and W. Silen, "Effect on diagnostic efficiency of analgesia for undifferentiated abdominal pain," *British Journal of Surgery*, vol. 90, no. 1, pp. 5–9, 2003.

[9] D. E. Fosnocht, E. R. Swanson, and P. Bossart, "Patient expectations for Pain Medicineication delivery," *American Journal of Emergency Medicine*, vol. 19, no. 5, pp. 399–402, 2001.

[10] P. S. Grant, "Analgesia delivery in the ED," *American Journal of Emergency Medicine*, vol. 24, no. 7, pp. 806–809, 2006.

[11] M. D. Melzer-Lange, C. M. Walsh-Kelly, G. Lea, C. A. Hillery, and J. P. Scott, "Patient-controlled analgesia for sickle cell pain crisis in a pediatric emergency department," *Pediatric Emergency Care*, vol. 20, no. 1, pp. 2–4, 2004.

[12] B. Bakhshayesh, S. M. Seyed Saadat, K. Rezania, H. Hatamian, and M. Hossieninezhad, "A randomized open-label study of sodium valproate vs sumatriptan and metoclopramide for prolonged migraine headache," *American Journal of Emergency Medicine*, vol. 31, pp. 540–544, 2013.

[13] E. Y. Gan, E. A. Tian, and H. L. Tey, "Management of herpes zoster and post-herpetic neuralgia," *American Journal of Clinical Dermatology*, vol. 14, no. 2, pp. 77–85, 2013.

[14] T. A. Smitherman, R. Burch, H. Sheikh, and E. Loder, "The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies," *Headache*, vol. 53, no. 3, pp. 427–436, 2013.

[15] G. Hayward, M. J. Thompson, R. Perera, P. P. Glasziou, C. B. Del Mar, and C. J. Heneghan, "Corticosteroids as standalone or add-on treatment for sore throat," *Cochrane Database of Systematic Reviews*, vol. 10, Article ID CD008268, 2012.

[16] J. A. Knopp-Sihota, C. V. Newburn-Cook, J. Homik, G. G. Cummings, and D. Voaklander, "Calcitonin for treating acute and chronic pain of recent and remote osteoporotic vertebral compression fractures: a systematic review and meta-analysis," *Osteoporosis International*, vol. 23, pp. 17–38, 2012.

[17] G. Cruccu and A. Truini, "Refractory trigeminal neuralgia. Non-surgical treatment options," *CNS Drugs*, vol. 27, pp. 91–96, 2013.

[18] M. Singh, "The pregnant dental patient," *Journal of the Massachusetts Dental Society*, vol. 60, pp. 32–34, 2012.

[19] L. Haslam, A. Lansdown, J. Lee, and M. van der Vyver, "Survey of current practices: peripheral nerve block utilization by ED physicians for treatment of pain in the Hip fracture patient population," *Canadian Geriatrics Journal*, vol. 16, pp. 16–21, 2013.

[20] L. Haines, E. Dickman, S. Ayvazyan et al., "Ultrasound-guided fascia iliaca compartment block for hip fractures in the emergency department," *Journal of Emergency Medicine*, vol. 43, pp. 692–697, 2012.

[21] J. Ducharme, "Emergency pain management: a Canadian Association of Emergency Physicians (CAEP) consensus document," *Journal of Emergency Medicine*, vol. 12, no. 6, pp. 855–866, 1994.

[22] J. Lotsch, C. Walter, M. J. Parnham, B. G. Oertel, and G. Geisslinger, "Pharmacokinetics of non-intravenous formulations of fentanyl," *Clinical Pharmacokinetics*, vol. 52, pp. 23–36, 2013.

[23] S. H. Thomas, C. K. Stone, V. G. Ray, and T. W. Whitley, "Intravenous versus rectal prochlorperazine in the treatment of benign vascular or tension headache: a randomized, prospective, double-blind trial," *Annals of Emergency Medicine*, vol. 24, no. 5, pp. 923–927, 1994.

[24] M. L. Shear, J. N. Adler, S. Shewakramani et al., "Transbuccal fentanyl for rapid relief of orthopedic pain in the ED," *American Journal of Emergency Medicine*, vol. 28, no. 8, pp. 847–852, 2010.

[25] P. DeVellis, S. H. Thomas, and S. K. Wedel, "Prehospital and emergency department analgesia for air-transported patients with fractures," *Prehospital Emergency Care*, vol. 2, no. 4, pp. 293–296, 1998.

[26] S. H. Thomas, "Fentanyl in the prehospital setting," *American Journal of Emergency Medicine*, vol. 25, no. 7, pp. 842–843, 2007.

[27] P. S. Wilkins and M. W. Beckett, "Audit of unexpected return visits to an accident and emergency department," *Archives of Emergency Medicine*, vol. 9, no. 4, pp. 352–356, 1992.

[28] I. Imsuwan, "Characteristics of unscheduled emergency department return visit patients within 48 hours in Thammasat University Hospital," *Journal of the Medical Association of Thailand*, vol. 94, no. 7, pp. S73–S80, 2011.

[29] A. L. Drendel, R. Lyon, J. Bergholte, and M. K. Kim, "Outpatient pediatric pain management practices for fractures," *Pediatric Emergency Care*, vol. 22, no. 2, pp. 94–99, 2006.

[30] J. Porter and H. Jick, "Addiction rare in patients treated with narcotics," *New England Journal of Medicine*, vol. 302, no. 2, p. 123, 1980.

[31] A. Birnbaum, D. Esses, P. E. Bijur, L. Holden, and E. J. Gallagher, "Randomized double-blind placebo-controlled trial of two intravenous morphine dosages (0.10 mg/kg and 0.15 mg/kg) in emergency department patients with moderate to severe acute pain," *Annals of Emergency Medicine*, vol. 49, no. 4, pp. 445–e2, 2007.

[32] A. K. Chang, P. E. Bijur, J. B. Lupow, and E. John Gallagher, "Randomized clinical trial of efficacy and safety of a single 2-mg intravenous dose of hydromorphone versus usual care in the management of acute pain," *Academic Emergency Medicine*, vol. 20, pp. 185–192, 2013.

[33] B. Gharaei, A. Jafari, H. Aghamohammadi et al., "Opioid-sparing effect of preemptive bolus low-dose ketamine for moderate sedation in opioid abusers undergoing extracorporeal shock wave lithotripsy: a randomized clinical trial," *Anesthesia & Analgesia*, vol. 116, pp. 75–80, 2013.

[34] J. Talbot-Stern and R. Paoloni, "Prophylactic metoclopramide is unnecessary with intravenous analgesia in the ED," *American Journal of Emergency Medicine*, vol. 18, no. 6, pp. 653–657, 2000.

[35] T. Voepel-Lewis, S. Merkel, A. R. Tait, A. Trzcinka, and S. Malviya, "The reliability and validity of the face, legs, activity, cry, consolability observational tool as a measure of pain in children with cognitive impairment," *Anesthesia & Analgesia*, vol. 95, no. 5, pp. 1224–1229, 2002.

[36] V. Warden, A. C. Hurley, and L. Volicer, "Development and psychometric evaluation of the pain assessment in advanced dementia (PAINAD) scale," *Journal of the American Medical Directors Association*, vol. 4, no. 1, pp. 9–15, 2003.

[37] S. A. McLean, R. M. Domeier, H. K. DeVore, E. M. Hill, R. F. Maio, and S. M. Frederiksen, "The Feasibility of Pain Assessment in the Prehospital Setting," *Prehospital Emergency Care*, vol. 8, no. 2, pp. 155–161, 2004.

[38] A. Lozner, A. Reisner, M. L. Shear, S. Patel, and S. H. Thomas, "ED pain assessment: do patients want to give a number?" *American Journal of Emergency Medicine*, 2009.

[39] A. Arthur, S. Whiteside, L. Brown, C. Minor, and S. H. Thomas, "Patient use of tablet computers to facilitate ED pain assessment and documentation," *ISRN Emergency Medicine*, vol. 2012, Article ID 254530, 6 pages, 2012.

[40] A. W. Lozner, A. Reisner, M. L. Shear et al., "Pain severity is the key to emergency department patients' preferred frequency of pain assessment," *European Journal of Emergency Medicine*, vol. 17, no. 1, pp. 30–32, 2010.

[41] S. H. Thomas and L. M. Andruszkiewicz, "Ongoing visual analog score display improves Emergency Department pain care," *Journal of Emergency Medicine*, vol. 26, no. 4, pp. 389–394, 2004.

[42] J. E. Wilson and J. M. Pendleton, "Oligoanalgesia in the emergency department," *American Journal of Emergency Medicine*, vol. 7, no. 6, pp. 620–623, 1989.

[43] C. C. Reyes-Gibby and K. H. Todd, "Oligo-evidence for oligoanalgesia: a non sequitur?" *Annals of Emergency Medicine*, vol. 61, pp. 373–374, 2013.

[44] S. M. Green, "There is oligo-evidence for oligoanalgesia," *Annals of Emergency Medicine*, vol. 60, pp. 212–214, 2012.

[45] P. Paris and R. Stewart, "Analgesia and sedation," in *Emergency Medicine Concepts and Clinical Practice*, P. Rosen, Ed., pp. 201–209, Mosby, St. Louis, Miss, USA, 3 edition, 1992.

[46] J. Ducharme, "Acute pain and pain control: state of the art," *Annals of Emergency Medicine*, vol. 35, no. 6, pp. 592–603, 2000.

[47] P. M. Paris, "Pain management in the child," *Emergency Medicine Clinics of North America*, vol. 5, no. 4, pp. 699–707, 1987.

[48] S. M. Selbst and M. Clark, "Analgesic use in the emergency department," *Annals of Emergency Medicine*, vol. 19, no. 9, pp. 1010–1013, 1990.

[49] R. D. Waldrop and C. Mandry, "Health professional perceptions of opioid dependence among patients with pain," *American Journal of Emergency Medicine*, vol. 13, no. 5, pp. 529–531, 1995.

[50] K. H. Todd, N. Samaroo, and J. R. Hoffman, "Ethnicity as a risk factor for inadequate emergency department analgesia," *Journal of the American Medical Association*, vol. 269, no. 12, pp. 1537–1539, 1993.

[51] L. M. Lewis, L. C. Lasater, and C. B. Brooks, "Are emergency physicians too stingy with analgesics?" *Southern Medical Journal*, vol. 87, no. 1, pp. 7–9, 1994.

[52] S. Abbühl, F. Shofer, and I. Reyes, "Pelvic inflammatory disease: do we treat for pain?" *Annals of Emergency Medicine*, vol. 21, article 640, 1992.

[53] S. M. Selbst, "Analgesia in children. Why is it underused in emergency departments?" *Drug Safetyety*, vol. 7, no. 1, pp. 8–13, 1992.

[54] L. R. Friedland and R. M. Kulick, "Emergency department analgesic use in pediatric trauma victims with fractures," *Annals of Emergency Medicine*, vol. 23, no. 2, pp. 203–207, 1994.

[55] M. P. Khahi, M. R. Khajavi, A. Nadjafi, R. S. Moharari, F. Imani, and I. Rahimi, "Attitudes of anesthesiology residents and faculty members towards pain management," *Middle East Journal of Anesthesiology*, vol. 21, pp. 521–528, 2013.

[56] T. J. Jantos, P. M. Paris, J. J. Menegazzi, and D. M. Yealy, "Analgesic practice for acute orthopedic trauma pain in Costa Rican emergency departments," *Annals of Emergency Medicine*, vol. 28, no. 2, pp. 145–150, 1996.

[57] B. Krauss and D. Zurakowski, "Sedation patterns in pediatric and general community hospital emergency departments," *Pediatric Emergency Care*, vol. 14, no. 2, pp. 99–102, 1998.

[58] K. Todd, C. Warner, A. D'Adamo, and L. Goe, "Ethnicity and emergency department analgesia," *Academic Emergency Medicine*, vol. 4, article 424, 1997.

[59] M. C. Plewa, "Analgesic prescriptions for ED patients with pelvic or dental pain," *American Journal of Emergency Medicine*, vol. 15, no. 3, pp. 326–328, 1997.

[60] J. Davis, S. Santen, and J. Glasser, "Factors affecting pain perception in the ED," *Annals of Emergency Medicine*, vol. 30, article 377, 1997.

[61] T. E. Wiswell, "Circumcision circumspection," *New England Journal of Medicine*, vol. 336, no. 17, pp. 1244–1245, 1997.

[62] M. A. Hostetler, P. Auinger, and P. G. Szilagyi, "Parenteral analgesic and sedative use among ED patients in the United States: combined results from the National Hospital Ambulatory Medical Care Survey (NHAMCS) 1992–1997," *American Journal of Emergency Medicine*, vol. 20, no. 2, pp. 83–87, 2002.

[63] T. J. Luger, W. Lederer, M. Gassner, A. Löckinger, H. Ulmer, and I. H. Lorenz, "Acute pain is underassessed in out-of-hospital emergencies," *Academic Emergency Medicine*, vol. 10, no. 6, pp. 627–632, 2003.

[64] J. C. Ballantyne and J. Mao, "Opioid therapy for chronic pain," *New England Journal of Medicine*, vol. 349, no. 20, pp. 1943–1953, 2003.

[65] B. Wilsey, S. Fishman, J. S. Rose, and J. Papazian, "Pain management in the ED," *American Journal of Emergency Medicine*, vol. 22, no. 1, pp. 51–57, 2004.

[66] S. A. Godwin, D. A. Caro, S. J. Wolf et al., "Clinical policy: procedural sedation and analgesia in the emergency department," *Annals of Emergency Medicine*, vol. 45, no. 2, pp. 177–196, 2005.

[67] K. D. Young, "Pediatric procedural pain," *Annals of Emergency Medicine*, vol. 45, no. 2, pp. 160–171, 2005.

[68] K. M. Terrell, K. Heard, and D. K. Miller, "Prescribing to older ED patients," *American Journal of Emergency Medicine*, vol. 24, no. 4, pp. 468–478, 2006.

[69] J. M. Pines and J. E. Hollander, "Emergency department crowding is associated with poor care for patients with severe pain," *Annals of Emergency Medicine*, vol. 51, no. 1, pp. 1–5, 2008.

[70] P. Bijur, A. Bérard, J. Nestor, Y. Calderon, M. Davitt, and E. J. Gallagher, "No racial or ethnic disparity in treatment of long-bone fractures," *American Journal of Emergency Medicine*, vol. 26, no. 3, pp. 270–274, 2008.

[71] S. Quazi, M. Eberhart, J. Jacoby, and M. Heller, "Are racial disparities in ED analgesia improving? Evidence from a national database," *American Journal of Emergency Medicine*, vol. 26, no. 4, pp. 462–464, 2008.

[72] L. Dong, A. Donaldson, R. Metzger, and H. Keenan, "Analgesic administration in the emergency department for children requiring hospitalization for long-bone fracture," *Pediatric Emergency Care*, vol. 28, pp. 109–114, 2012.

[73] A. Sacchetti, R. Schafermeyer, M. Gerardi et al., "Pediatric analgesia and sedation," *Annals of Emergency Medicine*, vol. 23, no. 2, pp. 237–250, 1994.

[74] D. M. Williams, K. E. Rindal, J. T. Cushman, and M. N. Shah, "Barriers to and enablers for prehospital analgesia for pediatric patients," *Prehospital Emergency Care*, vol. 16, pp. 519–526, 2012.

[75] F. M. Gloth, "Geriatric pain: factors that limit pain relief and increase complications," *Geriatrics*, vol. 55, no. 10, pp. 46–54, 2000.

[76] A. Lukas, T. Niederecker, I. Gunther, B. Mayer, and T. Nikolaus, "Self- and proxy report for the assessment of pain in patients with and without cognitive impairment: experiences gained in a geriatric hospital," *Zeitschrift fur Gerontologie und Geriatrie*, vol. 46, no. 3, pp. 214–221, 2013.

[77] P. G. Fine, "Treatment guidelines for the pharmacological management of pain in older persons," *Pain Medicine*, vol. 13, no. 2, supplement, pp. S57–S66, 2012.

[78] O. Cinar, R. Ernst, D. Fosnocht et al., "Geriatric patients may not experience increased risk of oligoanalgesia in the emergency department," *Annals of Emergency Medicine*, vol. 60, pp. 207–211, 2012.

[79] M. R. Cury, F. E. Martinez, and A. P. Carlotti, "Pain assessment in neonates and infants in the post-operative period following cardiac surgery," *Postgraduate Medical Journal*, vol. 89, pp. 63–67, 2013.

[80] J. H. Lee, K. Kim, T. Y. Kim et al., "A randomized comparison of nitrous oxide versus intravenous ketamine for laceration repair in children," *Pediatric Emergency Care*, vol. 28, pp. 1297–1301, 2012.

[81] Y. M. Weng, Y. C. Chang, and Y. J. Lin, "Triage pain scales cannot predict analgesia provision to pediatric patients with long-bone fracture," *American Journal of Emergency Medicine*, vol. 28, no. 4, pp. 412–417, 2010.

[82] B. Bailey, S. Bergeron, J. Gravel, and R. Daoust, "Comparison of four pain scales in children with acute abdominal pain in a pediatric emergency department," *Annals of Emergency Medicine*, vol. 50, no. 4, pp. 379–383, 2007.

[83] L. Regan, A. R. Chapman, A. Celnik, L. Lumsden, R. Al-Soufi, and N. P. McCullough, "Nose and vein, speed and pain: comparing the use of intranasal diamorphine and intravenous morphine in a Scottish paediatric emergency department," *Emergency Medicine Journal*, vol. 30, pp. 49–52, 2013.

[84] M. H. James and C. V. Dayas, "What about me...? The PVT: a role for the paraventricular thalamus (PVT) in drug-seeking behavior," *Frontiers in Behavioral Neuroscience*, vol. 7, article 18, 2013.

[85] S. Y. Lee, I. J. You, M. J. Kim et al., "The abuse potential of oxethazaine: effects of oxethazaine on drug-seeking behavior and analysis of its metabolites in plasma and hair in animal models," *Pharmacology Biochemistry and Behavior*, vol. 105, pp. 98–104, 2013.

[86] A. Lembke, "Why doctors prescribe opioids to known opioid abusers," *New England Journal of Medicine*, vol. 367, pp. 1580–1581, 2012.

[87] J. L. Goulet, C. Brandt, S. Crystal et al., "Agreement between electronic medical record-based and self-administered pain numeric rating scale: clinical and research implications," *Medical Care*, vol. 51, pp. 245–250, 2013.

[88] L. Montali, C. Monica, P. Riva, and R. Cipriani, "Conflicting representations of pain: a qualitative analysis of health care professionals' discourse," *Pain Medicine*, vol. 12, pp. 1585–1593, 2011.

[89] E. A. Laugsand, G. Jakobsen, S. Kaasa, and P. Klepstad, "Inadequate symptom control in advanced cancer patients across Europe," *Support Care Cancer*, vol. 19, pp. 2005–2014, 2011.

[90] E. A. Laugsand, M. A. G. Sprangers, K. Bjordal, F. Skorpen, S. Kaasa, and P. Klepstad, "Health care providers underestimate symptom intensities of cancer patients: a multicenter European study," *Health and Quality of Life Outcomes*, vol. 8, article 104, 2010.

[91] T. C. Lee, S. G. Goodman, R. T. Yan et al., "Disparities in management patterns and outcomes of patients with non-ST-elevation acute coronary syndrome with and without a history of cerebrovascular disease," *American Journal of Cardiology*, vol. 105, no. 8, pp. 1083–1089, 2010.

[92] K. M. Prkachin and E. M. Rocha, "High levels of vicarious exposure bias pain judgments," *Journal of Pain*, vol. 11, no. 9, pp. 904–909, 2010.

[93] L. R. Shugarman, J. R. Goebel, A. Lanto et al., "Nursing staff, patient, and environmental factors associated with accurate pain assessment," *Journal of Pain and Symptom Management*, vol. 40, no. 5, pp. 723–733, 2010.

[94] J. S. Jahr, P. Filocamo, and S. Singh, "Intravenous acetaminophen: a review of pharmacoeconomic science for perioperative use," *American Journal of Therapeutics*, vol. 20, pp. 189–199, 2013.

[95] C. C. Apfel, A. Turan, K. Souza, J. Pergolizzi, and C. Hornuss, "Intravenous acetaminophen reduces postoperative nausea and vomiting: a systematic review and meta-analysis," *Pain*, vol. 154, no. 5, pp. 677–689, 2013.

[96] J. S. Blanco, S. L. Perlman, H. S. Cha, and K. Delpizzo, "Multimodal pain management after spinal surgery for adolescent idiopathic scoliosis," *Orthopedics*, vol. 36, pp. 33–35, 2013.

[97] K. S. Tsang, J. Page, and P. Mackenney, "Can intravenous paracetamol reduce opioid use in preoperative hip fracture patients?" *Orthopedics*, vol. 36, pp. 20–24, 2013.

[98] P. F. Lachiewicz, "The role of intravenous acetaminophen in multimodal pain protocols for perioperative orthopedic patients," *Orthopedics*, vol. 36, pp. 15–19, 2013.

[99] I. Ceelie, S. N. de Wildt, M. van Dijk et al., "Effect of intravenous paracetamol on postoperative morphine requirements in neonates and infants undergoing major noncardiac surgery: a randomized controlled trial," *Journal of the American Medical Association*, vol. 309, pp. 149–154, 2013.

[100] "Injectable paracetamol in children: yet more cases of 10-fold overdose," *Prescrire International*, vol. 22, pp. 44–45, 2013.

[101] J. L. Kwiatkowski and P. L. Walker, "Intravenous acetaminophen in the emergency department," *Journal of Emergency Nursing*, vol. 39, pp. 92–96, 2013.

[102] M. Craig, R. Jeavons, J. Probert, and J. Benger, "Randomised comparison of intravenous paracetamol and intravenous morphine for acute traumatic limb pain in the emergency department," *Emergency Medicine Journal*, vol. 29, pp. 37–39, 2012.

[103] C. K. S. Ong, R. A. Seymour, P. Lirk, and A. F. Merry, "Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain," *Anesthesia & Analgesia*, vol. 110, no. 4, pp. 1170–1179, 2010.

[104] M. A. Turturro, P. M. Paris, and D. C. Seaberg, "Intramuscular ketorolac versus oral ibuprofen in acute musculoskeletal pain," *Annals of Emergency Medicine*, vol. 26, no. 2, pp. 117–120, 1995.

[105] J. M. Wright, S. D. Price, and W. A. Watson, "NSAID use and efficacy in the emergency department: single doses of oral ibuprofen versus intramuscular ketorolac," *Annals of Pharmacotherapy*, vol. 28, no. 3, pp. 309–312, 1994.

[106] J. Castellsague, N. Riera-Guardia, B. Calingaert et al., "Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project)," *Drug Safety*, vol. 35, pp. 1127–1146, 2012.

[107] A. Rios, H. Vargas-Robles, A. M. Gamez-Mendez, and B. Escalante, "Cyclooxygenase-2 and kidney failure," *Prostaglandins & Other Lipid Mediators*, vol. 98, pp. 86–90, 2012.

[108] T. Green, A. A. Gonzalez, K. D. Mitchell, and L. G. Navar, "The complex interplay between cyclooxygenase-2 and angiotensin II in regulating kidney function," *Current Opinion in Nephrology and Hypertension*, vol. 21, pp. 7–14, 2012.

[109] Y. Guo, D. N. Tukaye, W. J. Wu et al., "The COX-2/PGI2 receptor axis plays an obligatory role in mediating the cardioprotection conferred by the late phase of ischemic preconditioning," *PLoS ONE*, vol. 7, Article ID e41178, 2012.

[110] Y. Yu, E. Ricciotti, R. Scalia et al., "Vascular COX-2 modulates blood pressure and thrombosis in mice," *Science Translational Medicine*, vol. 4, p. 132ra54, 2012.

[111] M. Bultitude and J. Rees, "Management of renal colic," *British Medical Journal*, vol. 345, Article ID e5499, 2012.

[112] E. Cevik, O. Cinar, N. Salman et al., "Comparing the efficacy of intravenous tenoxicam, lornoxicam, and dexketoprofen trometamol for the treatment of renal colic," *American Journal of Emergency Medicine*, vol. 30, pp. 1486–1490, 2012.

[113] A. Dash, R. Maiti, T. K. Akantappa Bandakkanavar, and P. Arora, "Intramuscular drotaverine and diclofenac in acute renal colic: a comparative study of analgesic efficacy and safety," *Pain Medicine*, vol. 13, pp. 466–471, 2012.

[114] Z. Harel, "Dysmenorrhea in adolescents and young adults: an update on pharmacological treatments and management strategies," *Expert Opinion on Pharmacotherapy*, vol. 13, pp. 2157–2170, 2012.

[115] S. Schrager, J. Falleroni, and J. Edgoose, "Evaluation and treatment of endometriosis," *American Family Physician*, vol. 87, pp. 107–113, 2013.

[116] P. Bartolucci and F. Galacteros, "Clinical management of adult sickle-cell disease," *Current Opinion in Hematology*, vol. 19, pp. 149–155, 2012.

[117] M. Baker and J. W. Hafner, "What is the best pharmacologic treatment for sickle cell disease pain crises?" *Annals of Emergency Medicine*, vol. 59, pp. 515–516, 2012.

[118] C. Carter, "NSAIDs for relieving renal colic in patients with kidney stones," *American Family Physician*, vol. 85, article 1127, 2012.

[119] P. Giannoidis, A. Furlong, D. Macdonald, P. deBoer, and R. Smith, "Non-union of the femoral diaphysis: the influence of reaming and non-steroidal anti-inflammatory drugs (NSAIDs)," *The Journal of Bone and Joint Surgery*, vol. 82, pp. 655–658, 2000.

[120] S. M. Green and B. Krauss, "Should I give ketamine IV or IM?" *Annals of Emergency Medicine*, vol. 48, no. 5, pp. 613–614, 2006.

[121] R. F. Bell, J. B. Dahl, R. A. Moore, and E. Kalso, "Perioperative ketamine for acute postoperative pain," *Cochrane Database of Systematic Reviews*, no. 1, Article ID CD004603, 2006.

[122] E. Cevik, S. Bilgic, E. Kilic et al., "Comparison of ketamine-low-dose midozolam with midazolam-fentanyl for orthopedic emergencies: a double-blind randomized trial," *American Journal of Emergency Medicine*, vol. 31, pp. 108–113, 2013.

[123] P. Asadi, H. B. Ghafouri, M. Yasinzadeh, S. M. Kasnavieh, and E. Modirian, "Ketamine and atropine for pediatric sedation: a prospective double-blind randomized controlled trial," *Pediatric Emergency Care*, vol. 29, no. 2, pp. 136–139, 2013.

[124] T. S. Sherwin, S. M. Green, A. Khan, D. S. Chapman, and B. Dannenberg, "Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial," *Annals of Emergency Medicine*, vol. 35, no. 3, pp. 229–238, 2000.

[125] S. M. Green and J. Li, "Ketamine in adults: what emergency physicians need to know about patient selection and emergence reactions," *Academic Emergency Medicine*, vol. 7, no. 3, pp. 278–281, 2000.

[126] S. M. Green, N. Kuppermann, S. G. Rothrock, C. B. Hummel, and M. Ho, "Predictors of adverse events with intramuscular ketamine sedation in children," *Annals of Emergency Medicine*, vol. 35, no. 1, pp. 35–42, 2000.

[127] S. M. Green and B. Krauss, "Clinical practice guideline for emergency department ketamine dissociative sedation in children," *Annals of Emergency Medicine*, vol. 44, no. 5, pp. 460–471, 2004.

[128] V. F. Owens, T. L. Palmieri, C. M. Comroe, J. M. Conroy, J. A. Scavone, and D. G. Greenhalgh, "Ketamine: a safe and effective agent for painful procedures in the pediatric burn patient," *Journal of Burn Care and Research*, vol. 27, no. 2, pp. 211–216, 2006.

[129] S. M. Green, M. G. Roback, B. Krauss et al., "Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8,282 children," *Annals of Emergency Medicine*, vol. 54, no. 2, pp. 158–168, 2009.

[130] S. M. Green, M. G. Roback, B. Krauss et al., "Predictors of emesis and recovery agitation with emergency department ketamine sedation: an individual-patient data meta-analysis of 8,282 children," *Annals of Emergency Medicine*, vol. 54, no. 2, pp. 171–180, 2009.

[131] S. M. Green, M. G. Roback, and B. Krauss, "Anticholinergics and ketamine sedation in children: a secondary analysis of atropine versus glycopyrrolate," *Academic Emergency Medicine*, vol. 17, no. 2, pp. 157–162, 2010.

[132] L. C. Chang, S. R. Raty, J. Ortiz, N. S. Bailard, and S. J. Mathew, "The emerging use of ketamine for anesthesia and sedation in traumatic brain injuries," *CNS Neuroscience & Therapeutics*, 2013.

[133] G. Bar-Joseph, Y. Guilburd, A. Tamir, and J. N. Guilburd, "Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension: clinical article," *Journal of Neurosurgery*, vol. 4, no. 1, pp. 40–46, 2009.

[134] J. E. Wathen, M. G. Roback, T. Mackenzie, and J. P. Bothner, "Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-blind, randomized, controlled, emergency department trial," *Annals of Emergency Medicine*, vol. 36, no. 6, pp. 579–588, 2000.

[135] S. Sener, C. Eken, C. H. Schultz, M. Serinken, and M. Ozsarac, "Ketamine with and without midazolam for emergency department sedation in adults: a randomized controlled trial," *Annals of Emergency Medicine*, vol. 57, no. 2, pp. 109–114, 2011.

[136] J. H. Chong, S. P. Chew, and A. S. Ang, "Is prophylactic atropine necessary during ketamine sedation in children," *Journal of Paediatrics and Child Health*, vol. 49, no. 4, pp. 309–312, 2013.

[137] J. S. Lee, W. C. Jeon, and E. J. Park, "Adjunctive atropine versus metoclopramide: can we reduce ketamine-associated vomiting in young children? a prospective, randomized, open, controlled study," *Academic Emergency Medicine*, vol. 19, pp. 1128–1133, 2012.

[138] A. L. Bredlau, M. P. McDermott, H. R. Adam et al., "Oral ketamine for children with chronic pain: a pilot phase 1 study," *Journal of Pediatrics*, 2013.

[139] W. Leppert, "Ketamine in the management of cancer pain," *Journal of Clinical Oncology*, 2013.

[140] C. Norambuena, J. Yanez, V. Flores, P. Puentes, P. Carrasco, and R. Villena, "Oral ketamine and midazolam for pediatric burn patients: a prospective, randomized, double-blind study," *Journal of Pediatric Surgery*, vol. 48, pp. 629–634, 2013.

[141] W. P. McKay, "Intravenous analgesia for out-of-hospital traumatic pain in adults: ketamine gives a greater reduction in pain than morphine but causes more adverse effects," *Evidence-Based Nursing*, vol. 16, pp. 58–59, 2013.

[142] M. Komorowski, S. D. Watkins, G. Lebuffe, and J. B. Clark, "Potential anesthesia protocols for space exploration missions," *Aviation, Space, and Environmental Medicine*, vol. 84, pp. 226–233, 2013.

[143] P. A. Jennings, P. Cameron, S. Bernard et al., "Morphine and ketamine is superior to morphine alone for out-of-hospital trauma analgesia: a randomized controlled trial," *Annals of Emergency Medicine*, vol. 59, pp. 497–503, 2012.

[144] A. A. Herring, T. Ahern, M. B. Stone, and B. W. Frazee, "Emerging applications of low-dose ketamine for pain management in the ED," *American Journal of Emergency Medicine*, vol. 31, pp. 416–419, 2013.

[145] G. Z. Shlamovitz, A. Elsayem, and K. H. Todd, "Ketamine for palliative sedation in the emergency department," *Journal of Emergency Medicine*, vol. 44, pp. 355–357, 2013.

[146] J. R. Richards and R. E. Rockford, "Low-dose ketamine analgesia: patient and physician experience in the ED," *American Journal of Emergency Medicine*, vol. 31, pp. 390–394, 2013.

[147] E. R. Thal, S. J. Montgomergy, J. M. Atkins, and B. G. Roberts, "Self-administered analgesia with nitrous oxide. Adjunctive aid for emergency medical care systems," *Journal of the American Medical Association*, vol. 242, no. 22, pp. 2418–2419, 1979.

[148] K. D. McKinnon, D. Culver, and J. M. Prno, "Nitrous oxide/oxygen analgesia in emergency care," *Canadian Family Physician*, vol. 26, pp. 83–87, 1980.

[149] J. M. Nieto and P. Rosen, "Nitrous oxide at higher elevations," *Annals of Emergency Medicine*, vol. 9, no. 12, pp. 610–612, 1980.

[150] J. P. Tourtier, L. Raynaud, I. Murat, and O. Gall, "Audit of protocols for treatment of paediatric burns in emergency departments in the Île de France," *Burns*, vol. 36, no. 8, pp. 1196–1200, 2010.

[151] N. Grandcolas, J. Galéa, R. Ananda et al., "Stonefish stings: difficult analgesia and notable risk of complications," *Presse Medicale*, vol. 37, no. 3, pp. 395–400, 2008.

[152] W. L. Hennrikus, A. Y. Shin, and C. E. Klingelberger, "Self-administered nitrous oxide and a hematoma block for analgesia in the outpatient reduction of fractures in children," *Journal of Bone and Joint Surgery Series A*, vol. 77, no. 3, pp. 335–339, 1995.

[153] D. C. Seaberg, D. M. Yealh, and K. Ilkhanipour, "Effect of nitrous oxide analgesia on pneumothorax," *Academic Emergency Medicine*, vol. 2, no. 4, pp. 287–292, 1995.

[154] F. E. Babl, E. Oakley, C. Seaman, P. Barnett, and L. N. Sharwood, "High-concentration nitrous oxide for procedural sedation in children: adverse events and depth of sedation," *Pediatrics*, vol. 121, no. 3, pp. e528–e532, 2008.

[155] J. L. Ducasse, G. Siksik, M. Durand-Bechu et al., "Nitrous oxide for early analgesia in the emergency setting: a randomized, double-blind multicenter prehospital trial," *Academic Emergency Medicine*, vol. 20, pp. 178–184, 2013.

[156] R. W. Seith, T. Theophilos, and F. E. Babl, "Intranasal fentanyl and high-concentration inhaled nitrous oxide for procedural sedation: a prospective observational pilot study of adverse events and depth of sedation," *Academic Emergency Medicine*, vol. 19, pp. 31–36, 2012.

[157] H. Kariman, A. Majidi, A. Amini et al., "Nitrous oxide/oxygen compared with fentanyl in reducing pain among adults with isolated extremity trauma: a randomized trial," *Emergency Medicine Australasia*, vol. 23, pp. 761–768, 2011.

[158] J. Pershad, S. C. Steinberg, and T. M. Waters, "Cost-effectiveness analysis of anesthetic agents during peripheral intravenous cannulation in the pediatric emergency department," *Archives of Pediatrics and Adolescent Medicine*, vol. 162, no. 10, pp. 952–961, 2008.

[159] P. A. Robinson, S. Carr, S. Pearson, and C. Frampton, "Lignocaine is a better analgesic than either ethyl chloride or nitrous oxide for peripheral intravenous cannulation," *Emergency Medicine Australasia*, vol. 19, no. 5, pp. 427–432, 2007.

[160] F. E. Babl, E. Oakley, A. Puspitadewi, and L. N. Sharwood, "Limited analgesic efficacy of nitrous oxide for painful procedures in children," *Emergency Medicine Journal*, vol. 25, no. 11, pp. 717–721, 2008.

[161] A. H. Ilsley, J. L. Plummer, M. J. Cousins, R. L. Fronsko, and J. E. Gilligan, "Atmospheric concentrations of nitrous oxide in ambulances during Entonox administration," *Anaesthesia and Intensive Care*, vol. 17, no. 1, pp. 83–85, 1989.

[162] "Teratogenicity of nitrous oxide," *FDA Drug Bulletin*, vol. 11, article 7, 1981.

[163] S. Senthilkumaran, N. Balamurugan, and R. G. Menezes, "Thirumalaikolundusubramanian P. Nitrous oxide toxicity: technical and therapeutic aspects," *American Journal of Emergency Medicine*, vol. 31, article 406, 2013.

[164] A. Young, M. Ismail, A. G. Papatsoris, J. M. Barua, J. G. Calleary, and J. Masood, "Entonox(R) inhalation to reduce pain in common diagnostic and therapeutic outpatient urological procedures: a review of the evidence," *Annals of The Royal College of Surgeons of England*, vol. 94, pp. 8–11, 2012.

[165] A. Jimenez, D. Blazquez, J. Cruz et al., "Use of combined transmucosal fentanyl, nitrous oxide, and hematoma block for fracture reduction in a pediatric emergency department," *Pediatric Emergency Care*, vol. 28, pp. 676–679, 2012.

[166] N. E. Kelley and D. E. Tepper, "Rescue therapy for acute migraine, part 2: neuroleptics, antihistamines, and others," *Headache*, vol. 52, pp. 292–306, 2012.

[167] P. McKenna, M. Leonard, P. Connolly, S. Boran, and D. McCormack, "A comparison of pediatric forearm fracture reduction between conscious sedation and general anesthesia," *Journal of Orthopaedic Trauma*, vol. 26, pp. 550–555, 2012.

[168] D. Zamanillo, L. Romero, M. Merlos, and J. Miguel Vela, "Sigma 1 receptor: a new therapeutic target for pain," *European Journal of Pharmacology*, 2013.

[169] H. Mizoguchi, C. Watanabe, T. Sakurada, and S. Sakurada, "New vistas in opioid control of pain," *Current Opinion in Pharmacology*, vol. 12, pp. 87–91, 2012.

[170] R. Taylor Jr., J. V. Pergolizzi Jr., F. Porreca, and R. B. Raffa, "Opioid antagonists for pain," *Expert Opinion on Investigational Drugs*, vol. 22, pp. 517–525, 2013.

[171] C. Gaveriaux-Ruff, "Opiate-induced analgesia: contributions from Mu, Delta and Kappa opioid receptors mouse mutants," *Current Pharmaceutical Design*, 2013.

[172] R. Wightman, J. Perrone, I. Portelli, and L. Nelson, "Likeability and abuse liability of commonly prescribed opioids," *Journal of Medical Toxicology*, vol. 8, pp. 335–340, 2012.

[173] R. C. Francis, F. Bubser, W. Schmidbauer et al., "Effects of a standard operating procedure on prehospital emergency care of patients presenting with symptoms of the acute coronary syndrome," *European Journal of Emergency Medicine*, 2013.

[174] D. Ryan, A. M. Craig, L. Turner, and P. R. Verbeek, "Clinical events and treatment in prehospital patients with ST-segment elevation myocardial infarction," *Prehospital Emergency Care*, vol. 17, pp. 181–186, 2012.

[175] K. E. Bakkelund, E. Sundland, S. Moen, G. Vangberg, S. Mellesmo, and P. Klepstad, "Undertreatment of pain in the prehospital setting: a comparison between trauma patients and patients with chest pain," *European Journal of Emergency Medicine*, 2012.

[176] M. D. Smith, Y. Wang, M. Cudnik, D. A. Smith, J. Pakiela, and C. L. Emerman, "The effectiveness and adverse events of morphine versus fentanyl on a physician-staffed helicopter," *Journal of Emergency Medicine*, vol. 43, pp. 69–75, 2011.

[177] X. B. Ona, I. Solà, and X. B. Cosp, "Drug therapy for preventing post-dural puncture headache," *Cochrane Database of Systematic Reviews*, no. 3, Article ID CD001792, 2009.

[178] A. E. Patanwala, K. L. Holmes, and B. L. Erstad, "Analgesic response to morphine in obese and morbidly obese patients in the emergency department," *Emergency Medicine Journal*, 2013.

[179] A. Birnbaum, C. Schechter, V. Tufaro, R. Touger, E. J. Gallagher, and P. Bijur, "Efficacy of patient-controlled analgesia for patients with acute abdominal pain in the emergency department:

a randomized trial," *Academic Emergency Medicine*, vol. 19, pp. 370–377, 2012.

[180] P. E. Bijur, D. Esses, A. K. Chang, and E. J. Gallagher, "Dosing and titration of intravenous opioid analgesics administered to ED patients in acute severe pain," *American Journal of Emergency Medicine*, vol. 30, pp. 1241–1244, 2012.

[181] A. E. Patanwala, C. J. Edwards, L. Stolz, R. Amini, A. Desai, and U. Stolz, "Should morphine dosing be weight based for analgesia in the emergency department?" *Journal of Opioid Management*, vol. 8, pp. 51–55, 2012.

[182] P. E. Bijur, M. K. Kenny, and E. J. Gallagher, "Intravenous morphine at 0.1 mg/kg is not effective for controlling severe acute pain in the majority of patients," *Annals of Emergency Medicine*, vol. 46, no. 4, pp. 362–367, 2005.

[183] J. Chrubasik, H. Wust, G. Friedrich, and E. Geller, "Absorption and bioavailability of nebulized morphine," *British Journal of Anaesthesia*, vol. 61, pp. 228–230, 1988.

[184] S. K. Ballas, E. R. Viscusi, and K. R. Epstein, "Management of acute chest wall sickle cell pain with nebulized morphine," *American Journal of Hematology*, vol. 76, no. 2, pp. 190–191, 2004.

[185] G. J. Fulda, F. Giberson, L. Fagraeus, P. B. Angood, and L. M. Gentilello, "A prospective randomized trial of nebulized morphine compared with patient-controlled analgesia morphine in the management of acute thoracic pain," *Journal of Trauma*, vol. 59, no. 2, pp. 383–390, 2005.

[186] W. Lasheen, A. Panneerselvam, and M. P. Davis, "Can we really say that nebulized morphine works?" *Journal of Pain and Symptom Management*, vol. 32, no. 2, pp. 101–102, 2006.

[187] V. Bounes, J. L. Ducassé, A. M. Bona, F. Battefort, C. H. Houze-Cerfon, and D. Lauque, "Nebulized morphine for analgesia in an emergency setting," *Journal of Opioid Management*, vol. 5, no. 1, pp. 23–26, 2009.

[188] A. K. Chang, P. E. Bijur, R. H. Meyer, M. K. Kenny, C. Solorzano, and E. J. Gallagher, "Safety and efficacy of hydromorphone as an analgesic alternative to morphine in acute pain: a randomized clinical trial," *Annals of Emergency Medicine*, vol. 48, no. 2, pp. 164–172, 2006.

[189] N. B. Jasani, R. E. O'Conner, and J. K. Bouzoukis, "Comparison of hydromorphone and meperidine for ureteral colic," *Academic Emergency Medicine*, vol. 1, no. 6, pp. 539–543, 1994.

[190] P. Tanabe, N. Artz, D. M. Courtney et al., "Adult emergency department patients with sickle cell pain crisis: a learning collaborative model to improve analgesic management," *Academic Emergency Medicine*, vol. 19, no. 4, pp. 430–438, 2010.

[191] A. K. Chang, P. E. Bijur, A. Napolitano, J. Lupow, and E. J. Gallagher, "Two milligrams IV hydromorphone is efficacious for treating pain but is associated with oxygen desaturation," *Journal of Opioid Management*, vol. 5, no. 2, pp. 75–80, 2009.

[192] A. K. Chang, P. E. Bijur, and E. J. Gallagher, "Randomized clinical trial comparing the safety and efficacy of a hydromorphone titration protocol to usual care in the management of adult emergency department patients with acute severe pain," *Annals of Emergency Medicine*, vol. 58, pp. 352–359, 2011.

[193] C. R. Chudnofsky, S. W. Wright, S. C. Dronen, S. W. Borron, and M. B. Wright, "The safety of fentanyl use in the Emergency Department," *Annals of Emergency Medicine*, vol. 18, no. 6, pp. 635–639, 1989.

[194] S. P. Ros, "Outpatient pediatric analgesia—a tale of two regimens," *Pediatric Emergency Care*, vol. 3, no. 4, pp. 228–230, 1987.

[195] W. C. Krauss, S. Shah, S. Shah, and S. H. Thomas, "Fentanyl in the out-of-hospital setting: variables associated with hypotension and hypoxemia," *Journal of Emergency Medicine*, vol. 40, no. 2, pp. 182–187, 2011.

[196] S. H. Thomas, O. Rago, T. Harrison, P. D. Biddinger, and S. K. Wedel, "Fentanyl trauma analgesia use in air medical scene transports," *Journal of Emergency Medicine*, vol. 29, no. 2, pp. 179–187, 2005.

[197] P. Devellis, S. H. Thomas, S. K. Wedel, J. P. Stein, and R. J. Vinci, "Prehospital fentanyl analgesia in airtransported pediatric trauma patients," *Pediatric Emergency Care*, vol. 14, no. 5, pp. 321–323, 1998.

[198] B. R. Wenderoth, E. T. Kaneda, A. Amini, R. Amini, and A. E. Patanwala, "Morphine versus fentanyl for pain due to traumatic injury in the emergency department," *Journal of Trauma Nursing*, vol. 20, pp. 10–15, 2013.

[199] M. N. Bulloch and A. M. Hutchison, "Fentanyl pectin nasal spray: a novel intranasal delivery method for the treatment of breakthrough cancer pain," *Expert Review of Clinical Pharmacology*, vol. 6, pp. 9–22, 2013.

[200] J. A. Ellerton, M. Greene, and P. Paal, "The use of analgesia in mountain rescue casualties with moderate or severe pain," *Emergency Medicine Journal*, 2013.

[201] H. S. Smith, "Considerations in selecting rapid-onset opioids for the management of breakthrough pain," *Journal of Pain Research*, vol. 6, pp. 189–200, 2013.

[202] S. Grassin-Delyle, A. Buenestado, E. Naline et al., "Intranasal drug delivery: an efficient and non-invasive route for systemic administration: focus on opioids," *Pharmacology and Therapeutics*, vol. 134, pp. 366–379, 2012.

[203] P. M. Middleton, P. M. Simpson, G. Sinclair, T. A. Dobbins, B. Math, and J. C. Bendall, "Effectiveness of morphine, fentanyl, and methoxyflurane in the prehospital setting," *Prehospital Emergency Care*, vol. 14, no. 4, pp. 439–447, 2010.

[204] M. S. Hansen and J. B. Dahl, "Limited evidence for intranasal fentanyl in the emergency department and the prehospital setting—a systematic review," *Danish Medical Journal*, vol. 60, Article ID A4563, 2013.

[205] J. S. Furyk, W. J. Grabowski, and L. H. Black, "Nebulized fentanyl versus intravenous morphine in children with suspected limb fractures in the emergency department: a randomized controlled trial," *Emergency Medicine Australasia*, vol. 21, no. 3, pp. 203–209, 2009.

[206] T. H. Stanley and M. A. Ashburn, "Novel delivery systems: oral transmucosal and intranasal transmucosal," *Journal of Pain and Symptom Management*, vol. 7, no. 3, pp. 163–171, 1992.

[207] S. A. Schutzman, E. Liebelt, M. Wisk, and J. Burg, "Comparison of oral transmucosal fentanyl citrate and intramuscular meperidine, promethazine, and chlorpromazine for conscious sedation of children undergoing laceration repair," *Annals of Emergency Medicine*, vol. 28, no. 4, pp. 385–390, 1996.

[208] A. O. Arthur and P. Holder, "A review of transbuccal fentanyl use in the emergency department," *Pain Research and Treatment*, vol. 2012, Article ID 768796, 3 pages, 2012.

[209] S. Kapoor, "Intranasal sufentanil and its emerging clinical applications: beyond its role in the emergency department," *Journal of Opioid Management*, vol. 8, article 341, 2012.

[210] R. Stephen, E. Lingenfelter, C. Broadwater-Hollifield, and T. Madsen, "Intranasal sufentanil provides adequate analgesia for emergency department patients with extremity injuries," *Journal of Opioid Management*, vol. 8, pp. 237–241, 2012.

[211] J. Steenblik, M. Goodman, V. Davis et al., "Intranasal sufentanil for the treatment of acute pain in a winter resort clinic," *American Journal of Emergency Medicine*, vol. 30, pp. 1817–1821, 2012.

[212] V. Bounes, R. Barthélémy, O. Diez, S. Charpentier, J. L. Montastruc, and J. L. Ducassé, "Sufentanil is not superior to morphine for the treatment of acute traumatic pain in an emergency setting: a randomized, double-blind, out-of-hospital trial," *Annals of Emergency Medicine*, vol. 56, no. 5, pp. 509–516, 2010.

[213] T. Silfvast and L. Saarnivaara, "Comparison of alfentanil and morphine in the prehospital treatment of patients with acute ischaemic-type chest pain," *European Journal of Emergency Medicine*, vol. 8, no. 4, pp. 275–278, 2001.

[214] "Leading article: analgesia in acute abdominal pain," *British Medical Journal*, vol. 2, article 1093, 1979.

[215] A. R. Attard, M. J. Corlett, N. J. Kidner, A. P. Leslie, and I. A. Fraser, "Safety of early pain relief for acute abdominal pain," *British Medical Journal*, vol. 305, no. 6853, pp. 554–556, 1992.

[216] B. Bailey, S. Bergeron, J. Gravel, J. F. Bussières, and A. Bensoussan, "Efficacy and impact of intravenous morphine before surgical consultation in children with right lower quadrant pain suggestive of appendicitis: a randomized controlled trial," *Annals of Emergency Medicine*, vol. 50, no. 4, pp. 371–378, 2007.

[217] E. J. Gallagher, D. Esses, C. Lee, M. Lahn, and P. E. Bijur, "Randomized clinical trial of morphine in acute abdominal pain," *Annals of Emergency Medicine*, vol. 48, no. 2, pp. 150–160, 2006.

[218] R. D. Goldman, D. Crum, R. Bromberg, A. Rogovik, and J. C. Langer, "Analgesia administration for acute abdominal pain in the pediatric emergency department," *Pediatric Emergency Care*, vol. 22, no. 1, pp. 18–21, 2006.

[219] M. K. Kim, R. T. Strait, T. T. Sato, and H. M. Hennes, "A randomized clinical trial of analgesia in children with acute abdominal pain," *Academic Emergency Medicine*, vol. 9, no. 4, pp. 281–287, 2002.

[220] J. S. Lee, I. G. Stiell, G. A. Wells, B. R. Elder, K. Vandemheen, and S. Shapiro, "Adverse outcomes and opioid analgesic administration in acute abdominal pain," *Academic Emergency Medicine*, vol. 7, no. 9, pp. 980–987, 2000.

[221] S. Pace and T. F. Burke, "Intravenous morphine for early pain relief in patients with acute abdominal pain," *Academic Emergency Medicine*, vol. 3, no. 12, pp. 1086–1092, 1996.

[222] S. R. Ranji, L. E. Goldman, D. L. Simel, and K. G. Shojania, "Do opiates affect the clinical evaluation of patients with acute abdominal pain?" *Journal of the American Medical Association*, vol. 296, no. 14, pp. 1764–1774, 2006.

[223] J. E. Smith, M. Rocket, R. Squire, and C. J. Hayward, "Pain solutions in the emergency setting; a protocol for two open-label randomised trials of patient-controlled anaglesia versus routine care in the emergency department," *British Medical Journal*, vol. 3, Article ID e002577, 2013.

[224] B. Vermeulen, A. Morabia, P. F. Unger et al., "Acute appendicitis: influence of early pain relief on the accuracy of clinical and US findings in the decision to operate—a randomized trial," *Radiology*, vol. 210, no. 3, pp. 639–643, 1999.

[225] H. Oguzturk, D. Ozgur, M. G. Turtay et al., "Tramadol or paracetamol do not effect the diagnostic accuracy of acute abdominal pain with significant pain relief—a prospective, randomized, placebo controlled double blind study," *European Review for Medical and Pharmacological Sciences*, vol. 16, pp. 1983–1988, 2012.

[226] C. Villain, H. Wyen, S. Ganzera et al., "Early analgesic treatment regimens for patients with acute abdominal pain," *Langenbeck's Archives of Surgery*, vol. 398, pp. 557–564, 2013.

[227] S. H. Thomas, W. Silen, F. Cheema et al., "Effects of morphine analgesia on diagnostic accuracy in Emergency Department patients with abdominal pain: a prospective, randomized trial," *Journal of the American College of Surgeons*, vol. 196, pp. 18–31, 2003.

[228] J. M. Bartfield, R. D. Flint, M. McErlean, and J. Broderick, "Nebulized fentanyl for relief of abdominal pain," *Academic Emergency Medicine*, vol. 10, no. 3, pp. 215–218, 2003.

[229] C. E. Lucas, A. L. Vlahos, and A. M. Ledgerwood, "Kindness kills: the negative impact of pain as the fifth vital sign," *Journal of the American College of Surgeons*, vol. 205, no. 1, pp. 101–107, 2007.

[230] S. H. Thomas, W. Benevelli, D. F. M. Brown, and S. K. Wedel, "Safety of fentanyl for analgesia in adults undergoing air medical transport from trauma scenes," *Air Medical Journal*, vol. 15, no. 2, pp. 57–59, 1996.

[231] "Intranasal diamorphine in children with trauma," *Emergency Nursing*, vol. 20, pp. 14–19, 2013.

[232] M. A. Frakes, W. R. Lord, C. Kociszewski, and S. K. Wedel, "Efficacy of fentanyl analgesia for trauma in critical care transport," *American Journal of Emergency Medicine*, vol. 24, no. 3, pp. 286–289, 2006.

[233] R. J. Kearns, L. Moss, and J. Kinsella, "A comparison of clinical practice guidelines for proximal femoral fracture," *Anaesthesia*, vol. 68, pp. 159–166, 2013.

[234] J. D. Losek and S. Reid, "Effects of initial pain treatment on sedation recovery time in pediatric emergency care," *Pediatric Emergency Care*, vol. 22, no. 2, pp. 100–103, 2006.

[235] M. C. Beckwith, E. R. Fox, and J. Chandramouli, "Removing meperidine from the health-system formulary—frequently asked questions," *Journal of Pain and Palliative Care Pharmacotherapy*, vol. 16, no. 3, pp. 45–59, 2002.

[236] D. R. Thompson, "Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis," *American Journal of Gastroenterology*, vol. 96, no. 4, pp. 1266–1272, 2001.

[237] D. K. Ziegler, "Opioids in headache treatment: is there a role?" *Neurologic Clinics*, vol. 15, no. 1, pp. 199–207, 1997.

[238] K. A. Sporer, "Buprenorphine: a primer for emergency physicians," *Annals of Emergency Medicine*, vol. 43, no. 5, pp. 580–584, 2004.

[239] G. P. Hubbard, K. R. Wolfe, M. Nazario, and M. M. Perreault, "Meperidine misuse in a patient with sphincter of Oddi dysfunction," *Annals of Pharmacotherapy*, vol. 37, no. 4, pp. 534–537, 2003.

[240] M. L. Berg, U. Idrees, R. Ding, S. A. Nesbit, H. K. Liang, and M. L. McCarthy, "Evaluation of the use of buprenorphine for opioid withdrawal in an emergency department," *Drug and Alcohol Dependence*, vol. 86, no. 2-3, pp. 239–244, 2007.

[241] T. Gilmore, A. Saccheti, and T. Cortese, "Buprenorphine/naloxone inhibition of remifentanil procedural sedation," *American Journal of Emergency Medicine*, vol. 30, article 1655, pp. e3–e4, 2012.

[242] M. Jalili, M. Fathi, M. Moradi-Lakeh, and S. Zehtabchi, "Sublingual buprenorphine in acute pain management: a double-blind randomized clinical trial," *Annals of Emergency Medicine*, vol. 59, pp. 276–280, 2012.

[243] R. B. Raffa, E. Friderichs, W. Reimann, R. P. Shank, E. E. Codd, and J. L. Vaught, "Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an "atypical" opioid analgesic," *Journal of Pharmacology and Experimental Therapeutics*, vol. 260, no. 1, pp. 275–285, 1992.

[244] R. Pellicano and L. Guerra, "Skin ulcer pain," *Minerva Medica*, vol. 103, pp. 525–531, 2012.

[245] R. R. Reeves and R. S. Burke, "Tramadol: basic pharmacology and emerging concepts," *Drugs of Today*, vol. 44, no. 11, pp. 827–836, 2008.

[246] W. Leppert, "Tramadol as an analgesic for mild to moderate cancer pain," *Pharmacological Reports*, vol. 61, no. 6, pp. 978–992, 2009.

[247] L. J. M. Mortelmans, D. Desruelles, J. A. Baert, K. R. Hente, and G. G. Tailly, "Use of tramadol drip in controlling renal colic pain," *Journal of Endourology*, vol. 20, no. 12, pp. 1010–1015, 2006.

[248] Z. Engindeniz, C. Demircan, N. Karli et al., "Intramuscular tramadol versus diclofenac sodium for the treatment of acute migraine attacks in emergency department: a prospective, randomised, double-blind study," *Journal of Headache and Pain*, vol. 6, no. 3, pp. 143–148, 2005.

[249] O. Eray, Y. Çete, C. Oktay et al., "Intravenous single-dose tramadol versus meperidine for pain relief in renal colic," *European Journal of Anaesthesiology*, vol. 19, no. 5, pp. 368–370, 2002.

[250] M. A. Turturro, P. M. Paris, and G. L. Larkin, "Tramadol versus hydrocodone-acetaminophen in acute musculoskeletal pain: a randomized, double-blind clinical trial," *Annals of Emergency Medicine*, vol. 32, no. 2, pp. 139–143, 1998.

[251] B. R. Close, "Tramadol: does it have a role in emergency medicine?" *Emergency Medicine Australasia*, vol. 17, no. 1, pp. 73–83, 2005.

[252] H. Yarkan Uysal, B. Bilimgut, B. Dikmen, N. Inan, G. Ülger, and S. Eruyar, "Epileptic seizure following IV tramadol in a patient with mental retardation and cerebellar ataxia," *Pain Medicineicine*, vol. 12, no. 5, pp. 833–836, 2011.

[253] S. S. Mazor, K. W. Feldman, N. F. Sugar, and M. Sotero, "Pediatric tramadol ingestion resulting in seizurelike activity: a case series," *Pediatric Emergency Care*, vol. 24, no. 6, pp. 380–381, 2008.

[254] R. Kamel, A. Mahmoud, and G. El-Feky, "Double-phase hydrogel for buccal delivery of tramadol," *Drug Development and Industrial Pharmacy*, vol. 38, pp. 468–483, 2012.